

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
 {Suchitra Balakrishnan, MD, Ph.D. }
 {NDA212097}
 {G-voke HypoPen and PFS, Glucagon injection}

CLINICAL REVIEW

Application Type	NDA [505(b)(2)]
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Division/Office	CDER/OND/ODE2/DMEP
Reviewer Name(s)	Suchitra Balakrishnan, MD, PhD.
Review Completion Date	August 27, 2019
Established/Proper Name	G-Pen (glucagon injection)
(Proposed) Trade Name	GVoke Hypopen and GVoke PFS
Applicant	Xeris Pharmaceuticals Inc.
Dosage Form(s)	Liquid for Subcutaneous injection (s.c.) by autoinjector (AI) and Pre-filled Syringe (PFS)
Applicant Proposed Dosing Regimen(s)	1mg (adults) or 0.5 mg (pediatrics) by s.c. injection p.r.n.
Applicant Proposed Indication(s)/Population(s)	Treatment of severe hypoglycemia
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Patients with diabetes mellitus

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Glossary

This glossary should include all acronyms used in your review. The sample list below includes commonly used acronyms and may be used as a starting point.

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Xeris Pharmaceuticals, Inc. (Xeris) have developed G-Pen (glucagon for subcutaneous [s.c.] injection) for the treatment of severe hypoglycemia in patients with diabetes.

Glucagon is a 29-amino acid polypeptide (non-steroid) hormone produced by the pancreatic alpha cells. It increases blood glucose by binding to glucagon receptors in the liver, causing liver cells to convert glycogen polymers into glucose molecules. Glucagon also relaxes smooth muscle of the gastrointestinal tract¹. A single glucagon gene encodes a larger proglucagon biosynthetic precursor in mammals. Tissue-specific processing of proglucagon gives rise to glucagon, glicentin, oxyntomodulin, glucagon-like peptide-1 (GLP-1), and GLP-2.

G-Pen is a sterile, subcutaneous injectable, non-aqueous solution formulation of synthetic human glucagon. G-Pen has been developed in two presentations, a pre-filled syringe (PFS) with an auto-injector (AI) (referred to as Configuration A) and a PFS with a manual plunger rod and backstop (referred to as Configuration B). The same G-Pen PFS is common to both Configuration A and Configuration B, and will be offered in two fill volumes, 0.5 mg for pediatric patients under 12 years of age and 1 mg for patients 12 years and older. The proposed tradenames for the two presentations are Gvoke HypoPen and Gvoke PFS.

Two glucagon products are currently available to treat severe hypoglycemia by s.c., intramuscular (i.m.) or intravenous (i.v.) injection. Each product is sold as a vial of lyophilized glucagon powder and a needle/syringe that contains a liquid diluent. They require reconstitution by the patient or caregiver and immediate use after reconstitution. Therefore, the applicant believes that G-Pen addresses an unmet clinical need for a ready-to-use glucagon product that can be administered with reliability and ease, based on the premise that the G-Pen presentations would obviate the need for reconstitution and withdrawal of the solution prior to injection.

Xeris is submitting this New Drug Application (NDA) using the 505(b)(2) approval pathway, referencing the previous findings of safety for the reference product, Glucagon Emergency Kit (Glucagon for Injection), NDA 020928, manufactured by Eli Lilly and Company.

¹ The Physiology of Glucagon; Gerald J Taborsky, Jr, Ph.D.; J Diabetes Sci Technol. 2010 Nov; 4(6): 1338–1344

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of G-Pen for the treatment of severe hypoglycemia. G-Pen (1 mg) in comparison to Lilly glucagon (1 mg) was evaluated in two pivotal studies (XSGP-301 and XSGP-303), conducted in adult patients with Type 1 DM. G-Pen met the criteria for non-inferiority to Lilly glucagon, for the clinically relevant endpoint of an increase in plasma glucose to greater than 70 mg/dL or to 20 mg/dL above baseline plasma glucose within 30 minutes of administration. The evidence from the clinical development program supports approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Xeris Pharmaceuticals, Inc. (Xeris) have developed G-voke (referred to as G-Pen in the review), a non-aqueous solution formulation of synthetic human glucagon for subcutaneous [s.c.] injection) that is ready to administer without reconstitution. The proposed indication is for the treatment of severe hypoglycemia in patients with diabetes. I recommend approval of the product.

Severe hypoglycemia in patients with diabetes is a medically serious condition which can be fatal if untreated. All patients with Type 1 DM and patients with Type 2 DM on insulin or sulfonylureas are at risk. Patients with brittle or poorly controlled diabetes, children and elderly are at increased risk. Oral glucose is the primary treatment of hypoglycemia if the patient is able and willing to consume carbohydrate by mouth. However, patients with severe hypoglycemia are frequently unconscious or with an impaired level of consciousness that precludes oral intake. The currently marketed glucagon rescue kits in the US for severe hypoglycemia treatment require reconstitution (combining the powder in a vial with diluent in syringe) by the patient or caregiver before use and immediate administration after reconstitution since the solution becomes unstable. There are reports of medication errors with the currently marketed kits², including injection of diluent alone, suggesting an unmet medical need for glucagon products that are easier to administer, especially by users who are not health care professionals.

G-Pen did not demonstrate pharmacokinetic bioequivalence to the reference listed drug (Glucagon for injection, Eli Lilly) in this 505(b)(2) application. The Applicant conducted two pivotal single-dose, cross-over trials comparing the efficacy and safety of G-pen to Lilly

² Institute for Safe Medication Practices Medication Safety Alert-Acute Care (www.ismp.org), March 10, 2005-Volume 10, Issue 5 & July 17, 2014 -Volume 19, Issue 14

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glucagon. In both studies, the assessment of non-inferiority (NI) to Lilly Glucagon was based on analysis of failure scores for the primary endpoint, an increase in plasma glucose concentration from below 50 mg/dL to > 70 mg/dL within 30 minutes after receiving glucagon. G-Pen did not satisfy the NI criterion for the primary endpoint of failure scores in one of the studies. However, G-Pen demonstrated non-inferiority compared to Lilly glucagon for an increase in absolute plasma glucose concentration > 70 mg/dL or ≥ 20 mg/dL increase from baseline within 30 minutes after study drug administration. It was felt that in addition to an increase to an absolute blood glucose threshold value of 70 mg/dL, a relative increase of at-least 20 mg/dL from baseline may be clinically important, especially for a patient with severe hypoglycemia and nadir blood glucose values well below 50 mg/dL. Therefore, it was felt that this endpoint was clinically meaningful, and it would be consistent with the primary endpoint for other recent glucagon development programs.

There was a time lag observed in the G-pen pharmacodynamic response compared to Lilly glucagon. In the pooled analyses of both studies, the mean (SD) time to achieve plasma glucose > 70 mg/dL or increase in plasma glucose > 20 mg/dL above baseline was 13.8 (5.6) minutes for G-pen, compared to 10 (3.6) minutes for Lilly Glucagon. The risk from this delay in effect can be mitigated by including language in the indications section of the PI advising providers to instruct caregivers/patients to seek immediate emergency assistance after administration of G-Pen for severe hypoglycemia. The injectable glucagon products currently approved for this indication require reconstitution of the powdered glucagon, which may delay and/or limit their use as caregivers may not be familiar with administering a product that requires reconstitution, as suggested by post-marketing reports of medication errors (including injection of diluent alone²). G-pen offers the potential for greater ease of administration with lower potential for medication errors.

Common adverse events (nausea, vomiting) were similar and consistent with the adverse event profile of approved glucagon products. There was an increased incidence of injection site edema and pain compared to Lilly glucagon. These were not severe in intensity and can be described in the adverse reactions section of the package insert.

I recommend approval of G-Pen based on the efficacy demonstrated in the pivotal clinical studies and considering the added benefit of ease of administration with lower potential for medication errors, especially by non-medical personnel. Except as noted above, the safety profile of G-Pen is consistent with the well-established safety profiles of currently marketed glucagon products. Relevant safety information can be communicated through product labeling and monitoring for adverse events in the post-market setting can be achieved through routine pharmacovigilance. For that reason, I do not recommend a REMS or post-marketing requirements (PMRs).

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Severe hypoglycemia is defined by the American Diabetes Association (ADA) and the Endocrine Society as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. - Hypoglycemia is more likely to occur in the context of treatment with a sulfonylurea, glinide, or insulin and occurs about two to three times more frequently in patients with Type 1 DM than in Type 2 DM. The incidence increases with the duration of diabetes. - Event rates for severe hypoglycemia for patients with type 1 DM range from 115 to 320 events per 100 patient-years. Severe hypoglycemia in patients with Type 2 DM has been shown to occur at rates of 35 to 70 events per 100 patient-years. - Hypoglycemia results in morbidity (including poor glycemic control from fear of hypoglycemia, cognitive deficits, confusion and falls especially in the elderly) and is sometimes fatal. The mortality rate reported in the literature from severe	Severe hypoglycemia in patients with diabetes is a medically serious condition which can be fatal if untreated. All patients with Type 1 DM, and patients with Type 2 DM on insulin or sulfonylureas are at risk. Patients with brittle or poorly controlled diabetes, children and the elderly are at increased risk.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hypoglycemia in type 1 DM range from 6-10%.	
Current Treatment Options	- The ADA recommends that glucose (15–20 g) is the preferred treatment for the conscious individual with blood glucose < 70 mg/dL [3.9 mmol/L]), although any form of carbohydrate that contains glucose may be used. Currently approved glucagon products include injectable options and an intranasal option. - The current marketed injectable glucagon rescue kits in the US for severe hypoglycemia treatment require reconstitution.	Oral glucose is the primary treatment of severe hypoglycemia if the patient is able and willing to consume carbohydrate by mouth. There is potentially an unmet medical need for glucagon products that are easier to administer.
Benefit	In both Efficacy and Safety studies, non-inferiority to Lilly Glucagon was based on analysis of failure scores for the primary endpoint, an increase in plasma glucose concentration from below 50 mg/dL to > 70 mg/dL within 30 minutes after receiving glucagon. The non-inferiority criterion for this pre-specified primary endpoint was not satisfied in Study 301 but was satisfied in Study 303. However, G-Pen demonstrated non-inferiority compared to Lilly glucagon for an increase in absolute plasma glucose concentration > 70 mg/dL or ≥ 20 mg/dL increase from baseline within 30 minutes after	Both Study 301 and Study 303 provide evidence of effectiveness for G-Pen. It was felt that in addition to an increase to an absolute blood glucose threshold value of 70 mg/dL, a relative increase of at-least 20 mg/dL from baseline may be clinically important, especially for a patient with severe hypoglycemia and nadir blood glucose values well below 50 mg/dL. Therefore, it was felt that this endpoint was clinically meaningful, and it would be consistent with the primary endpoint for other recent glucagon development programs.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	study drug administration. An uncontrolled sequential efficacy and safety study in 31 pediatric patients with Type 1 DM was also conducted. The study met the primary efficacy endpoint for all age groups, with a demonstrated increase in plasma glucose after administration of G-Pen.	The study limitations included a lack of control group and applicability of the results to conditions of real use (severe hypoglycemia). However, all subjects demonstrated a robust pharmacodynamic (glucose) response to study drug.
Risk and Risk Management	The most common G-Pen TEAEs were in the Gastrointestinal Disorders SOC, with a slightly higher incidence of nausea (29.9% versus 22.9%, respectively) and vomiting (16.2% versus 9.6%, respectively) compared to Lilly glucagon treatment. Headaches were also numerically more frequent following G-pen treatment (G-pen 8 [5.2%], Lilly-6 [3.8%]). All these events were reported as mild or moderate in severity. In the investigator reported assessment of local tolerability, moderate and severe injection site edema at 30 minutes was reported in 5.2% and 1.3% of G-Pen treated subjects respectively compared with none in the Lilly glucagon treatment sequence. Injection site pain was reported as an AE in 2 (1.3%) of G-Pen treated subjects. There was a time lag observed in the G-pen pharmacodynamic response compared to Lilly glucagon. In the pooled analyses	Common adverse events were similar and consistent with the adverse event profile of approved glucagon products except for an increased incidence of injection site edema and pain compared to Lilly glucagon. These were not severe in intensity and can be included in the adverse reactions section of the package insert.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of both studies, the mean (SD) time to achieve plasma glucose > 70 mg/dL or increase in plasma glucose > 20 mg/dL was 13.8 (5.6) minutes for G-pen, compared to 10 (3.6) minutes for Lilly Glucagon.	The risk from this delay may in part, be mitigated by the lack of the need for reconstitution. The G-pen offers the potential for greater ease of administration with lower potential for medication errors

1.4. Patient Experience Data

A hypoglycemia symptom questionnaire was completed by patients in studies 301 and 303 and analyzed as a secondary endpoint. The Clinical Outcomes Assessment (COA) staff were consulted regarding the validity of the instrument and applicability to conditions of actual use (i.e. treatment of severe hypoglycemia in patients who have reduced level of consciousness or seizures).

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

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	Sections 6.1.1, 6.2.1, 6.1.2 and 6.2.2
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Hypoglycemia is defined in patients with diabetes as all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm. It causes recurrent morbidity in most patients with type 1 diabetes mellitus (Type 1 DM) and patients requiring insulin with type 2 diabetes mellitus (Type 2 DM), and is sometimes fatal³.

Low plasma glucose concentrations cause an array of symptoms by signaling central nervous system-mediated autonomic nervous system responses and by limiting neuronal metabolism. Neurogenic (autonomic) symptoms include, but are not limited to, palpitations, tremor, hunger, and sweating. Neuroglycopenic symptoms often include behavioral changes, difficulty thinking, and/or frank confusion. Less common neuroglycopenic manifestations include seizure, coma, and even death². The clinical syndrome is most reliably documented by Whipple's triad⁴: symptoms consistent with hypoglycemia, a low plasma glucose concentration, and relief of those symptoms when the plasma glucose concentration is raised. Symptoms of hypoglycemia may also be idiosyncratic and non-specific.

Severe hypoglycemia is defined by the American Diabetes Association (ADA) and the Endocrine Society as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration⁵.

Recurrent hypoglycemia has been shown to lead to hypoglycemia unawareness. The first sign of hypoglycemia in these patients is confusion, and they often must rely on the assistance of others to recognize and treat low blood glucose. Defective glucose counter-regulation and hypoglycemia unawareness are the components of hypoglycemia-associated autonomic failure (HAAF) in patients with diabetes. HAAF is caused by recurrent iatrogenic hypoglycemia and is

³ American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes. *Diabetes Care* 2005;28(5):1245-49

⁴ Whipple AO: The surgical therapy of hyperinsulinism. *J Int Chir* 3:237-276, 1938

⁵ Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care* 2013;36:1384-1395

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reported to be at least partly reversible by scrupulous avoidance of hypoglycemia⁶. HAAF is associated with increased risk of severe hypoglycemia⁷ with its morbidity and potential mortality during intensive glycemictreatment⁸.

Hypoglycemia can occur on treatment with a sulfonylurea, glinide, or insulin and occurs about two to three times more frequently in Type 1 DM than in Type 2 DM. The incidence increases with the duration of diabetes⁹. Rates for severe hypoglycemia for patients with type 1 DM range from 115 to 320 events per 100 patient-years. Severe hypoglycemia in patients with type 2 diabetes has been shown to occur at rates of 35 to 70 events per 100 patient-years¹⁰.

Hypoglycemia is the critical limiting factor in the glycemictreatment of diabetes in both the short and long term¹¹. Intensive glycemictreatment both decreased the frequency of long-term complications of hyperglycemia and increased the frequency of hypoglycemia in the Diabetes Control and Complications Trial (DCCT)^{12, 13}.

⁶ Dagogo-Jack S, Rattarasam C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes* 1994;43: 1426–1434

⁷ WhiteNH, SkorDA, Cryer PE, Levandoski LA, Bier DM, Santiago JV. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med* 1983;308:485–491

⁸ Cryer PE. Death during intensive glycemictreatment of diabetes: mechanisms and implications. *Am J Med* 2011;124: 993–996

⁹ Heller SR, Choudhary P, Davies C, et al.; UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007; 50:1140–1147

¹⁰ Donnelly LA, Morris AD, Frier BM, et al.; DARTS/MEMO Collaboration. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabet Med* 2005;22:749–755

¹¹ Cryer PE, Davis SN, Shamon H: Hypoglycemia in diabetes. *Diabetes Care* 26: 1902–1912, 2003

¹² The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993

¹³ The Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997

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The mortality rate reported in the literature from severe hypoglycemia in type 1 DM range from 6-10%.^{14, 15, 16, 17.} In 2014, over 245,000 emergency department visits occurred for hypoglycemia^{18.} Three large trials examined the effect of glucose lowering on cardiovascular events in patients with type 2 diabetes: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial)^{19, 20, 21.} In all three studies, an episode of severe hypoglycemia was associated with an increased risk of subsequent mortality.

In addition to mortality risk, severe hypoglycemia may significantly impact morbidity, quality of life and activities of daily living in various patient populations. Hypoglycemia/hypoglycemia unawareness may impair the ability to operate a vehicle or heavy machinery and increase risk for car collisions^{22.} Ongoing maturation of the central nervous system puts younger children at risk for cognitive deficits as a consequence of hypoglycemia^{23.} Older adults with diabetes have a disproportionately high number of clinical complications and comorbidities, all of which can be exacerbated by and sometimes contribute to episodes of hypoglycemia^{24.}

¹⁴ Patterson CC, Dahlquist G, Harjutsalo V, et al. Early mortality in EURODIAB population-based cohorts of type 1 diabetes diagnosed in childhood since 1989. *Diabetologia* 2007;50:2439–2442

¹⁵ Jacobson AM, Musen G, Ryan CM, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007;356:1842–1852

¹⁶ Feltbower RG, Bodansky HJ, Patterson CC, et al. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes: results from the Yorkshire Register of Diabetes in Children and Young Adults. *Diabetes Care* 2008;31: 922–926

¹⁷ Skriverhaug T, Bangstad HJ, Stene LC, Sandvik L, Hanssen KF, Joner G. Longterm mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia* 2006;49:298–305

¹⁸ Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. <https://www.cdc.gov/diabetes/data/statistics/statistics-report.html>

¹⁹ Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in , veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139

²⁰ Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b4909

²¹ Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010; 363:1410–1418

²² Cox DJ, Kovatchev B, Vandecar K, Gonder-Frederick L, Ritterband L, Clarke W. Hypoglycemia preceding fatal car collisions. *Diabetes Care* 2006;29:467–468

²³ Hannonen R, Tupola S, Ahonen T, Riiikonen R. Neurocognitive functioning in children with type-1 diabetes with and without episodes of severe hypoglycaemia. *Dev Med Child Neurol* 2003; 45:262–268

²⁴ Bruce DG, Casey GP, Grange V, et al. Cognitive impairment, physical disability and depressive symptoms in older diabetic patients: the Fremantle Cognition in Diabetes Study. *Diabetes Res Clin Pract* 2003;61:59–67

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In summary, severe hypoglycemia is a serious medical condition with significant impact on patient quality of life, morbidity and mortality for most patients with Type 1 DM and patients with type 2 DM who require treatment with insulin.

2.2. Analysis of Current Treatment Options

Professional societies emphasize prevention as the main treatment strategy for hypoglycemia. Recurrent hypoglycemia increases the risk of severe hypoglycemia and the development of hypoglycemia unawareness and HAAF. Effective approaches known to decrease the risk of iatrogenic hypoglycemia include patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and conscientious surveillance by the clinician. The glycemic target established for any given patient should be individualized depend on the patient's age, life expectancy, comorbidities, preferences, and an assessment of how hypoglycemia might impact his or her life⁵. Continuous glucose monitoring (CGM) with automated low glucose suspend has been shown to be effective in reducing hypoglycemia in patients with type 1 diabetes on insulin pumps²⁵.

Severe hypoglycemic events require urgent treatment. As a consequence, the majority of severe hypoglycemic events are treated where they occur, which is typically outside of a healthcare facility. The ADA recommends that glucose (15–20g) is the preferred treatment for the conscious individual with blood glucose < 70 mg/dL [3.9 mmol/L]), although any form of carbohydrate that contains glucose may be used. Fifteen minutes after treatment, if self-monitored blood glucose (SMBG) shows continued hypoglycemia, the treatment should be repeated. Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia²⁶. Glucagon should be prescribed for all individuals at increased risk of level 2 hypoglycemia, defined as blood glucose < 54 mg/dL (3.0 mmol/L), so it is available should it be needed. The use of glucagon is indicated for the treatment of hypoglycemia in people unable or unwilling to consume carbohydrates by mouth. The guidelines recommend that caregivers, school personnel, and family members of these individuals should be instructed on the use of glucagon kits. Glucagon administration is not limited to health care professionals. Intravenous (i.v.) dextrose or glucose is the preferred treatment of severe hypoglycemia in emergency medical facilities and in patients failing to respond to glucagon. Seeking emergency assistance is recommended immediately after administration of glucagon²⁷.

²⁵ Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold based insulin-pump interruption for reduction of hypoglycemia. *N Engl J Med* 2013;369:224–232

²⁶ American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes 2019. *Diabetes Care* 2019;42(Suppl. 1):S61–S70

²⁷ https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020928s0561bl.pdf;
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020918s0521bl.pdf

The currently marketed injectable glucagon rescue kits in the US for severe hypoglycemia treatment are Eli Lilly's Glucagon Emergency Kit and Novo Nordisk's GlucaGen HypoKit, both approved since 1998. These products require reconstitution by the patient or caregiver before use. Each product is sold as a vial of lyophilized glucagon powder with a needle/syringe that contains a liquid diluent. The glucagon powder must be combined with the liquid diluent at the time of use and drawn into the syringe. The currently marketed products must be used immediately after re-constitution because once the lyophilized glucagon is combined with water, the solution becomes unstable and can fibrillate, rendering it inactive and potentially toxic. There are reports of medication errors, including injection of diluent alone with these products². The impact of such medication errors on clinical outcomes (morbidity and mortality from severe hypoglycemia) is unknown at this point, but these errors suggest an unmet medical need exists for glucagon products that are easier to administer, especially by users who are not health care professionals.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Two injectable glucagon products were approved in 1998 for marketing in the US: Eli Lilly's Glucagon Emergency Kit (NDA 020928) and Novo Nordisk's GlucaGen HypoKit (NDA 020918). Baqsimi, an intranasally administered glucagon (NDA 210134) was recently approved.

3.2. Summary of Presubmission/Submission Regulatory Activity

505(b)(2) ASSESSMENT:

This 505(b)(2) NDA application references Glucagon for Injection (NDA 020928) as the reference list drug. This application provides for a change in dosage form, from lyophilized powder to a premixed solution. The scientific bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s). The applicant relied on FDA's finding of nonclinical safety of Lilly's Glucagon (glucagon injection) (NDA 020928). To bridge for this limited purpose,

- the applicant conducted two efficacy and safety studies comparing the proposed product to the listed drug. The results of these studies show that the proposed drug and

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the listed drug are sufficiently similar such that reliance on FDA's finding of the nonclinical safety for Glucagon is appropriate.

- In addition, the Applicant conducted a 14-day repeat dose comparative toxicity study where rats were treated with Xeris's proposed glucagon product or the relied-upon listed drug, Lilly's Glucagon (glucagon injection) (NDA 020928). Both Xeris's proposed product and Lilly's Glucagon were well tolerated and showed a comparable toxicological profile. A glucose extension study revealed that rats treated repeatedly with Xeris's proposed product or Lilly's Glucagon had comparable increases in blood glucose.
- There is no analytical comparability assessment of the proposed product with the Lilly's Glucagon in the application and the CMC reviewers determined that this assessment is not necessary for the limited reliance on Lilly's Glucagon for nonclinical safety. At the drug substance level there is characterization data to support that it is glucagon.

Other Regulatory Activity:

The US IND (115091) was submitted in December 2012. The IND was initially placed on clinical hold for inadequate non-clinical information. The applicant was asked to submit data that supported comparability of their glucagon product to a U.S. listed drug in an adequate 2-week toxicity study in a single species²⁸. The clinical hold was removed on September 25, 2013 after the applicant addressed these issues and Study XSGP 201 was allowed to proceed.

The End of Phase -2 meeting was held on August 27, 2014. The applicant was given the following advice regarding establishment of bioequivalence: "Your selection of 1.0 mg dose for the pivotal study (XSGP-301) seems appropriate. However, we do not agree with your proposal to demonstrate only the pharmacodynamics (PD) equivalence in your pivotal study. PD for glucagon products may not be a sensitive marker to differentiate between products, as also reflected in your results showing similar PD response for 0.5 mg and 1.0 mg dose in study XSGP-201. Therefore, in your proposed pivotal study you should include both pharmacokinetic (PK) and PD parameters as the main study endpoints. For the test product to be considered equivalent to the reference product, bioequivalence should be demonstrated for both PK and PD AUC and Cmax parameters. Inability to demonstrate this may require that additional study of your product will be needed to support the application."

In addition, the applicant was given the following advice regarding the pivotal phase 3 study: "The pivotal Phase 3 study should be an active-comparator controlled study evaluating the efficacy and safety of Xeris G-Pen 1 mg versus active comparator, to provide more definitive evidence of efficacy. The primary endpoint should be the proportion of subjects achieving an increase in glucose over 70 mg/dL within 30 minutes of receiving study glucagon and without receiving any other measure to increase the blood glucose levels such as intravenous glucose, additional glucagon, or oral carbohydrates. Other outcomes assessed could include:

²⁸ IND clinical hold letter dated January 24, 2013, IND 115091, DARRTs ID 3250000

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- a) Time from treatment to return of blood glucose to >70 mg/dL, and
- b) Safety and tolerability observations, including injection site reactions, nausea/vomiting and recovery from clinical symptoms of hypoglycemia.”

The pre-NDA meeting was held on December 7, 2017. Multiple disciplines had comments for the applicant regarding requirements for the NDA application: CMC- acceptance criteria for glucagon content, limits for total degradants, impurities content and drug product release specifications; CDRH- reliability testing for the G-pen PFS and autoinjector, needle bio-compatibility evaluation; DMEPA- Human Factors (HF) validation study²⁹. The applicant was advised to conduct a comparative pharmacokinetic/pharmacodynamic study to serve as a scientific bridge between the auto-injector and pre-filled syringe presentations. The applicant was also advised to clearly identify the information from NDA 020928 that they intend to rely upon to support their application.

A fast-track designation request was submitted by the applicant to the IND on May 20, 2015 on the basis that their product will provide for “a simple, ready-to-use, auto-injector [and] is expected to have a significant impact [on] reducing morbidities and even deaths from severe hypoglycemia”. This was denied on the basis that the development plan does not include plans to directly and rigorously establish this morbidity/mortality benefit³⁰. The Applicant also requested a Priority review designation when submitting the NDA on June 10, 2018. The basis was treatment of a serious condition and virtual elimination of dosing errors in simulated emergency studies. The review was classified as “Standard”³¹. The rationale was that there was no evidence of substantial benefit over approved therapies for severe hypoglycemia, in the absence of a proven morbidity or mortality benefit.

The applicant has conducted an uncontrolled, open -labelled pediatric efficacy and safety study (302) in 31 pediatric patients aged 2-17 years with Type 1 DM, which has been included in the NDA submission. They also requested a partial waiver of pediatric studies for patients under two years of age, based on low incidence of Type 1 DM in this age group and feasibility. In addition, they submitted a request for Pediatric exclusivity determination with the NDA submission. They were informed that they were ineligible for pediatric exclusivity, because a Written Request as required by Section 505A was never issued for G-Pen31.

3.3. Foreign Regulatory Actions and Marketing History

²⁹ PreNDA meeting minutes dated January 3, 2018, IND 115091, DARRTs ID 4201936

³⁰ Fast-track designation determination dated June 17, 2015, DARRTs ID 3780334

³¹ Filing Communication for NDA 212097 dated October 22, 2018, DARRTs ID 4338164

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G-Pen is not approved or marketed in any country

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

4.1. Office of Scientific Investigations (OSI)

For details refer to the OSI review by Dr. Cynthia Kleppinger dated May 2, 2019, DARRTs ID 4427821

Because this is the first NDA submitted by the applicant to DMEP, the division requested OSI to inspect clinical sites and the applicant to ensure adequate study conduct and acceptability of the data for NDA review. OSI inspected three domestic clinical sites, in addition to the contract research organization (CRO) and the applicant.

OSI identified regulatory deficiencies in one clinical site (ProSciento Inc., site 2) with 20 enrolled subjects in study 301 and 13 in study 303. The final conclusion was that these findings are unlikely to have a significant impact on overall results, and the compliance classification for the investigator Dr. Peters) is Voluntary Action Indicated (VAI). Details of the findings will be discussed with the individual study results (section 6.1.2 and 6.2.2)

For the applicant inspection, the OSI inspector noted that the firm failed to have written procedures or a systematic practice in place to ensure that all vendor correspondence with respect to time frame of database transfers, database unlocks and changes was maintained. This concern was shared with the review team while the inspection was ongoing. The time frame of database transfers, unlocks and changes made had to be reconstructed by reviewing e-mails, meeting minutes, and forms obtained from the contractors during the FDA inspection. Documentation was collected during the inspection to try to reconstruct what took place during this time-frame, but the OSI reviewer noted that it cannot be determined if all documentation regarding the database transfers were provided. However, the final conclusion by the inspector was that there was adequate adherence to the regulations. The inspector also identified subjects participating in both adult trials. The statistical reviewer identified 9 subjects who received study treatment in both studies³². There was a concern that patients who responded well to G-Pen in Study 301 were selectively enrolled in Study 303. However, the primary endpoint results for Study 303 did not change on exclusion of these subjects.

³² Table 5 and Appendix A (Table 13), Statistical review NDA 212097 by Dr. Anna Ketterman
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The inspection of the CRO (b) (4) was added after discussion with the review team, after the site inspections revealed that not all source data generated was kept at the clinical sites (see section 6.2.2 for details). Laptop computers and software provided by (b) (4) were used to record subjects' plasma glucose (PG) values for study 303. After entry of PG values, the computer software generated source data (including the 8-minute algorithm-predicted PG value) which were not documented elsewhere and was relied on by the site to make glucagon dosing related decisions. Anytime the clinical investigator did not follow the algorithm, the system required the investigator to enter a justification. The laptops were returned to the vendor on study completion. During the (b) (4) inspection, this source data was inspected. There was no indication during the inspection that data had been altered from the original output and no other issues were identified on review of the data audit trail.

OSI recommended that overall, the study data generated are considered acceptable and may be used in support of this NDA.

4.2. Product Quality

Refer to the Office of Product Quality (OPQ) review by Dr. Muthukumar Ramaswamy dated May 10, 2019 in Panorama for additional details.

Glucagon is a single chain polypeptide with 29 amino acid residues. G-Pen is a sterile, subcutaneous injectable, non-aqueous solution formulation of synthetic human glucagon. Synthetic glucagon drug substance is cGMP grade material, manufactured and released under ICH Q7 guidelines by Bachem A.G. The applicant states that the proprietary delivery platform is designed (b) (4) of the glucagon peptide. The formulation components of the drug product are shown in the table below. All excipients associated with the drug product are present in approved products.

Table 1: Formulation Components of G-Pen (Glucagon Injection)

Component	Function	Reference to Quality Standard
Glucagon	Drug Substance	Manufacturer a-
Trehalose, dihydrate	Excipient	USP
Dimethyl Sulfoxide (DMSO)	(b) (4)	USP
(b) (4) (Sulfuric Acid)		NF

a-Acceptance Criteria based on Bachem, Xeris, and USP/EP monographs for Glucagon HCl ; USP- United States Pharmacopeial Convention, NF- National Formulary and Drug Standards Laboratory

Source: Table 1, Non-clinical Introduction, eCTD-2.6.1

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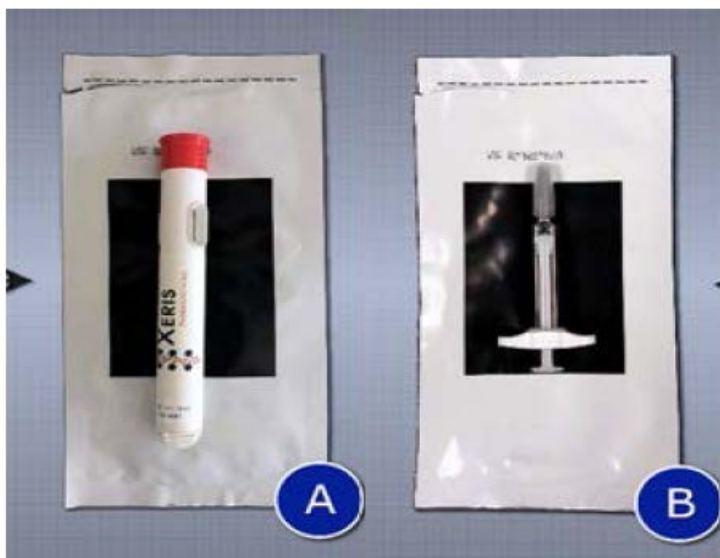
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G-Pen will be offered in two presentations, a pre-filled syringe with an auto-injector (Configuration A) and a pre-filled syringe with a manual plunger rod and backstop (Configuration B) (see figure below). The same G-Pen pre-filled syringe is common to both Configuration A and Configuration B, and will be offered in two fill volumes, 0.5 mg for pediatric patients and 1 mg for patients 12 years and older. Both pre-filled pen and auto-injector are further packaged in foil pouches to prevent degradation from light exposure. The product is intended for storage at 25°C with an expiration period of 24 months. Short-term excursions are permitted between 15° and 30°C (59° and 86°F). The product is not intended for storage in the refrigerator or in the freezer.

Figure 1: G-Pen Configuration



Source: Figure 1, Non-clinical Introduction, eCTD-2.6.1

The formulation of G-Pen was modified between Phase 2 and Phase 3 clinical trials

(b) (4)

(b) (4)

(b) (4)

during manufacturing. The applicant indicates that the Phase 3 formulation was developed to improve stability and simplify the manufacturing process. The pharmacokinetics of the two formulations were compared in a rat study and found to be bioequivalent.

OPQ reviewed the drug substance information, components associated with the primary container closure system, extractables and leachables data. They concluded that the stability data provided in the application supported the compatibility of active ingredient with excipients and container closure components. The final recommendation was that there are no

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outstanding deficiencies related to drug substance, drug product, microbiology, biopharmaceutics environmental analysis, container and carton label.

During a recent inspection of the drug product manufacturing site Pyramid Laboratories, Inc (PLI). for this NDA, the field investigator observed objectionable conditions at the facility. Pre-approval inspection (PAI) findings indicated that finished drug testing methods do not conform to the application. The impurity testing method specified in the NDA has not been transferred or run at the manufacturing site. Product testing conducted to date did not utilize the application test method (indicated during NDA filing). Therefore, the firm's current method does not quantitate individual impurities as per the NDA. This was conveyed to the representative of the facility at the close of the inspection and a FDA form 483 was issued. The inspector recommended withholding approval of the NDA until this issue is resolved. OPQ and the Office of Process and Facilities (OPF) reviewers have therefore recommended a Complete response. The review clock for the NDA was extended to September 10, 2019 due to a major amendment (see section 4.6). During this period, OPF re-evaluated the facility assessment based on (i) 483 observations, (ii) Establishment Inspection Report (EIR) and other exhibits from the investigation, (iii) Pyramid Laboratories (PLI) response to the 483 and (iv) PLI response to FDA's Request for Additional Information sent on June 26, 2019. The reviewer notes that PLI updated their finished drug test methods for the proposed commercial product to align with the NDA application test methods. PLI also qualified the impurities determination method and provided the method qualification report. Based on these findings the OPF reviewer concluded that Pyramid laboratories is deemed as acceptable as drug product manufacturer for the current drug product. The office of Product Quality now recommends approval of the NDA.

4.3. Clinical Microbiology

For details refer to the Microbiology review by Dr. Renee Marcsisin dated March 18, 2019 in Panorama.

The drug product is sterile (b) (4)
(b) (4)
The syringes and (b) (4) plunger stoppers are received ready-to-use.

The microbiology reviewer assessed the container closure component (b) (4) information and integrity of the container closure system during storage and handling. She also reviewed the microbiological controls used in the drug product manufacturing process. This included information on (b) (4) processing, drug product specification for sterility, container closure integrity (dye ingress test), bacterial endotoxin method for release testing, (b) (4) validation,

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depyrogenation (b) (4), media fill studies, hold times, and post-approval stability commitment to determine the microbiological quality of the drug product over the 24-month storage period. She concluded that microbiological controls are adequate to support the NDA and identified no deficiencies.

4.4. Nonclinical Pharmacology/Toxicology

Refer to the Pharmacology /Toxicology review by Dr. Elena Brathwaite dated May 2, 2019 in DARRTs for additional details.

Toxicology, pharmacokinetic and local tolerance studies were performed to compare profiles for G-Pen and Lilly glucagon and to qualify potential impurities after deliberate degradation designed to simulate the product at the end of its shelf life.

As mentioned earlier, the applicant relied on FDA's finding of nonclinical safety of Lilly's Glucagon (glucagon injection) (NDA 020928). As part of the scientific bridge for this limited purpose, the applicant conducted a 14-day repeat dose comparative toxicity study where rats were treated with Xeris's proposed glucagon product or the reference listed drug, Lilly's Glucagon (glucagon injection) (NDA 020928). Both Xeris's proposed product and Lilly's Glucagon were well tolerated and showed a comparable toxicological profile. A glucose extension study revealed that rats treated repeatedly with Xeris's proposed product or Lilly's Glucagon had comparable increases in blood glucose. The high dose (HD) Xeris glucagon-treated rats had minimal to marked, reversible injection site reactions that appeared to be more severe after the recovery period when compared to Lilly glucagon-treated rats. The NOAEL for both Xeris and Lilly glucagon was the highest dose examined resulting in a 19-fold exposure multiple to the maximum recommended human dose (MRHD). Both acute and sub-chronic studies in rats indicate that Xeris and Lilly glucagon were well tolerated and had similar toxicity profiles. A unique finding in the liver after treatment with Xeris glucagon was noted (increased liver weights and liver weight ratios that correlated with minimal to moderate glycogen-type vacuolation and minimal to mild subcapsular necrosis). The non-clinical reviewer indicates that this has been previously reported in the literature after exposure to glucagon (Arstila and Trump 1968) and is not thought to occur due to formulation differences. Dr. Brathwaite recommends approval of G-Pen.

4.5. Clinical Pharmacology

Refer to the Clinical pharmacology review by Dr. Sang Chung dated May 10, 2019 in DARRTs for additional details. Data from Studies 301 and 303 are discussed in Sections 6 and 7

Study 201:

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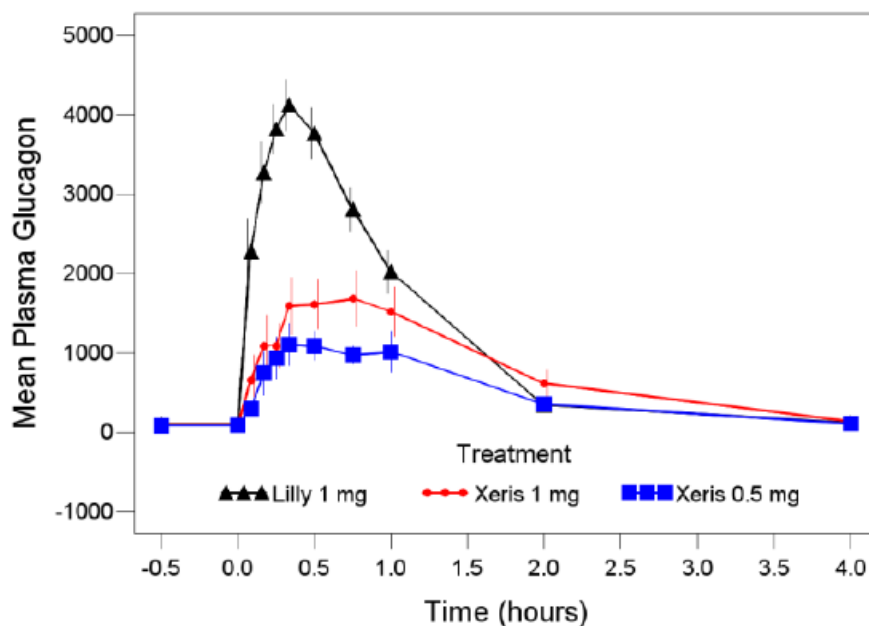
This was a randomized, Phase 2, double-blind, 3-way crossover study in healthy subjects. It compared the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of a single dose of G-Pen (glucagon injection) administered as 0.5 mg and 1.0 mg injections, versus Lilly Glucagon for injection [rDNA origin] 1.0 mg (reference). Each subject received a single subcutaneous (SC) injection in the upper arm on each of the three treatment days, with a period of 3-14 days between doses. A total of 30 subjects were enrolled and 28 subjects completed treatment.

Mean plasma glucagon levels by time and treatment are displayed in the figure below. The plot indicated variation with treatment, with Lilly 1.0 mg concentrations being uniformly greater than the Xeris 1.0 mg and Xeris 0.5 mg concentrations between 0.5 and 1 hour. The reason for the difference in plasma glucagon levels is unclear. The applicant indicates that the radioimmunoassay (RIA) method used to measure plasma glucagon levels also detects glucagon-like peptides (GLP), and significantly greater peptide content is observed in the Lilly formulation, which utilizes recombinant glucagon. They speculate that the lower plasma glucagon concentration with the G-Pen formulation was due to the purer synthetic glucagon and lower content of glucagon-like peptides. However, the clinical pharmacology reviewer does not agree with this speculation regarding cross-reactivity in bioanalytical methods. They indicate that the GLP concentration in the Lilly formulation is expected to be significantly higher than the observed impurity levels (in addition to endogenous GLP), and therefore does not explain the plasma glucagon difference.

Treatment groups differed significantly ($p < 0.001$) with regard to mean glucagon AUC₀₋₂₄₀ overall due to the increased mean (SD) glucagon AUC₀₋₂₄₀ in Lilly 1.0 mg relative to Xeris 0.5 mg and Xeris 1.0 mg (Lilly 1.0 mg: 4781.7 [2222.9] pg·min/mL, Xeris 1.0 mg: 3259.9 [3447.5] pg·min/mL, Xeris 0.5 mg: 2105.3 [2381.9] pg·min/mL).

Treatment groups also differed significantly ($p < 0.001$) with regard to mean glucagon T_{max} due to the decreased mean (SD) glucagon T_{max} in Lilly 1.0 mg relative to Xeris 0.5 mg and Xeris 1.0 mg (Lilly 1.0 mg: 18.8 [9.9] minutes, Xeris 1.0 mg: 37.6 [15.2] minutes, Xeris 0.5 mg: 33.3 [13.2] minutes). These means were not pairwise bioequivalent.

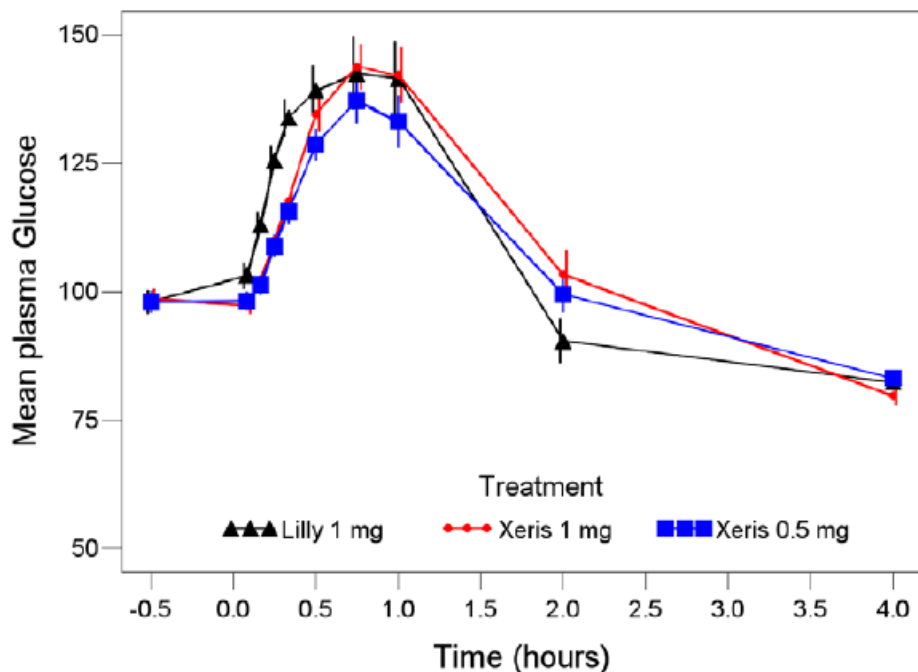
Figure 2: Mean plasma glucagon (ng/mL) by time and treatment



Source: Figure 7, CSR for study 201.

The applicant claimed bioequivalence based on pharmacodynamic (PD) response. Plasma glucose for subjects in the three treatment groups, Xeris G-Pen (glucagon injection) 0.5 mg, Xeris G-Pen (glucagon injection) 1.0 mg, and Lilly Glucagon for injection [rDNA origin] 1.0 mg plotted by time are shown in the figure below.

Figure 3: Mean plasma glucose (mg/dL) by time and treatment



Source: Figure 6, CSR for Study 201.

The applicant reports that treatment groups did not differ significantly with regard to mean glucose AUC₀₋₂₄₀ in original or in natural log values ($p > 0.05$ for all comparisons). Treatment groups were pharmacodynamically equivalent with regard to the mean glucose AUC₀₋₂₄₀. All 90% pairwise CIs for the ratio of means were contained in the interval of 0.80 to 1.25. All treatment groups did not differ significantly with regard to mean plasma glucose T_{max}, and the T_{max} means were pairwise pharmacodynamically equivalent. The FDA clinical pharmacology reviewer observed that following 1.0 mg Lilly glucagon apparent maximal drug effect (E_{max}) was achieved based on the glucagon concentration- glucose response curve, but not following G-Pen 1.0 or 0.5 mg. He speculates this may explain the PD similarity with the significant PK difference among treatments³³.

Reviewer's Comment: As indicated earlier in Section 3.2, the applicant was advised that an additional study to evaluate efficacy was required in the absence of PK bioequivalence.

The AI (configuration A) and the PFS (configuration B) met the pre-specified criteria for bioequivalence in study XSGP 101³⁴: Inferential analyses were performed on plasma glucagon AUC₍₀₋₂₄₀₎ and C_{max}, and plasma glucose AUC (0-240), C_{max}, and T_{max} in healthy subjects administered Xeris glucagon 1 mg SC in the abdomen via AI and PFS. Statistical analysis of

³³ Clinical Pharmacology review by Dr. Sang Chung dated May 10, 2019, DARRTs ID 4432084

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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 80-125% for geometric mean ratios and confidence intervals.

The Clinical Pharmacology reviewer did not identify any deficiencies and recommended approval of the NDA.

4.6. Devices and Companion Diagnostic Issues

Refer to the Center for devices and Radiological Health (CDRH) review by Dr. Jacqueline Gertz dated August 6, 2019 and Division of Medication Error Prevention and Analysis (DMEPA) reviews of labelling and Human factors results by Dr. Ariane Conrad dated March 4, 2019 and May 3, 2019 in DARRTs.

CDRH reviewed the device constituent of the combination product for performance, biocompatibility of the patient contacting components and release specifications for the device constituent. The CDRH reviewer had sent multiple information requests to the applicant about combination product reliability testing for the auto-injector including the fault tree analysis (FTA) throughout the review cycle³⁴. In a February 2018 communication, a reliability specification of 99.999% for successful activation of the auto-injector (i.e. Failure to Fire) was requested. The applicant was also advised to include in-use conditions such as injection through clothing, activation orientation, etc. as part of the reliability study protocol. The initial FTA provided by the applicant in the NDA submission had fundamental structural issues. On May 22, 2019, the FDA reviewer concluded that the FTA needed to be restructured to address the deficiencies. A response was received on May 30, 2019, and the review clock was extended to September 10, 2019 to review this additional information (major amendment). Two additional issues were identified on inspection of the revised FTA: 1) Failure modes (for assembly defects) with probability, P=1.0 without supporting explanation; and, 2) Inspection steps repeated multiple times without explanation. Additional information requests were sent out by the CDRH reviewers on July 1, 2019 to clarify these issues. The applicant's responses for the reliability analysis were determined to be adequate by the CDRH reviewers. They have provided additional comments to the applicant regarding maintaining the fault tree analysis to assure ongoing product reliability and other quality systems issues. The requested changes to the Standard Operating procedures (SOP) have been made and CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

³⁴ NDA212097GLycagon CDRH-ODE review, ICC 1800683, pages 17-35, 42- 55 and Appendix A-section 13.4 (assessment of device reliability data-pages 55-63).

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The Applicant conducted Human Factors Validation Studies, which included 75 participants who were trained or untrained, and included 15 untrained adolescent caregivers, first responders and other adult caregivers who were experienced with glucagon use or glucagon -naïve. DMEPA reviewers did not identify any approvability issues and have provided recommendations for the PI, Instructions for Use (IFU) and carton and container labelling. The applicant has made the requested changes to the carton / container and foil pouch labeling.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical program included one Phase 1, two Phase 2, two controlled Phase 3 studies in adult subjects, and one uncontrolled Phase 3 study in pediatric subjects. They were all single dose studies. Except for the pediatric study, they were all cross-over studies.

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Table 2: Listing of Clinical Trials

Trial Identity	Trial Design	Regimen/ schedule	Study Objectives	No. of patients, Study Population
XSGP-101	Randomized, open-label, 2-way cross-over	G-pen; 1 mg via Autoinjector (AI) or pre-filled syringe (PFS), s.c.	Bioequivalence, PK/PD	32, Healthy adults
XSGP-201	Randomized, double-blind, 3-way cross-over	G-Pen (0.5 mg and 1 mg) via PFS, Lilly Glucagon 1 mg, s.c.	Comparative PK/PD	30, Healthy adults
XSGP-202	Randomized, open-label, 2-way cross-over	G-Pen (0.5 and 1 mg), vial & syringe, s.c.	Pilot study for hypoglycemia induction procedure, Safety, Efficacy	7, Adults with Type 1 DM
XSGP-301	Randomized, double-blind, 2-way cross-over	G-Pen (1 mg) via AI, Lilly Glucagon 1 mg, s.c.	Plasma glucose recovery from < 50 mg/dL, Efficacy/Safety	80, Adults with Type 1 DM
XSGP-303-	Randomized, open-label, 2-way cross-over	G-Pen (1 mg) via AI, Lilly Glucagon 1 mg, s.c.	Plasma glucose recovery from < 50 mg/dL, Efficacy/Safety	81, Adults with Type 1 DM
XSGP-302-	Non-randomized, open label	G-Pen (0.5 mg) and G-Pen 1 mg (ages 12-18) via AI, s.c.	Plasma glucose recovery from < 80 mg/dL.	31, T1 DM (Pediatrics)

5.2. Review Strategy

As previously discussed, this 505(b)(2) NDA application references the Agency's previous findings of safety and efficacy for the reference list drug, Glucagon for Injection (NDA 020928). Both approved glucagon products (Glucagon for injection and GlucaGen) include no clinical trial data other than PK/PD data in healthy volunteers in their package inserts. These products are also approved as diagnostic aids in radiologic examination to temporarily inhibit movement of the gastrointestinal tract (Glucagon injection or GlucaGen diagnostic kit). Therefore, the safety data included in the package insert are mainly post-marketing data, known pharmacologic effects of glucagon and effects observed in patients with glucagonomas and other neuroendocrine tumors.

Since study 201 failed to demonstrate PK bioequivalence, the applicant was advised to conduct a controlled study evaluating the efficacy and safety of Xeris G-Pen 1 mg versus active comparator. At that time, it was agreed that the primary endpoint should be the proportion of subjects achieving an increase in glucose over 70 mg/dL within 30 minutes of receiving study glucagon and without receiving any other measure to increase the blood glucose levels. The applicant conducted a pilot study to establish the procedure to induce controlled hypoglycemia in patients with Type 1 DM (Study 202). This procedure and the limitations in its implementation for assessment of efficacy in real-world use will be discussed in sections 6 and 7.

The Efficacy review primarily involved review of the clinical study reports of phase 3 studies submitted by the applicant and the Efficacy analyses conducted by the statistical reviewer. During the clinical development program for Xeris G-pen, the division's thinking was evolving for endpoints used to establish efficacy for products intended for the treatment of severe hypoglycemia. It was felt that in addition to an increase to an absolute blood glucose threshold value of 70 mg/dL, a relative increase of at-least 20 mg/dL from baseline may be clinically meaningful, especially for a patient with severe hypoglycemia with nadir blood glucose values well below 40 mg/dL. Additionally, this would be consistent with other recent glucagon development programs. For this reason, the review of efficacy considered alternative endpoints other than the pre-specified primary endpoint. Given that these are single dose studies, safety information and analyses are limited to evaluation of the safety information presented in the applicant's clinical study report. Long-term safety data are lacking.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study XSGP-301

6.1.1. Study Design

Overview and Objective

Study 301 was an efficacy and safety study in patients with Type 1 DM comparing G-Pen to Lilly Glucagon for induced hypoglycemia rescue in adult patients with Type 1 DM. The primary objective of this study was to demonstrate the non-inferiority of G-Pen (glucagon injection) 1 mg to Lilly Glucagon (glucagon for injection [rDNA origin]) 1 mg in Type 1 DM patients who are in a state of insulin-induced hypoglycemia as assessed by the failure rate of plasma glucose to exceed 70.0 mg/dL within 30 minutes of administration of treatment.

Trial Design

This was a single-dose, randomized, controlled, double-blinded, 2-treatment, 2-way crossover comparative efficacy and safety study in subjects with Type 1 DM.

Subjects were to complete the screening procedures up to 60 days before dosing to determine eligibility before enrollment to the treatment phase. Eligible participants were to undergo two episodes of insulin-induced hypoglycemia and in random order to receive G-Pen glucagon 1 mg subcutaneously during one episode and Lilly glucagon 1 mg subcutaneously during the other episode.

Hypoglycemia Induction Procedure:

A combination of one or more IV bolus doses of insulin along with an IV infusion of insulin was used to decrease each subject's plasma glucose to a target <50.0 mg/dL. For hypoglycemia induction, the study utilized a comparatively lower rate of insulin infusion (one to two times the normal basal rate), compared to the description of the procedure cited in the literature³⁵. This was combined with an intravenous bolus. The applicant's rationale was that because hepatic glucose production is determined by the plasma glucagon to insulin ratio, the procedure as described in the literature may not create realistic circumstances for evaluating the effectiveness of glucagon in raising blood glucose.

Starting plasma glucose level (via ^{(b) (4)} analyzer) was determined by taking 3 measurements over 30 minutes upon the subject's arrival at the Clinical Research Center (CRC) (i.e., at 0, 15 and 30 minutes) to determine the subjects starting plasma glucose level. After the third measurement at 30 minutes, subjects were given an initial IV bolus push dose of regular insulin diluted in saline. A bolus dose of insulin was derived from the subject's own self-reported glucose correction factor and starting plasma glucose level. An additional bolus dose of insulin could be given as guided by the investigator's experience if the trajectory of plasma glucose after 30

³⁵ Nermoen I, Jorde R, Sager G, Sundsfjord J and Birkeland K. Effects of Exercise on Hypoglycaemic Responses in Insulin-Dependent Diabetes Mellitus. Diabetes & Metabolism. 1998. 24: 131-6.

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minutes was > 60 mg/dL. An IV infusion of regular insulin diluted in saline was started. The starting IV infusion rate was based on a subject's normal daily basal dose of insulin (see table below). Guided by experience and the subject's HbA1c value at screening, the investigator could adjust the starting basal rate at his discretion. As a guideline, increasing the basal rate by 25% had to be considered for subjects with an HbA1c > 8.0%.

Table 3: Calculation of Starting IV Insulin Infusion Rate

Subjects on Insulin Pump	Subjects on Long-Acting Injected Insulin	
1. Discontinue the pump	1. Calculate the basal rate in units / hr. (i.e., cumulative basal dose / 24 hrs.)	
2. Start IV insulin infusion at 1.5x the current basal rate	2. Did the subject take their normal daily dose either the evening before or the morning before the visit?	
	YES	NO
	3. Start IV insulin infusion at 1x the calculated basal rate	3. Start IV insulin infusion at 2x the calculated basal rate

Source Table 4, Protocol for XSGP301 v. 1.6

Thereafter, plasma glucose was determined every 15±5 minutes while the concentration was > 80.0 mg/dL and every 5±2 minutes once it was ≤ 80.0 mg/dL. Once an initial plasma glucose measurement < 50.0 mg/dL was achieved, the IV insulin infusion was stopped, and a confirmatory reading had to be obtained in 5 minutes. If plasma glucose has risen to ≥ 50.0 mg/dL, the IV insulin infusion had to be restarted and the sequence repeated until there are two consecutive plasma glucose readings < 50.0 mg/dL on record. Once the confirmatory glucose < 50.0 mg/dL was obtained, the subject was to be treated subcutaneously in the upper arm, leg or abdomen with either 1 mg Lilly Glucagon or 1 mg G-Pen. Plasma glucose was to be measured every 5±2 minutes until 90 minutes post-dosing.

Hypoglycemia Rescue:

At any time post-dosing if a subject exhibited signs of coma or convulsions, or if plasma glucose remained < 60.0 mg/dL at 30 minutes post-dosing, a 25 mL IV bolus dose of 50% dextrose was to be given. Signs and symptoms had to be monitored and if the subject's condition failed to improve within 15 minutes, additional dextrose or other intervention could be given at the discretion of the investigator.

At 240 minutes post-dosing, the subject was to resume pump therapy, if applicable, and

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given a meal. The subject could leave the clinic after plasma glucose was confirmed to be between 70 and 180 mg/dL.

Other Study Assessments:

The subject had to complete the Hypoglycemia Symptom Questionnaire at the following time points (see below), which was also analyzed as a secondary endpoint:

- Just before the IV bolus push dose of insulin was given at the start of the hypoglycemia induction procedure.
- Every time blood was drawn for evaluation of plasma glucose concentration during the induction procedure.
- Just before study drug was administered.
- Every 5±2 minutes after glucagon was administered, until all symptoms have abated (i.e., all symptoms have score = 1) or 45 minutes post-dosing, whichever occurred first.

Table 4: Hypoglycemia Symptom Questionnaire

Neuroglycopenic Symptoms	Severity Score (1-6)
Dizziness	
Blurred vision	
Difficulty in thinking	
Faintness	
Autonomic Symptoms	Severity Score (1-6)
Sweating	
Tremor	
Palpitations	
Feeling of nervousness	
Overall Assessment of Hypoglycemia	Yes/No
Do you currently feel hypoglycemic?	

Source: Appendix 1, Protocol for XSGP301

Study subjects also completed the following (details will be discussed in section 8):

- A Visual Analog (VAS) questionnaire for injection site discomfort at 10±5 and 30±5 minutes post-dosing, and again at 240±5 minutes post-dosing if VAS score reported at 30 minutes was > 0 mm.
- an Injection Site Discomfort Description and Duration Questionnaire at 10±5 minutes post-dosing. If discomfort was ongoing at 10 minutes post-dosing, the questionnaire was be updated before the subject left the clinic.

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- The modified Draize scales to assess erythema and edema formation at the injection site at 10±5 and 30±5 minutes following administration and again at 240±5 minutes post-dosing if persistent.

A central laboratory was utilized for analysis of all variables (including PK samples) with the exception of urine tests.

Dose Interruption or termination: for any SAE that occurred in a subject receiving treatment until causality was fully assessed by the Investigator. Dosing was to cease if the SAE was determined to be either drug related or unknown.

Blinding:

Both subject and investigator were to be blinded. The only unblinded study staff were a pharmacist, and depending on operational procedures at each site, one or more additional trained study staff member whose only role was to administer the glucagon (i.e., the unblinded staff administers the dose then leaves the room and does not participate in any other study procedures). The subject's ability to see the injection equipment and procedure was to be obstructed. The 1 mg G-Pen™ device makes a series of two audible clicks when the dose is administered. To help ensure blinding, the clinical staff were to move to an adjoining room during the process of drug administration by the unblinded staff. If operational considerations precluded leaving the room, the clinical staff was to look away and use means (e.g., headphones, fingers in ears and humming, etc.) to mask sound during dosing procedures. Blinding could be broken in emergency situations for reasons of subject safety.

Study Population:

Adult males or females diagnosed with type 1 DM for at least 24 months, C-peptide < 0.5 mg/ml and current usage of daily insulin treatment that includes having an assigned "correction factor" for managing hyperglycemia.

Significant Exclusion Criteria

1. For women of childbearing potential, there was a requirement for a negative urine pregnancy test and for agreement to use contraception and to refrain from breast feeding during the study and for at least 1 month after the last dose of study drug.
2. HbA1c >9.0% at Screening.
3. Renal insufficiency (serum creatinine greater than 3.0 mg/dL).
4. Serum ALT or AST equal to or greater than 3 times the upper limit of normal.

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5. Hepatic synthetic insufficiency as defined as a serum albumin of less than 3.0 g/dL; or serum bilirubin of over 2.0 mg/dL.
6. Hematocrit of less than or equal to 30%.
7. Mean of triplicate BP readings at Screening where SBP <90 or >140 mm Hg, and DBP <50 or >90 mm Hg.
8. Clinically significant ECG abnormalities.
9. Use of > 2.0 U/kg total insulin dose per day.
10. Inadequate bilateral venous access in both arms.
11. Congestive heart failure, NYHA class II, III or IV.
12. Active malignancy within 5 years from Screening, except basal cell or squamous cell skin cancers.
13. Major surgical operation within 30 days prior to Screening.
14. Current seizure disorder.
15. Current bleeding disorder, treatment with warfarin, or platelet count below 50,000.
16. Personal history of pheochromocytoma or disorder with increased risk of pheochromocytoma (MEN 2, neurofibromatosis, or Von Hippel-Lindau disease).
17. History of insulinoma.
18. History of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients (DMSO & trehalose) in the investigational formulation.
19. History of glycogen storage disease.
20. Subject tests positive for HIV, HCV or active HBV infection (HBsAg+) at Screening

Reviewer's Comment: Inclusion and exclusion criteria are acceptable.

Study Endpoints

Primary endpoint:

Treatment success in this study was based on a primary endpoint of an increase in plasma glucose concentration from below 50.0 mg/dL to greater than 70.0 mg/dL within 30 minutes after receiving glucagon. This is discussed further in the statistical analysis plan.

Reviewer's Comment:

This endpoint was agreed to in the EOP2 meeting after Study 201 failed to demonstrate PK bioequivalence between G-Pen and Lilly Glucagon (see section 3.2). The applicant proposed an alternative end-point post-hoc in a statistical analysis plan version dated August 7, 2017, which is discussed with the study results. This was not included in the last version of the protocol dated March 16, 2017.

The secondary endpoints for this study include:

- Pharmacodynamic endpoints, including: plasma glucose AUC, Cmax, Tmax and

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time to reach >70.0 mg/dL will be compared between the treatment groups.

- Symptoms of hypoglycemia (if present) as documented using the hypoglycemia symptom questionnaire
- Pharmacokinetic parameters include: descriptive analysis of AUC, Cmax and Tmax of the different ethnicities.
- Safety-related parameters

Statistical Analysis Plan

Please refer to the statistical review for additional details.

Study Populations:

The intent-to treat (ITT) population was defined as all subjects randomized. A subject's randomized treatment was to be used for analysis regardless of the actual treatment received. The modified intent-to treat (mITT) population was defined as all ITT subjects who received at least one dose of study medication and will be analyzed as administered. The mITT population was to be used for all analyses except the safety analyses. The Per-protocol (PP) population was the mITT population, excluding the subjects who have at least one major protocol violation. The safety population was defined as all subjects randomized who received at least one dose of study medication. However, the actual treatment received was to be used for analysis.

Efficacy Analysis- Primary Endpoint:

The primary comparison was to be performed using the intent-to treat (ITT) cohort defined as all subjects randomized to one of the two sequence groups: G-Pen followed by control, or control followed by G-Pen. A failure for either treatment was to be recorded if plasma glucose remains ≤ 70.0 mg/dL throughout the 30-minute period from the drug administration.

The following scoring system was to be applied to all subjects in the ITT cohort. If a G-Pen failure is observed then the treatment failure score = 1; similarly the control failure score = 1 if a control failure is observed. If the G-Pen treatment outcome is missing, then the treatment failure score = 0.2. A missing control outcome yields a control failure score = 0.1. An observed successful plasma glucose rising above 70.0 mg/dL within 30 minutes yields a failure score = 0, for either treatment. Therefore, all subjects in the ITT cohort were to have G-Pen and control failure scores.

The G-pen acceptance criterion was to be based on the sample mean of the treatment minus control failure scores from each subject in the ITT population. If $\bar{D}_{ht}$ is the sample mean of the G-Pen minus control failure difference, and SE is the estimated standard error of $\bar{D}_{ht}$ (square root of the estimated G-Pen minus control variance divided by the sample size), then the G-Pen was to be accepted provided:

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

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$D_{ht} + 2.6 \text{ SE} \leq 0.1$.

According to the applicant:

"This criterion, particularly the value 2.6, came from Monte-Carlo simulations from selected scenarios where the population G-Pen failure rate exceeded the control rate by (b) (4). Under these circumstances the rate of G-Pen acceptance was found to be within (b) (4) using this criterion, with missing data rates within (b) (4)%. This bound of (b) (4) on the type 1 error rate was observed for control failure rates up to (b) (4)%. Monte Carlo simulation rather than asymptotic normality is necessary because an observed failure from either G-Pen or control is expected to be low, less than (b) (4)%."

Sample size calculation:

Using the above criterion, the applicant reported that a calculated sample size of 75 subjects yields probabilities of G-Pen acceptance of over (b) (4)% if the population failure rates of G-Pen and control are equal, and the rate of missing observations is within (b) (4)%. These results were obtained using Monte Carlo simulations with G-Pen and control total failure rates up to (b) (4)%, and with G-Pen success -Control failure, or G-Pen failure -Control success within (b) (4)%. Eighty subjects were to be randomized at 8 clinical sites.

Protocol Amendments

The last version of the protocol (v 1.6) was dated March 16, 2017. The major change in the Statistical analysis plan (dated August 8, 2017) was made after the data from Study 301 were known. In this version, an alternative endpoint was included by the applicant where a failure is defined as an event where plasma glucose of a subject remains ≤ 70 mg/dL or increased less than (not equal to) 20 mg/dl throughout the 0-30 minute period from the administration of study drug. This was proposed since non-inferiority to Lilly glucagon was not achieved with the ITT population, and will be further discussed with the study results.

This is also discussed under section 4.1. Also refer to section 6.1.2 for discussion.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that all studies were conducted in full conformance with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

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Financial Disclosure

The Applicant certifies they have a completed financial disclosure form on file for all listed principal and sub-investigators who participated in the six clinical trials of G-Pen. They state that none of them reported disclosable financial arrangements or information.

Patient Disposition

In total 132 subjects were screened, and eighty subjects were randomized in this cross-over study and included in the ITT population (see table below). All 80 subjects (100.0%) received at least one dose of study drug. Seventy-seven subjects (96.3%) received the randomized G-Pen treatment and 78 subjects (97.5%) received the randomized Lilly Glucagon treatment; of the subjects randomized to receive G-Pen, one subject (1.25%) received treatment in the reverse order, one subject (1.25%) received Lilly Glucagon at both visits and one subject withdrew from the study.

As per protocol the mITT population was defined as all ITT subjects who received at least one dose of study medication and will be analyzed as administered. The applicant included 78 patients on G-Pen and 79 patients who received Lilly glucagon in the mITT analysis.

The Per-protocol (PP) population is the mITT population, excluding the subjects who have at least one major protocol violation. The applicant also defined a revised Per-Protocol population. This is further discussed in the section below.

Table 5: Summary of Patient disposition, Study-301

Disposition	G-Pen 1 mg n (%)	Lilly Glucagon 1 mg n (%)
Randomized	80 (100)	80 (100)
Intent-to-Treat	80 (100)	80 (100)
Randomized treatment received, analyzed as treated	77 (96.3)	78 (97.5)
Reverse treatment sequence, analyzed as treated	1 (1.3)	1 (1.3)
Incorrect treatment received, (data censored)	1 (1.3)	0
Missed visits (missing data not imputed)	1 (1.3)	1 (1.3)
Modified Intent-to-Treat Population (mITT)	78 (97.5)	79 (98.8)
Randomized treatment received - Protocol violations (Primary Endpoint imputed)	6 (7.5)	4 (5.0)
Pre-specified Per-Protocol Population (PPROT)	71 (88.8)	74 (92.5)
Revised Per-Protocol Population (RPPROT)	76 (95.0)	77 (96.3)

(Source: Adapted from Table 14.1.1.2 and 14.1.1.3, CSR for XSGP-301)

Protocol Violations/Deviations

In the SAP a major protocol violation was defined as having any bolus dose within 20 minutes of glucagon injection or when the basal rate was increased < 20 minutes pre-glucagon when the glucose dropping rate of change was > 1mg/dl/minute. Four patients receiving Lilly glucagon and six patients receiving G-pen were excluded from the pre-specified PP population due to this violation. In the final CSR (which was finalized after study completion), the applicant included a “revised” PP population where a major protocol violation was redefined as only having an increase in basal rate insulin dose within 20 minutes of glucagon injection, but included those subjects who had received a bolus dose within 20 minutes of glucagon injection. Only two subjects (Patient ID (b) (6)) were excluded from the revised per-protocol population based on this re-definition.

On review of the subject listing, some of the listed deviations were due to lack of completion of some pages in the informed consent, lab shipment issues, late blood draw due to iv access issues, blood draws drawn after window time period, incorrect glucagon site administration, original (b) (4) reading printout not retained, vital signs recording, drug storage temperatures and PK sample handling. These violations and deviations should not significantly impact interpretation of the efficacy and safety results.

Demographic Characteristics

The median age of subjects randomized was 45.5 years (range: 18.0 to 74.0 years), 45.0% of the subjects were female. The majority of the subjects were White (73 subjects [91.3%]). Mean (SD) weight was 83 (20.2) kg and mean BMI 28 (6.2) kg/m².

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

Concomitant medications were consistent with those used in patients with Type 1 DM and the subjects' medical history.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not relevant since this was a single dose study

Efficacy Results – Primary Endpoint

Of 80 subjects randomized, 78 and 79 subjects were included in the mITT population for G-Pen and Lilly, respectively. Of these, 74 subjects (94.9%) and 79 subjects (100%) had plasma glucose > 70 mg/dL within 30 minutes after administration of G-Pen and Lilly Glucagon, respectively. Based on the test result of the difference of failure scores (calculated as discussed in the SAP), G-Pen did not satisfy the non-inferiority criterion for Lilly Glucagon for the ITT and Pre-Specified PP population. The applicant states that the non-inferiority criterion was satisfied for the “revised” PP population as defined above (see protocol violations/deviations). This included 76 subjects in the G-Pen group and 77 subjects in the Lilly Glucagon group.

Table 6: Test Result of the Difference of Failure Scores – D_{ht}

	D_{ht}	$SE_{D(ht)}$	$D_{ht} + 2.6 \times SE_{D(ht)}$	Non-inferiority Criterion
ITT population	(b) (4)			Not Satisfied
Pre-specified PP Population				Not Satisfied
Revised PP population	0.043	0.022	0.099	Satisfied

D_{ht} - the sample mean of the G-Pen minus control failure difference, and $SE_{D(ht)}$ - the estimated standard error of D_{ht}

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

Proposed alternative primary endpoint:

Since the study failed to meet the pre-specified primary end-point, the applicant proposed an alternative endpoint in the SAP finalized on August 8, 2017 after unblinded review of the study data. For this end-point, failure is defined as an event when plasma glucose of a subject remains ≤ 70 mg/dL or increased less than (not equal to) 20 mg/dl throughout the 30-minute period from the administration of study drug. Seventy-six subjects (97.4%) and 79 subjects (100%) had plasma glucose > 70 mg/dL or an increase in plasma glucose ≥ 20 mg/dL within 30 minutes after administration of G-Pen and Lilly Glucagon, respectively. Based on the test result of the difference of failure scores, G-Pen did satisfy the non-inferiority criterion to Lilly

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Glucagon for the alternate primary glucose response endpoint for the ITT, prespecified and revised PP populations (see table below).

Table 7: Test Result of the Combined Glucose-Response Endpoints Using Alternate Endpoint – D_{htex}

Analysis Set	D_{htex}	$SE_D(htex)$	$D_{htex} + 2.6 \times SE_D(htex)$	Non-inferiority Criterion
ITT population	0.029	0.018	0.075	Satisfied
Pre-specified PP Population	0.039	0.019	0.087	Satisfied
Revised PP population	0.030	0.018	0.077	Satisfied

D_{htex} - the sample mean of the G-Pen minus control failure difference for the alternate endpoint and $SE_D(htex)$ - the estimated standard error of D_{htex}

Source: table 11, table 14.2.2.2, CSR for Study 301

The applicant attributes the failure to meet the pre-specified primary end-point to low plasma glucose values from the induction procedure. They state that the procedure relied heavily on investigator discretion. In some cases, the investigators infused an excessive amount of insulin and even increased insulin infusion rates when the plasma glucose rate was on target at 1 mg/(dL*min). According to the applicant, this undercut the ability to achieve the desired steady state, and about a third of the procedures across the treatment groups had glucose concentrations less than 40 mg/dL post- insulin dosing.

Reviewer's Assessment of G-Pen failures:

I did note that as indicated by the applicant, several subjects had a nadir glucose value below 40 mg/dL. This often occurred 5 -10 minutes post-glucagon dosing. However, this also happened during some Lilly Glucagon treatment sequences, and can be expected during real-use conditions. It possibly reflects the continued effects of insulin on board; the time lag for glucagon effects (glucose release from hepatic glycogenolysis), which could vary between treatment sequences depending on dose of insulin used for induction, nutritional status of the patient etc.; and the additional delay in the efficacy response for G-Pen compared to Lilly Glucagon. In order to confirm this, an information request was submitted to the applicant on April 5, 2019. The applicant responded on April 17, 2019. In their response, they listed pre-dose and post-dose values up to 15 minutes for G-Pen and Lilly glucagon for individual subjects in a side-by side comparison (Listing 16.2.6.1.6, Study XSGP-301). Notably, the five patients whose pre-dose blood glucose was less than 40 mg/dL in the G-Pen or Lilly glucagon dosing sequence had a robust glucose response to both Lilly glucagon and G-Pen (see table below). It was also noted that, in general, a greater increase in blood glucose compared to pre-dose values (or a higher nadir value) was observed with Lilly glucagon compared to G-Pen in the immediate post-dosing time points.

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Table 8: Glucose values for subjects with pre-dose glucose < 40 mg/dL

subjid	Pre-Dose BG (mg/dL)		Nadir BG-Post dose (mg/dL)		BG- 30 minutes (mg/dL)		Change in BG at 30 min (mg/dL)	
	Lilly	G-Pen	Lilly	G-Pen	Lilly	G-Pen	Lilly	G-Pen
(b) (6)	40.8	39.7	38.7	37	111	99.2	70.2	59.5
	37.4	43.5	55	50.6	137	148	99.6	104.5
	33.7	48.5	68.1	58.5	136	127	102.3	78.5
	47.2	37.2	55.9	41.8	140	87.7	92.8	50.5
	46.8	29.7	52.6	40.7	145.7	120.9	98.9	91.2

Source: Statistical reviewer's analyses and Table 16.2.6.1.1

The glucose values of the four subjects who failed to meet the primary endpoint are shown below. Of these, only subject (b) (6) was excluded from the pre-specified and revised PP population for an increase in basal insulin rate within 20 minutes of glucagon injection by at least 20%, as discussed under protocol violations/deviations. It is notable that among the G-pen treatment failures, one subject (b) (6), who had a post-glucagon injection nadir glucose value of 26.2 mg/dl at 10 minutes, which suggests excess insulin from the insulin infusion may have played a role in lowering blood glucose beyond the set glucose threshold. All other patients in the G-pen treatment failure group had nadir glucose values post-glucagon dosing over 37 mg/dl (see Table below), but their post-dose blood glucose values did drop from pre-dose values. However, I did note that with the exception of patient (b) (6) who also had an increase of around 18 mg/dL from nadir, all others had an increase of over 20 mg/dL from their nadir glucose value post-dose by 30 minutes, and reached a blood glucose over 70 mg/dL by 45 min. These results are consistent with the greater time lag for the glucagon effects with G-Pen compared to Lilly glucagon. In addition, the clinical pharmacology reviewer also confirmed that all four subjects had detectable glucagon levels that were within observed variability (see figure below). The risk from this delay can be mitigated by a statement under the indications section of the PI advising caregivers/patients to call for emergency assistance soon after administration of G-Pen when instructed about G-Pen use.

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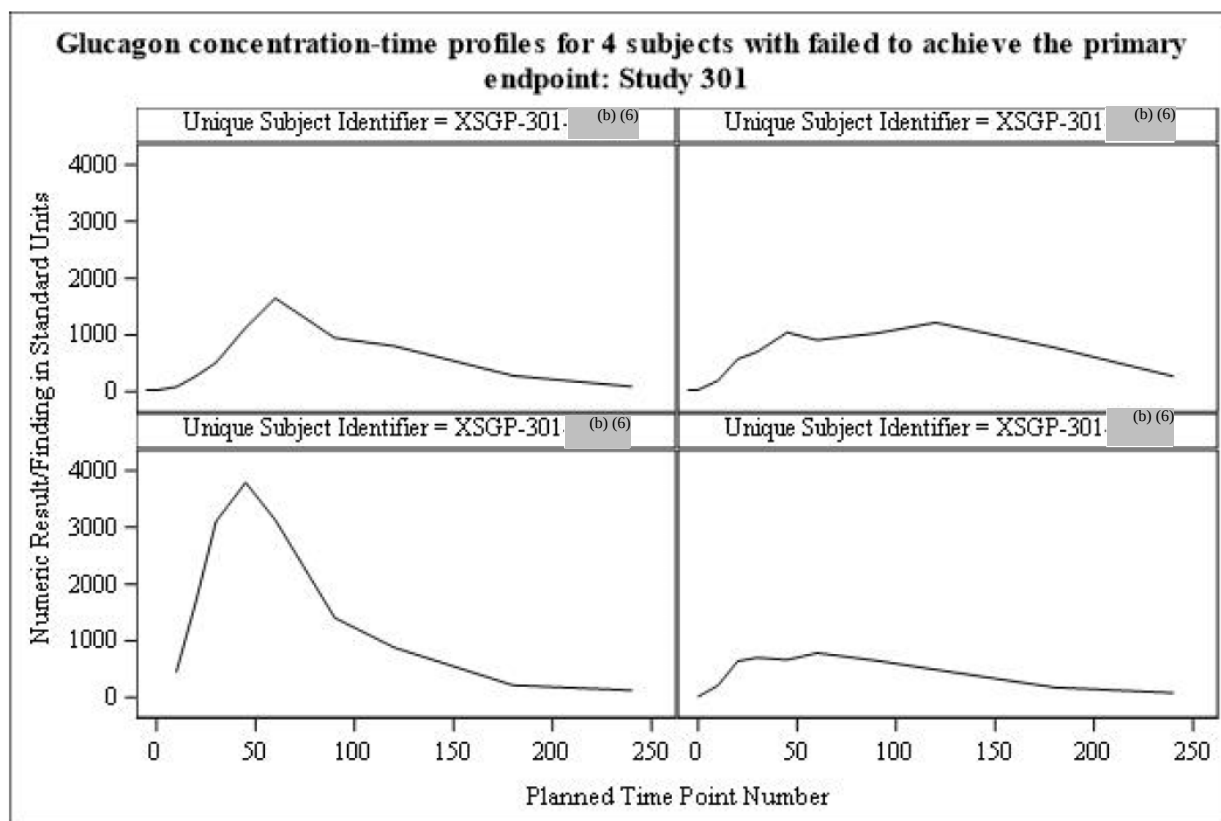
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Table 9: Blood Glucose values for G-Pen Failures, mITT Population

subjid	Pre-Dose BG (mg/dL)		Nadir BG-Post dose (mg/dL)		BG- 30 minutes (mg/dL)		Change in BG at 30 min (mg/dL)	
	G-Pen	Lilly	G-Pen	Lilly	G-Pen	Lilly	G-Pen	Lilly
(b) (6)	44	42.2	38.2	40.4	63.6	123	19.6	80.8
	43.5	43.2	40.5	43.2	65.1	100	21.6	56.8
	42.7	46.0	26.3	40.2	56.1	80.5	13.4	34.5
	44.9	45.4	39.8	44.3	57.8	105.1	12.9	59.7

Source: Statistical reviewer's analyses and table 16.2.6.1.1

Figure 4: Glucagon PK profile for the G-Pen Failures in the mITT Population



Source: Generated by Clinical Pharmacology Reviewer Dr. Sang Chung

The study did not meet its pre-specified end-point, but the alternate primary endpoint proposed is consistent with the primary endpoint being used in other development programs for glucagon for the treatment of hypoglycemia. As discussed in 6.1.1, efficacy has to be interpreted predominantly based on the pharmacodynamic (blood glucose) results in this study (and phase 2 studies) in comparison to the reference product, since evaluation under

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conditions of indicated use (hypoglycemia with impaired consciousness or seizures) is not feasible. In addition, other supportive analyses conducted by the applicant and the statistical reviewer are supportive of effectiveness, albeit a less rapid increase in glucose, which will be discussed further below under additional analyses conducted by the applicant and the FDA and in Section 7.

Data Quality and Integrity

Also refer to Section 4.1 and the OSI review by Dr. Cynthia Kleppinger dated May 2, 2019 in DARRTs.

As discussed in Section 4.1, the inspectional findings of clinical site 2 (ProSciento Inc.,) noted observed regulatory deficiencies. For Study 301, there were 33 subjects screened at this site and 20 subjects enrolled into the study; 19 subjects completed the study. For both Study 301 and 303, source documentation was captured on paper worksheets, handwritten progress notes, and site coordinators relied on (b) (4) glucose analyzer printouts to complete hardcopy worksheets created by ProSciento. The data from the worksheets and questionnaires was then transcribed into the electronic data capture system (EDC).

At the conclusion of the inspection a form FDA-483 was issued for the following deficiencies: an investigation was not conducted in accordance with the investigational plan. Specifically, confirmatory plasma glucose (PG) measurements were not performed 5 minutes after the initial PG measurement < 50 mg/dL in 14 of 20 subjects, as required by protocol XSGP-301. On review of the data sample presented, confirmatory blood glucose was measures within 1-2 minutes. In addition, electronic case report forms (eCRF's) for two of twenty subjects enrolled in XSGP-301 did not accurately reflect pre-dose plasma glucose (PG) values obtained by the site (49.7 vs 48.4 mg/dl; 38.0 mg/dL vs. 47.3 mg/dL). These were noted to be isolated instances. It was felt that these deviations would not significantly impact study results. A response to the Form FDA 483 observations was received March 8, 2019 and determined to be adequate.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints specified in the protocol were predominantly PK/PD endpoints, and endpoints related to symptomatic relief of hypoglycemia, with no pre-specified multiplicity adjustments. The applicant also conducted exploratory analyses of other endpoints. Results relevant to interpretation of efficacy are discussed here.

Pharmacodynamic / Pharmacokinetic Results:

The plasma glucose response was consistent with the results reported in Study 201 (see section 4.5). The applicant reported PK data only for G-pen in this study.

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Similar results were observed for mean plasma glucagon Cmax, Tmax, and AUC values by Ethnicity/Race, when evaluated for the first 12 subjects receiving actual G-Pen injection. Mean plasma glucagon concentration (G-Pen glucagon) over time was highest when administered in the abdomen, followed by the arm, followed by the leg from approximately 20 to 60 minutes after administration.

Comparison of Treatments with Regard to Time (Minutes) to First Plasma Glucose > 70 mg/dL (mITT Population):

The applicant did compare treatments with regard to time to first plasma glucose $\geq$ 70 mg/dL in the mITT population using a mixed model with treatment, period and sequence as terms. Subjects in the Lilly Glucagon treatment group reached glucose levels of 70 mg/dL faster than subjects in the G-Pen treatment group (Lilly Glucagon: 14.23 [4.258] minutes, G-Pen: 19.86 [8.508] minutes; $p < 0.0001$).

Symptomatic relief of hypoglycemia:

Also refer to the clinical consult review from the Clinical Outcomes Assessment (COA) Staff dated May 30, 2019.

As discussed in section 6.1.1, individual subject data for symptoms of hypoglycemia were captured using a hypoglycemia symptom questionnaire (HSQ) that measured severity scores (1 to 6) for each of 4 Neuroglycopenic (ANS) Symptoms (dizziness, blurred vision, difficulty in thinking, and faintness), each of 4 Autonomic (AAS) Symptoms (sweating, tremor, palpitations, and feeling of nervousness), and an Overall Assessment of Hypoglycemia ("yes" or "no" answer to "Do you currently feel hypoglycemic?").

The symptom scores results were consistent with glucose effects, and patients attained minimum symptom scores (i.e. asymptomatic with resolution of symptoms - all ANS and AAS symptoms have score = 1) around 2 minutes earlier on Lilly glucagon (see table below). The applicant reports that time to first subject report of "No hypoglycemia" did not differ significantly between treatment groups.

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Table 10: Summary of Time (minutes) to the Minimal (Neuroglycopenic, Autonomic and Total) Score Post Baseline Modified Intent-to-Treat Population

Severity Scores	G-Pen (N=78)	Lilly (N=79)
ANS; Mean (SD)	16.7 (10.2)	14.3 (9)
AAS Mean (SD)	16.0 (11.5)	14.2 (9.4)
Average Total Score (ATS), Mean (SD)	19.8 (11.7)	17.0 (8.9)

Source Table 14.2.1.5.2, CSR for study 301

The validity of the questionnaire and interpretation of the data is further discussed in the COA team's review. The COA reviewers noted inadequacies in conduct (i.e. completion of the symptom questionnaires) since they were completed by study staff frequently and not the patient. The reviewers conclude that the HSQ appears to have face validity in term of including symptoms that are related to hypoglycemia events. However, it is inappropriate for use as a patient reported outcome (PRO) measure in the context of induced hypoglycemia to assess symptoms as patients in a state of or recovering from hypoglycemia may not be able to provide reliable ratings of their symptoms either physically or verbally. Therefore, no conclusions can be made from the results. Please see Dr. Susan Pretko's review for additional details³⁶.

Dose/Dose Response

Not applicable for this study, since only a single G-Pen dose was evaluated

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Will be discussed in Section 7.

³⁶ Clinical Outcome Assessment Staff Review dated May 30, 2019, DARRTs ID 4436263
CDER Clinical Review Template
Version date: September 6, 2017 for all NDAs and BLAs

6.2. Study XSGP303

6.2.1. Study Design

Overview and Objective

This was a non-inferiority, randomized, open-label, single (subject) blind, 2-way crossover comparative efficacy and safety study in 81 adult subjects with Type 1 DM. This study was initiated by the applicant after completion of Study 301. The primary objective of this study was similar to Study 301: demonstrate the non-inferiority to Lilly Glucagon 1 mg with regards to the primary endpoint of a return to plasma glucose >70 mg/dL within 30 minutes.

Trial Design

The study design differed from Study 301 in that the induction procedure was preceded by an overnight period of blood glucose optimization with modifications to the insulin administration algorithm, as well as an open label design. According to the applicant, about 30% of the procedures performed in XSGP-301 study resulted in plasma glucose (PG) <40 mg/dL. To achieve more precision in achieving a steady state of PG below 50 mg/dL, individual procedure data from the XSGP-301 study were fitted to a model of insulin action allowing identification of opportunities for algorithm enhancements. The algorithm was modified accordingly and tested in the model of the procedures representing a broad spectrum of subjects.

Reviewer's Comment: It appears that this procedure was designed to avoid the post-dose decline in PG below 40 mg/dL observed in study 301.

The study involved two daytime clinical research center (CRC) visits 7-28 days apart, with random assignment to receive G-Pen™ glucagon 1 mg during one period and Lilly Glucagon 1 mg during the other. In this study, each daytime visit was preceded by an overnight stay in the CRC. A continuous glucose monitor (CGM) ((b) (4)) to be provided by Xeris) was placed. Instead of placing a CGM, at Investigator discretion, blood glucose could be assessed periodically during the overnight stay via (b) (4) model analyzer. After midnight, the Investigator had to optimize blood glucose within a target range of 80.0-150.0 mg/dL through the administration of IV insulin and glucose. If operational considerations at a site preclude IV administration of insulin overnight, no catheter was placed, and oral glucose tablets and the subject's own insulin infusion pump or subcutaneous insulin was to be used to optimize blood glucose within a target range of 80.0-150.0 mg/dL.

In the morning of the inpatient study visit, CGM data was reviewed and verified to be not < 60 or greater than 270 mg/dL overnight to be confirmed eligible for continuation into the insulin induction procedure. The subject had to continue fasting the morning of the procedure.

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Baseline euglycemic steady state period began when the plasma glucose was confirmed to be within range of 70-270 mg/dL. IV insulin was to be administered to maintain the plasma glucose within the range of 75-115 mg/dL for 30 minutes. If the plasma glucose had been maintained within the range of 75-115 mg/dL for at least 30 minutes and the insulin infusion rate varied no more than +/- 20%, the induction procedure may commence.

For the induction, the starting plasma glucose level was to be determined as the average of three (b) (4) measurements taken over the final 30 minutes of the baseline steady state period. The following procedures were then undertaken:

1. Subjects continued the IV insulin infusion at the final rate of the baseline euglycemic steady state.
2. Subjects were then given an initial IV bolus push dose of regular insulin diluted in saline:
 - a. The dose was calculated as 75% of the dose estimated to reduce plasma glucose from the subject's starting plasma glucose level to 50 mg/dL based on the subject's self-reported glucose correction factor. This dose was referred to as "1 bolus (full bolus dose)" subsequently. The Investigator could use discretion to decrease the amount of the calculated bolus dose based upon the subject's insulin sensitivity factor. However, the Investigator was not allowed to increase the amount of the bolus dose.
 - b. PG was measured every 5 to 10 minutes, depending on the PG value (see Table below).
 - c. The first insulin adjustment was to be made no earlier than 20 minutes after the initial bolus but had to otherwise follow the directions for insulin adjustments shown in Table 11 below.

Adherence to the insulin dose adjustment algorithm was to be facilitated by real time data capture on computers. One laptop was to be used for entry of glucose values as the measurements became available from the (b) (4) glucose analyzer. The other laptop was to display the induction procedure, glucose values, insulin bolus doses, and insulin infusion rate data, to provide guidance on appropriate insulin dosing changes based on the subject's glucose trajectory.

The IV insulin infusion could be stopped when the plasma glucose first reached <50 mg/dL, or, guided as per the insulin dosing algorithm, when plasma glucose was > 50 mg/dL. Five minutes after this first plasma glucose <50 mg/dL, a confirmatory second plasma glucose reading (plasma glucose <50.0 mg/dL) had to be obtained. The Investigator had to determine whether a hypoglycemic steady state has been achieved, which was defined as two consecutive plasma glucose values between 43.0 and 49.9 mg/dL, and a linearly extrapolated 8-minute later glucose value $\geq$ 42.0 mg/dL. If plasma glucose was not in a steady state, the subject's plasma glucose had to be rechecked at a subsequent 5-minute interval. If this second confirmatory glucose was > 42.0 mg/dL and a linearly extrapolated 8-minute later glucose value $\geq$ 42.0 mg/dL was obtained, the subject was deemed to be within a hypoglycemic steady state.

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If the second confirmatory plasma glucose measurement was < 42.0 mg/dL, the subject could not be administered study glucagon, had to be treated instead with IV glucose or oral carbohydrates at the Investigator's discretion, verified to be euglycemic, and their visit rescheduled after a minimum 7-day wait.

The clinical study protocol gave the investigator discretion to override the hypoglycemia induction algorithm and made the investigator the final arbiter of whether a subject had achieved a hypoglycemic steady state. This "decision to dose" on behalf of the investigator was documented in real time using the computerized Medication Adherence and data entry system implemented at each site.

Table 11: Insulin Dose Adjustments, Study 303

PG (mg/dl)	PG (mM)	Measurement interval	Target Rate of PG decrease	Insulin Bolus Criteria	Insulin Basal Rate Adjustment Criteria
>80	>4.4	10 min.	>30 mg/(dl*hr) (>1.67 mM/hr)	If PG decrease < 9 mg/(dl*hr) (<0.5 mM/hr); give 1 bolus	If PG decrease <30 mg/dl*hr (<1.67 mM/hr); increase 20% (15 min)
61-80	3.4-4.4	5 min.	30 mg/(dl*hr) (1.67 mM/hr)	If PG decrease < 9 mg/(dl*hr) (<0.5 mM/hr); give 1/2 bolus	If PG decrease <30 mg/dl*hr (<1.67 mM/hr); increase 20% (15 min) If PG decrease >60 mg/dl*hr (>3.33 mM/hr); decrease 25% (15 min)
56-60	3.1-3.3	5 min.	15 mg/(dl*hr) (0.83 mM/hr)	Not allowed	If PG decrease <9 mg/dl*hr (<0.5 mM/hr); increase 20% (10 min), or set at 120% of previous rate if previously stopped or decreased by 50% (5 min) If PG decrease >30 mg/dl*hr (>1.67 mM/hr); decrease 50% (5 min) If PG decrease >60 mg/dl*hr (>3.33 mM/hr); Stop (5 min)
50-55	2.8-3.1	5 min.	15 mg/(dl*hr) (0.83 mM/hr)	Not allowed	If PG decrease <9 mg/dl*hr (<0.5 mM/hr); increase 20% (10 min), or set at 120% of previous rate if previously stopped or decreased by 50% (5 min) If PG decrease >30 mg/dl*hr (>1.67 mM/hr); Stop (5 min)
<50	<2.8	5 min.	0	Not allowed	Stop

Source: Table 4, Protocol for study 303, V1.2

After a hypoglycemic state was verified, similar to Study 301, the subject was eligible to receive either G-Pen or Lilly Glucagon in a randomized treatment sequence. In this study only the subject was blinded to study drug. The time of this "decision to dose" by investigator and actual administration had to be documented. Plasma glucose levels had to be monitored for 180 minutes post-dosing.

The applicant justified the single blind design since the requirement for investigators and staff to leave the clinic area to maintain double-blinding caused delays in dosing, leading to nadir

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glucoses < 40 mg/dl in 30% of subjects, and longer response times for both groups. Given that the primary endpoint of plasma glucose is an objective laboratory assessment, on balance, it was felt that a single-blind design was preferable. This design also allowed comparison of treatment preparation time between the arms, something that would have further delayed doing in a double-blind setting.

Reviewer's Comment: The justification for a single blind design seems acceptable. Limitations related to study design i.e. applicability to conditions of real use still apply, with the added caveat that the nadir blood glucose (and insulin on board) was additionally controlled in this study, but cannot be controlled in actual conditions of severe hypoglycemia. The applicant recently submitted a response to an information request which listed decision -to dose, algorithm predicted 8 minute blood glucose and post-dose values up to 15 minutes for G-Pen and Lilly glucagon for individual subjects in a side-by side comparison (Listing 16.2.6.1.6, Study XSGP-303). The algorithm appeared to underestimate the immediate post-dose blood glucose values compared to the higher values actually observed. This can be expected, possibly because the algorithm only considered insulin effects. However, these higher blood glucose values were observed to a larger extent for Lilly glucagon treatment sequence. This will be further discussed in section 6.2.2.

Study Endpoints

The prespecified primary endpoint was similar to study 301, and was an increase in plasma glucose concentration from below 50.0 mg/dL to greater than 70.0 mg/dL within 30 minutes after receiving glucagon.

The following secondary response endpoints were to be assessed

1. Return of plasma glucose to > 70 mg/dL or neuroglycopenic symptomatic relief within 30 minutes after receiving glucagon.
2. Return of plasma glucose to > 70 mg/dL or an increase in plasma glucose by ≥ 20 mg/dL within 30 minutes after receiving glucagon.
3. Increase in plasma glucose by ≥ 20 mg/dL within 30 minutes after receiving Glucagon
4. Neuroglycopenic symptomatic relief within 30 minutes after receiving Glucagon
5. Number of subjects having glucose >70 mg/dL within 30 minutes of receiving glucagon
6. Pharmacodynamic parameters
7. Hypoglycemia mean symptom scores, symptom relief, time to minimal score
8. Glucagon preparation time defined as the time between "decision to dose" and time of study drug administration to the abdomen.

Statistical Analysis Plan

The intent-to treat (ITT) population was defined as all subjects randomized. A subject's randomized treatment was to be used for analysis regardless of the actual treatment

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received.

The Per-protocol (PP) population for this study was defined as all randomized patients who, during both study periods, successfully complete the insulin induction procedure, fulfill the criteria for having achieved a hypoglycemic steady state, and successfully receive a dose of both study drugs (G-Pen followed by Lilly Glucagon, or Lilly Glucagon followed by G-Pen).

Protocol time zero was based on either receiving glucagon or decision to dose:

- Receiving glucagon: T0 = actual time stamp of glucagon injection
- Decision to dose: T0 = actual time stamp when dose decision is made

For any continuous (number) variable, the value at the protocol time was to be determined by linear interpolation between the two adjacent time points.

For any categorical (text) variable, the value at the protocol time was to be determined using the nearest value:

- Protocol time 5 – 85: -2 minute to +3 minutes
- Protocol time 90: -2 minute to 15 minutes

The analysis plan was similar to Study 301 except for a minor variation in the G-pen acceptance criterion. The sample mean of the G-Pen minus control failure difference (Dht) was to be accepted provided $Dht + 2.8 SE \leq 0.1$, which also came from Monte-Carlo simulations. I defer to the statistical reviewer's assessment for acceptability.

The applicant also states that a sample size of 85 randomized subjects yields probabilities of G-Pen acceptance of $(b)(4)\%$, if the population failure rate differences of G-Pen and control are within $(b)(4)\%$, and the rate of missing observations is within $(b)(4)\%$.

Protocol Amendments

There were no significant amendments for this study.

6.2.2. Study Results

Patient Disposition

Of the total 123 subjects screened, 81 were randomly assigned to a treatment sequence. Of the 81 randomized subjects, 76 (93.8%) completed G-Pen treatment and 78 (96.3%) completed Lilly Glucagon treatment. Of the 6 (7.4%) subjects who terminated early, 2 (2.5%) withdrew from the study before the first treatment (one due to the subject's decision to withdraw and one due to the investigator's decision to withdraw) and 4 (4.9%) withdrew from the study before the second treatment reported as due to subject decision.

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Protocol Violations/Deviations

There were 8 major protocol violations. Six subjects failed to complete both treatments and two subjects failed to meet the definition of hypoglycemia steady state prior to dosing at either treatment visits. One subject (b) (6) had an extrapolated glucose of 35 mg/dL and the other subject (b) (6) had a value of 60 mg/dL. Consistent with the SAP, these eight subjects were excluded from the PP analyses.

Although one of the confirmatory glucose values was < 43 or > 49.9 mg/dl, in some instances the investigator made a determination of steady state based on an extrapolated 8-minute value > 42 mg/dl. These were reported as minor deviations for nine subjects and a major deviation for subject (b) (6) as described above. Among the nine subjects reported as a minor deviation, the extrapolated 8- minute value was over 49.9 mg/dL in 4 subjects and over 48 mg/dL in three subjects respectively.

Other minor deviations reported were similar to study 301. There were reports of some sites using their own version of the GOLD scale (hypoglycemia unawareness questionnaire for screening) or DRAIZE scale for skin/injection site reactions. These violations did not have a significant impact on the interpretation of the efficacy or safety results.

Demographic Characteristics

Subjects in this study were younger with a lower mean weight and BMI as compared to Study 303. The mean (SD) age of subjects in this study was 38.2 (14.6) years, 54% were male and 87.7% were white. Mean (SD) weight was 78.3 (9.6) kg and BMI was 26.2 (3.8) kg/m².

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

Concomitant medications were consistent with those used in patients with Type 1 DM and the subjects' medical history.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable since this was a single dose study.

Efficacy Results – Primary Endpoint

In the SAP, The ITT population was defined as all subjects randomized. There were 81 subjects randomly assigned to one of two treatment sequence groups. In the final CSR, this ITT population was used for analysis regardless of the actual treatment received for the primary endpoint and the four binary response secondary endpoints; an outcome was imputed for missing visits. For the remaining secondary efficacy endpoints, the ITT analysis population

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consisted of the total of 76 (93.8%) subjects who completed G-Pen treatment and 78 (96.3%) subjects who completed Lilly Glucagon treatment.

The PP population was defined as all randomized subjects who, during both study periods, successfully completed the insulin induction procedure, fulfilled the criteria for having achieved a hypoglycemic steady state, and successfully received a dose of both study drugs (G-Pen followed by Lilly Glucagon, or Lilly Glucagon followed by G-Pen). Eight randomized subjects were excluded from the PP population due to failure to complete both treatments or failure to meet the definition of hypoglycemia steady state prior to dosing at either treatment visit.

Analysis of the sample means of the difference of failure scores between treatments, where failure was defined as plasma glucose remained ≤ 70 mg/dL from 0 to 30 minutes after glucagon injection based on Time from Receiving Glucagon and Time from Decision to Dose is shown in the table below. Similar to study 301, Dht is the sample mean of the difference of the success/failure scores between the two treatments (derived for each subject from the treatment score minus the control failure score). As defined in the SAP, G-Pen is noninferior, if $Dht + 2.8 \times SED(ht) \leq 0.1$. G-Pen satisfied the non-inferiority criterion compared to Lilly Glucagon in the ITT population based on both Receiving Glucagon time and Decision to Dose analyses. Similar findings were observed in the PP population.

Table 12: Analysis of the Primary Endpoint (ITT Population)

	Dht	SED(ht)	Test Statistic	Critical Value	Non-Inferiority
Analysis Based on Time from Receiving Glucagon Treatment	0.009	0.005	0.022	0.1	Yes
Analysis Based on Time from Decision to Dose	0.009	0.005	0.022	0.1	Yes

Source: Table 14, CSR for study 303

However, on review of number and percentages of subjects with plasma glucose > 70 mg/dL within 30 minutes, it was evident that more subjects achieved a plasma glucose > 70 mg/dL earlier with Lilly glucagon. This is consistent with the results of Study 301. At least twice the number of subjects attained a value over 70 mg/dl within 10 minutes with Lilly glucagon compared to G-Pen. This was noted both from time from receiving glucagon treatment and from time from decision to dose analyses (although the magnitude of the difference was decreased for the evaluation based on time from decision to dose).

Table 13: Number and Percentage of Subjects with Plasma Glucose > 70 mg/dL within 30 Minutes After Glucagon Treatment (ITT Population)

	Subjects with Plasma Glucose > 70 mg/dL within 30 Minutes after Treatment n (%)			
	G-Pen (N=76)		Lilly Glucagon (N=78)	
	Time Point	Cumulative	Time Point	Cumulative
Time (minutes) from Receiving Glucagon Treatment				
5	0	0	2 (2.6)	2 (2.56)
10	25 (32.9)	25 (32.9)	56 (71.8)	58 (74.4)
15	35 (46.1)	60 (78.9)	20 (25.6)	78 (100)
20	12 (15.8)	72 (94.7)	0	78 (100)
25	4 (5.3)	76 (100)	0	78 (100)
30	0	76 (100)	0	78 (100)
Time (minutes) from Decision to Dose				
5	0	0	0	0
10	14 (18.4)	14 (18.4)	29 (37.2)	29 (37.2)
15	37 (48.7)	51 (67.1)	45 (57.7)	74 (94.9)
20	21 (27.6)	72 (94.7)	4 (5.1)	78 (100)
25	4 (5.3)	76 (100)	0	78 (100)
30	0	76 (100)	0	78 (100)

Source: Table 16, CSR for study 303

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Data Quality and Integrity

Refer to the OSI review by Dr. Cynthia Kleppinger in DARRTs for additional details.

Data integrity issues specific to Study 303 are discussed here. Issues for the clinical program in general, including the contract research organization (b) (4) are discussed in Section 4.1. The same methods for data documentation in Study 301 were employed for Study 303, in addition to electronic systems/software provided by (b) (4). During treatment visits, site personnel used a pair of linked laptops provided by (b) (4) for real-time data entry. One of the laptops was configured for personnel to enter blood draw times and plasma glucose values in real time. The other laptop was used by investigators to enter the decision times for dosing and amounts of insulin doses. A time stamp was created when a user clicked an application button, such as “blood draw”. This system was called “Medication Adherence (MA)” by (b) (4). The MA system recorded procedures times in hours, minutes, and seconds. Sites were asked to keep back-up paper records of blood draw times, as well as insulin doses and times. In the case that basal or bolus doses were not entered in real-time (of which some instances were noted by the inspector), the site was to use their paper source to enter both the dose and time.

After entry of plasma glucose values, the computer software generated source data, including the algorithm predicted 8-minute plasma glucose value that was relied on by the site to make glucagon dosing related decisions. As discussed in Section 4.1, the data entered and generated by (b) (4) “Medication Adherence” software was not retained at the site, and was not available for review during the site inspection since the laptops were returned to the CRO (b) (4). Without the data it was not possible to verify during the inspection whether the site followed or deviated from dosing recommendations made by the “Medication Adherence” software, or to verify the accurateness of data entry or the software’s dosing recommendations. Using the calculation provided by (b) (4) and discussed during the FDA site inspection, all 8-minute extrapolated values were manually verified by Clinical site 2 for all subjects. In addition, following the site inspections, during the (b) (4) inspection, this source data, including the algorithm predicted 8-minute plasma glucose value stored in the (b) (4) laptops was inspected. There was no indication during the inspection that data had been altered from the original output and no other issues were identified on review of the data audit trail.

As mentioned earlier, OSI’s final recommendation was any regulatory deficiency observed was unlikely to significantly impact efficacy or safety analyses and the study data generated are considered reliable.

Efficacy Results – Secondary and other relevant endpoints

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As mentioned in the discussion of secondary endpoints for study 301, the applicant analyzed several endpoints related to the symptomatic relief of hypoglycemia. These are not reviewed for the same reasons cited in Section 6.1.2 for Study 301.

Return of Plasma Glucose to > 70 mg/dL or an Increase in Plasma Glucose by $\geq$ 20 mg/dL Within 30 Minutes After Receiving Glucagon and Decision to Dose:

The alternate primary endpoint proposed post-hoc in Study 301, was analyzed as a pre-specified secondary endpoint in this study, both based on time from receiving glucagon treatment and decision to dose. Essentially, these results were identical to the primary endpoint results for this study (see Table 14 below and Table 12).

Table 14: Analysis of the Sample Means of the Difference of Failure Scores Between Treatments: Failure Defined as Plasma Glucose Remained < 70 mg/dL and Increased < 20mg/dL from 0 to 30 min after Glucagon Injection (ITT Population)

Population	D _{htex}	SE _{D(htex)}	Test Statistic	Critical Value ₁	Non-Inferiority
Analysis Based on Time from Receiving Glucagon Treatment	0.009	0.005	0.022	0.1	Yes
Analysis Based on Time from Decision to Dose	0.009	0.005	0.022	0.1	Yes

Source: Table 20, CSR for study 303.

Time to First Plasma Glucose Value > 70 mg/dL and Time to Plasma Glucose Increase > 20 mg/dL:

Subjects in the Lilly glucagon group achieved plasma glucose > 70 mg/dL, 3.6 and 2.6 minutes faster on average (ITT population), compared to subjects in the G-Pen group, based on Receiving Glucagon and Decision to Dose, respectively. In the analysis based on time from receiving glucagon, the LS mean difference (SE) in first observed plasma glucose concentration of > 70 mg/dL (3.557 [0.395]) was statistically significant ($p < 0.0001$) with 95% confidence interval (2.899, 4.214) between treatment groups. Similar results were observed for mean time for subjects to achieve to plasma glucose increase > 20 mg/dL: subjects in the Lilly glucagon group achieved plasma glucose increase of at least 20 mg/dL, 3.4 and 2.4 minutes faster on average (ITT population), compared to subjects in the G-Pen group, based on Receiving Glucagon and Decision to Dose, respectively.

Table 15: Summary of the Mean Time (minutes) to Reach First Plasma Glucose 70 mg/dL Concentrations or Reach Plasma Glucose Increased by 20 mg/dL by Treatment (ITT Population)

	Treatment	
	G-Pen	Lilly Glucagon
Receiving Glucagon Treatment		
Mean (SD) Time (minutes) to Reach First Plasma Glucose 70 mg/dL	12.17 (3.604)	8.58 (2.026)
Mean (SD) Time (minutes) to Reach Plasma Glucose Increased by 20 mg/dL	11.36 (3.345)	8.02 (1.856)

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Decision to Dose		
Mean (SD) Time (minutes) to Reach First Plasma Glucose 70 mg/dL	13.27 (3.678)	10.70 (2.262)
Mean (SD) Time (minutes) to Reach Plasma Glucose Increased by 20 mg/dL	12.46 (3.436)	10.14 (2.116)

Source: Adapted from Tables 32 and 33, CSR for Study 303

Pharmacodynamic (PD) results:

Only PD results (not PK) were analyzed in this study. PD results were consistent with prior studies.

Dose/Dose Response

Not applicable, since only a single dose of G-Pen was evaluated.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

For this study, the applicant conducted an analyses of glucagon preparation time by CRU staff. As expected, on average, preparation time for G-Pen was less than 30 seconds, compared to more than 90 seconds for Lilly Glucagon (see table below). It is certainly feasible that the differences in preparation time would be longer in a real-world use setting, specifically by non-medical personnel, but actual data to support this assumption is not available.

Table 16: Analysis of Mean (SD) Glucagon Preparation Time (Seconds) by Treatment

Stopwatch Time (PP population)		Stopwatch Time ITT population)	
G-Pen	Lilly Glucagon	G-Pen	Lilly Glucagon
27.1 (20.02)	96.5 (45.50)	27.3 (19.66)	97.2 (45.06)

Source: Table 43, CSR for study 303

Statistical Reviewer's Assessment of Algorithm Performance:

The induction procedure in this study was designed to avoid low nadir glucose value post-dosing, using the algorithm predicted 8-minute glucose value. As a result, pre-dose glucose values were higher in this study and several subjects had baseline glucose values over 50

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mg/dL. Based on the statistical reviewer's assessment, the mean (95% CI) pre-dose glucose in study 301 was 44.8 mg/dL (44.1-45.6) for G-Pen and 45.2 mg/dL (44.6-45.8) for Lilly glucagon. In study 303 the mean (95% CI) pre-dose glucose was 47.7 mg/dL (47.2-48.2) for G-Pen and 48.7 mg/dL (48.2-49.3) for Lilly glucagon.

The algorithm estimated 8-minute values appeared to predict lower blood glucose than what was actually observed (i.e. the immediate post-dose blood glucose values were usually higher than the algorithm estimated 8-minute values). This is not unexpected, likely because the algorithm only considered insulin effects. However, higher actual blood glucose values, at the 5 and 10 minute time points, compared to the algorithm predicted 8-minute glucose values were observed to a larger extent for Lilly glucagon treatment sequence compared to a post-dose value for G-pen, especially at the 10-minute time point (see graphs generated by statistical reviewer below). This may be related to the pharmacodynamically slower response with G-Pen compared to Lilly glucagon.

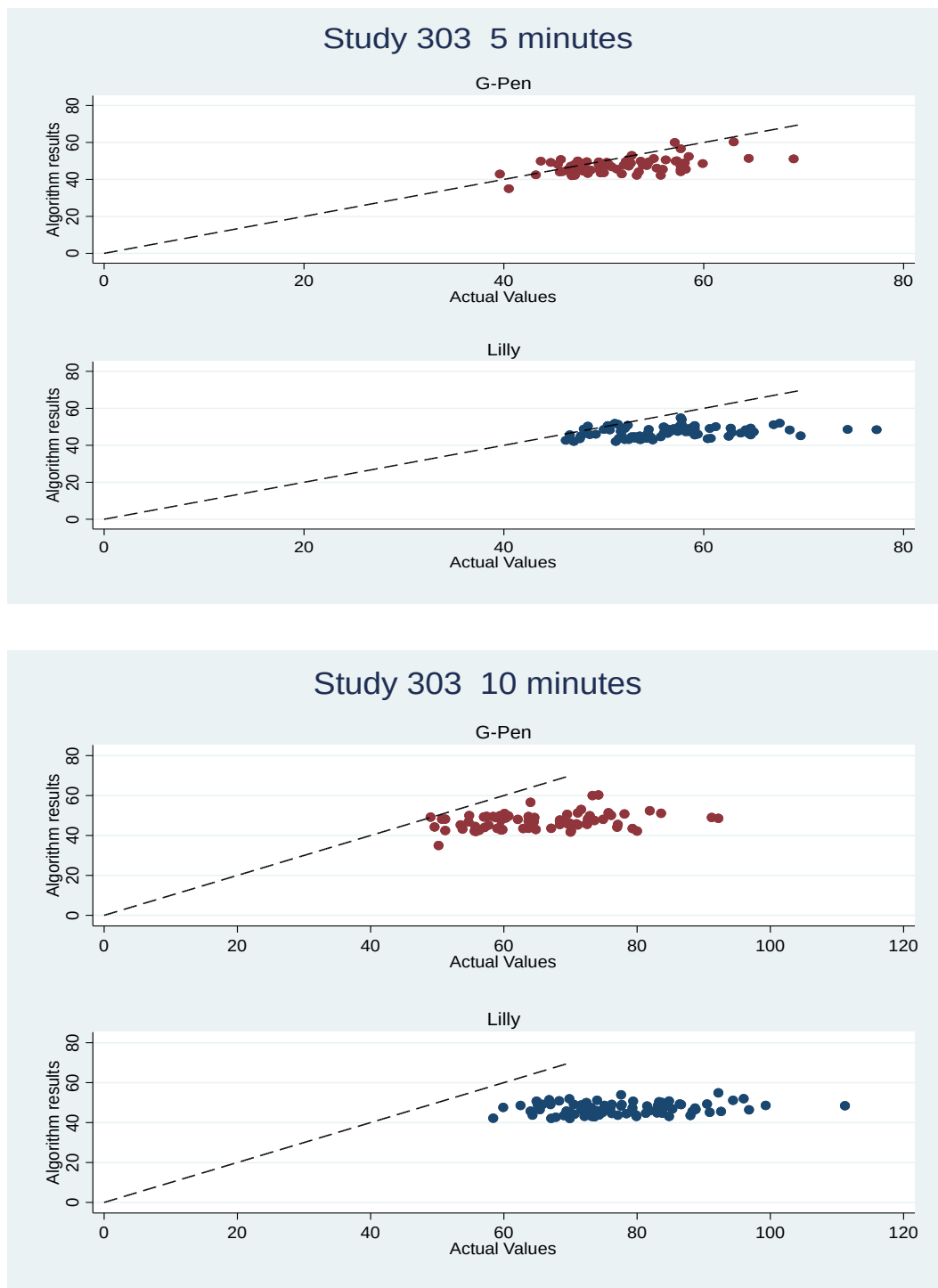
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Figure 5: Algorithm Predicted 8-minute Blood Glucose Values vs. Actual Values at 5 and 10 Minutes Post-Dose- Study 303.



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Source: Generated by Statistical reviewer, Dr. Anna Kettermann

Reviewer's Assessment:

This study met the pre-specified endpoint of an increase in plasma glucose concentration from below 50.0 mg/dL to greater than 70.0 mg/dL within 30 minutes after receiving glucagon. In addition, the study also met the pre-specified secondary endpoint of return of Plasma Glucose to > 70 mg/dL or an Increase in Plasma Glucose by ≥ 20 mg/dL Within 30 Minutes After Receiving Glucagon. The revised insulin algorithm resulted in higher baseline glucose values pre-dosing compared to study 301. However, a delay in the efficacy response with G-Pen by 3-4 minutes compared to Lilly glucagon was also observed in this study. The overall evidence for efficacy based on data from both studies will be further discussed in Section 7.

6.3 Study XSGP 302

6.3.1 Study Design

Overview and Objective

This was an uncontrolled, phase 3 study to evaluate the glucose response of G-Pen in pediatric patients with Type 1 DM to fulfill and Initial Pediatric Study Plan (iPSP). The primary objective of this study was to assess the increase in plasma glucose from baseline to 30 minutes in subjects in a low normal glycemic state after injection of an age-appropriate dose of G-Pen™ (glucagon injection), in each of three age groups (2.0-<6.0 years, 6.0-<12.0 years and 12.0-<18.0 years) for pediatric patients with type 1 DM.

Trial Design

This was an uncontrolled, phase 3 efficacy and safety study in pediatric patients with Type 1 DM. Subjects had to be administered insulin to induce a low normal glycemic state and then received an age appropriate dose of G-Pen in a clinical research center (CRC) or comparable setting. Subjects ages 2-<12 had to complete a single treatment visit and received a 0.5 mg dose of G-Pen. Subjects ages 12-<18 were to receive a 1 mg dose of G-Pen™ at an initial treatment visit, and were given the 0.5 mg dose at a second visit occurring 1-4 weeks later.

A low-normal glycemic state (target PG < 80 mg/dL) was induced. Given the ethical issues associated with hypoglycemia induction in children, this was appropriate. For subjects using injection insulin therapy, a combination of one or more bolus doses of insulin along an infusion

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of insulin was used. The insulin infusion had to be stopped once the plasma glucose was <80 mg/dL. For subjects using an insulin pump, the basal rate had to be increased until the target of < 80 mg/dL is reached. A priming bolus equal to approximately 1 hour of basal insulin could be given at the investigator discretion.

For all subjects, plasma glucose levels were measured using a bedside rapid glucose analyzer ((b) (4) or equivalent). During the insulin infusion, glucose levels were measured no more than 10 minutes apart while the plasma glucose level was ≥ 100 mg/dL and no more than 5 minutes apart when the plasma glucose level was <100 mg/dL.

After a confirmatory plasma glucose of <80 mg/dL was obtained at least 5 minutes after stopping the insulin infusion, the subject was treated subcutaneously in the upper arm, leg or abdomen with the age-appropriate dose of G-Pen administered by subcutaneous injection.

Blood glucose levels were monitored for 90 minutes post-dosing. After a wash-out period of 7 to 28 days, subjects ages 12.0- < 18.0 returned to the clinic and the procedure had to be repeated with each subject crossed over to the other treatment. Subjects had to complete age-appropriate questionnaires concerning injection site discomfort.

The pediatric doses were chosen based on weight-exposure modeling from Study 201, which indicated the appropriate transition from a pediatric 0.5 mg dose to the adult 1 mg dose was about 40 to 45 kg, as the exposure achieved with the 0.5 mg dose at that weight exceeded the exposure achieved with a 1 mg dose in a 70 kg subject. The transition to the 1 mg dose at 40 to 45 kg corresponded to the average weight at approximately 12 years of age.

Study Population:

This study was conducted in pediatric patients aged 2 to < 18 years with Type 1 DM diagnosed for at least 6 months at screening. Exclusion criteria were similar to the adult studies.

Study Endpoints

The primary endpoint for this study was an evaluation of change in plasma glucose following treatment with G-Pen, with an emphasis on baseline to 30 minutes postdosing. Secondary and safety endpoints were similar to the adult studies.

Statistical Analysis Plan:

In the Phase 2 study XSGP-201, healthy normal adults were dosed with G-Pen after an overnight fast with baseline plasma glucose values that were similar to the target (< 80 mg/dL) planned for this study. The mean increase in glucose at 30 minutes post-dosing was approximately 35 mg/dL (SD = 18). Based on these findings, the applicant estimated that a

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sample size of 6 subjects per cohort had been chosen to provide 90% power to detect an increase of plasma glucose from baseline to 30 minutes after treatment, assuming a type 1 error rate of 5%.

All endpoints had to be analyzed descriptively within each of the 3 age groups. Last observation carried forward (LOCF) was to be applied for subjects who drop out before 30 minutes post-dosing or who otherwise have missing primary endpoint data (e.g. missed blood draws). In addition to the descriptive summary, a simple t-test was to be used to compare the glucose change from baseline to zero change within each of the 3 age groups.

6.3.2 Study Results

Patient Disposition

Thirty-one subjects were enrolled in this study, of which 7 subjects were in the 2 to < 6 years age group, 13 subjects were in the 6 to < 12 years age group, and 11 subjects were in the 12 to < 18 years age group. All enrolled subjects completed all scheduled treatments.

Protocol Violations/Deviations

Most protocol deviations (24 subjects, 114 deviations) were due to PK or plasma glucose specimens collected outside of the window for the timepoint and were classified as minor. Others were due to procedure/assessment not performed as per protocol (12 subjects), not performed (5 subjects) or visit/procedure conducted outside of window (3 subjects). There was one protocol deviation categorized as major. This deviation involved a study nurse who was not documented on the G-PEN training log as having received “hands on training” with the G-PEN device. This nurse did review a power-point training presentation with instructions on device use and observe the administration of the study dose. The deviations reported did not affect interpretation of study results.

Table of Demographic Characteristics

The median ages of enrolled subjects in each age group were 5.3 years (2 to < 6 years group), 11.4 years (6 to < 12 years group), and 15.6 years (12 to < 18 years group). As shown in the table below, the majority of subjects in each age group were White. Mean (SD) body mass index (BMI) and duration of diabetes increased with mean age. The primary insulin delivery modality was insulin pump in each age group.

Table 17: Demographic and Baseline Characteristics by Age Group

Variable	Age Group		
	2 to < 6 years (N=7)	6 to < 12 years (N=13)	12 to <18 years (N=11)
Age, Years, Mean (SD)	4.96 (1.10)	9.95 (2.25)	15.48 (1.58)
Gender-Male-n%	2 (28.6)	8 (61.5)	5 (45.5)
Race, White- n%	5 (71.4)	12 (92.3)	11 (100.0)
BMI Kg/m ² , Mean (SD)	17.05 (1.55)	17.63 (4.01)	24.39 (5.35)
Duration of Type 1 DM (years), Mean (SD)	2.06 (1.24)	4.97 (3.03)	4.67 (2.99)
HbA1c-%, Mean (SD)	7.84 (0.77)	7.83 (0.99)	8.20 (1.14)
Primary Insulin Modality (Pump)- n%	6 (85.7)	11 (84.6)	10 (90.9)
Average daily Insulin dose by pump - units, Mean (SD)	13.5 (4.4)	30.8 (10.2)	70.9 (27.2)

Source: table 8, CSR for study XSGP-302

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

Disease characteristics were consistent with pediatric Type 1 DM.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not applicable, since this was a single dose study.

Efficacy Results – Primary Endpoint

Statistically significant increases from baseline in mean plasma glucose were observed in each age group ($p < 0.001$ for all groups) at 30 minutes following administration of an age-appropriate dose of G-Pen (see table below). The responses observed in the age group between 12 <18yrs were of a smaller magnitude with both the 0.5 or 1 mg dose, but still adequate from a clinical perspective.

Table 18: Plasma Glucose Before and 30 Minutes After Administration of G-Pen by Age Group

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: table 9 and 10, CSR for study XSGP-302

Secondary and other relevant endpoints.

Pharmacodynamic endpoints:

Glucose Exposures (AUC₀₋₉₀) were lower in the 12< 18 years age-group with both doses compared to the younger age groups with a longer time taken for mean increase of plasma glucose over 25 mg/dL (2 to < 6 years, 6 to < 12 years, and 12 to < 18 years age groups :16.4, 16.2, and 23.6 minutes, respectively). The exact reason for the lower glucose AUC₀₋₉₀ and slower response is unclear. This group had higher mean BMIs. However, Plasma glucagon exposures in the 12< 18 years age-group at the 1 mg dose were comparable to the younger age-groups (see Figure 6).

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Table 19: PD Endpoints and Time to Increase > 25 mg/dl from Baseline by Age-Group.

Age Group	G-Pen Dose	Summary Statistics	C _{max} (mg/dL)	t _{max} (min)	AUC ₍₀₋₉₀₎ (min*mg/dL)	Baseline-adjusted AUC ₍₀₋₉₀₎ (min*mg/dL) ^a	Time to increase by ≥ 25 mg/dL from Baseline (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	0.5 mg	N	10	10	10	10	11
		Mean (SD)	212.10 (40.619)	78.2 (11.55)	13809.58 (2096.187)	7042.85 (2011.071)	23.6 (5.95)
12 to < 18 years	1.0 mg	N	11	11	11	11	11
		Mean (SD)	197.00 (56.974)	81.2 (14.91)	13105.45 (3025.700)	6377.54 (2700.448)	23.6 (9.51)

Source: table 10 and 11, CSR for Study XSGP-302

Pharmacokinetics (Plasma Glucagon):

In contrast to the PD effect, administration of 0.5 mg G-Pen in the 12 to < 18 years age group resulted in lower mean plasma glucagon levels compared with 1 mg G-Pen (see figure below). Mean (SD) plasma glucagon C_{max} was 2.3 (1.08) ng/mL, 1.6 (0.84) ng/mL, 1.1 (0.49) ng/mL and 1.9 (1.18) ng/mL in the 2 to < 6 years, 6 to < 12 years, 12 to < 18 years (0.5 mg) , and 12 to < 18 years age (1mg) groups, respectively. Mean (SD) plasma glucagon t_{max} was 41.4 (12.82) minutes, 33.8 (14.96) minutes, 40.4 (15.38) and 51.0 (22.96) minutes in the 2 to < 6 years, 6 to < 12 years, 12 to < 18 years (0.5 mg) and 12 to < 18 years age groups (1 mg), respectively. Mean (SD) plasma glucagon AUC₍₀₋₁₈₀₎ was 138.9 (77.59) ng/mL*min, 104.7 (55.24) ng/mL*min, 73.4 (28.05) ng/mL*min and 134.3 (56.03) ng/mL*min in the 2 to < 6 years, 6 to < 12 years, 12 to < 18 years (0.5 mg) and 12 to < 18 years (1 mg) age groups, respectively.

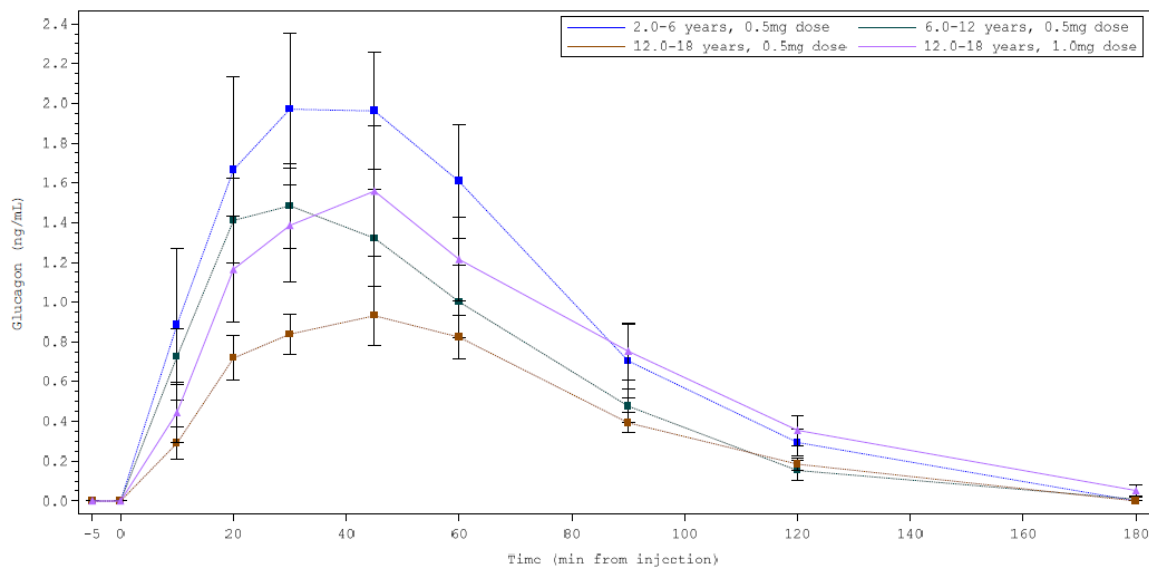
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Figure 6: Mean (SE) Plasma Glucagon at Each Time Point for Age/Dose Group



Source: Figure 4, CSR for study XSGP-302

The applicant indicates that these results support a dose of 1 mg G-Pen for the 12 to < 18 years age group as this dose resulted in similar exposure as the younger cohorts who were treated with the age-appropriate dose (0.5 mg G-Pen). This conclusion is acceptable.

Dose/Dose Response

Differences in the PD and PK response with the 0.5 and 1 mg dose in the 12< 18 years age-group are discussed in the prior section.

Durability of Response

Not applicable.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable.

Reviewer's Assessment: The study provides evidence of a pharmacodynamic response to glucagon (increase in plasma glucose) with G-Pen. Limitations include an uncontrolled design and reduction of blood glucose to low normal values, as induction of hypoglycemia would not be

feasible or ethical to evaluate in a pediatric population. Although the PD response to G-Pen was of a lower magnitude in the 12-18 years age-group compared to other age groups, the PD response was still statistically significant and clinically acceptable.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The applicant conducted two single-dose efficacy and safety trials (XSGP-301 and 302) in adults to support this 505(b)(2) application, since PK bioequivalence to the RLD was not established in Phase 2 study 201.

The applicant conducted Study 302, an uncontrolled, single dose, sequential efficacy and safety study in pediatric subjects with Type 1 DM to fulfill the PSP requirement. The results for Study 302 have been discussed in Section 6.3.2. I will only discuss results from the controlled studies 301 and 303 in Sections 7.1 and 7.2 for the integrated assessment of Efficacy, since the primary endpoint and study design were different in Study 302.

7.1.1. Primary Endpoints

For the Integrated Summary of Efficacy, the applicant conducted a pooled analyses of subjects from Studies 301 and 303 combining the mITT population from study 301 and the ITT population from study 303. Of the subjects treated with G-Pen in these studies, 97.4% of the pooled patients achieved a plasma glucose level > 70 mg/dL within 30 minutes for the mITT population and 98% for the PP population compared to 100% with Lilly Glucagon.

Table 20: Number of Subjects with Plasma Glucose > 70 mg/dL Within 30 Minutes of Dosing: Adult Phase 3 Type 1 Diabetic Subjects

Time Point	Pooled Analysis (301, 303)			
	mITT		Per Protocol	
	G-Pen (N=154)	Lilly (N=157)	G-Pen (N=150)	Lilly (N=153)
Within 30 mins post-dose	150 (97.4)	157 (100.0)	147 (98.0)	153 (100.0)

Source: ISE Table 3.2.1 and 3.2.2

The pre-specified primary endpoint proposed was agreed upon in the end-of Phase 2 meeting (see Section 3.1). At that time, the division's thinking was evolving regarding the appropriate endpoint that would be clinically meaningful for glucagon products under clinical development in the absence of PK equivalence to the approved products. It was felt that in addition to an

increase to an absolute blood glucose threshold value of 70 mg/dL, a relative increase of at-least 20 mg/dL from baseline may be clinically meaningful, especially for a patient with severe hypoglycemia and nadir blood glucose values well below 40 mg/dL. Also, this would be consistent with other recent glucagon development programs. This alternative primary endpoint is further discussed in Section 7.1.2.

7.1.2. Secondary and Other Endpoints

The Applicant evaluated several secondary endpoints, which included a combined glucose-response endpoint (an increase in plasma glucose concentration > 70 mg/dL or increased $\geq$ 20 mg/dL within the 0 to 30-minute period after study drug administration). As discussed in Sections 6.1.2 and 6.2.2, this endpoint was proposed post-hoc by the applicant for Study 301 and as a prespecified secondary endpoint in Study 303. There was no adjustment for multiplicity. The non-inferiority criteria were satisfied for this endpoint in both studies.

In the pooled analyses of studies 301 and 303, 98.7% had a plasma glucose > 70 mg/dL or an increase of $\geq$ 20 mg/dL within 30 minutes compared to 100% with Lilly Glucagon.

Table 21: Efficacy Results for Proposed Alternate Primary Endpoint: Number of Subjects with Plasma Glucose > 70 mg/dL or $\geq$ 20 mg/dL Increase Within 30 Minutes of Dosing: Adult Phase 3 Type 1 Diabetic Subjects, mITT population.

EndPoints-Within 30 mins post-dose	Pooled Analysis (301, 303)	
	G-Pen (N=154)	Lilly (N=157)
Plasma Glucose > 70 mg/dL or $\geq$ 20mg/dL Increase	152 (98.7)	157 (100.0)
Plasma Glucose > 70 mg/dL	150 (97.4)	157 (100.0)
Plasma Glucose Increase $\geq$ 20 mg/dL	152 (98.7)	157 (100.0)

Source: ISE tables: 3.2.1, 3.4.1 and 3.6.1

Reviewer comment: The Applicant met the non-inferiority margin for the alternate primary endpoint. As previously discussed in 7.1.1, this alternate primary endpoint is both clinically meaningful and is consistent with other glucagon development programs. In addition to an increase to an absolute blood glucose threshold value of 70 mg/dL, a relative increase of at-least 20 mg/dL from baseline may be clinically meaningful, especially for a patient with severe hypoglycemia and nadir blood glucose values well below 40 mg/dL. Therefore, I agree with the inclusion of this endpoint in product labelling for G-Pen.

As discussed in review of the individual studies, multiple secondary endpoints related to symptomatic relief of hypoglycemia were analyzed and included in the proposed PI. The COA staff have indicated that the hypoglycemia symptom questionnaire (HSQ) evaluation may not

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be adequate since staff frequently completed the questionnaire instead of patients. They concluded that the HSQ was inappropriate for use as a patient reported outcome (PRO) measure in the context of induced hypoglycemia. Therefore, the data are not informative of the patient experience.

7.1.3. Subpopulations

Comparison of results for number of subjects with a plasma glucose >70 mg/dL in 30 minutes within subpopulations were performed on data from pooled studies 301 and 303 for the mITT population. Since there were only 4 subjects in the G-pen sequence who failed to achieve a blood glucose value > 70 mg/dL within 30 minutes the results were comparable to the overall response when analyzed by age, sex, race, weight or duration of diabetes.

7.1.4. Dose and Dose-Response

Not applicable for the pivotal controlled studies.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

As discussed in the sections 6.1.2 and 6.2.2 (Table 15), the applicant compared treatments with regard to time (Minutes) to first plasma glucose > 70 mg/dL. In the pooled analysis of studies 301 and 303, the mean (SD) time to achieve plasma glucose > 70 mg/dL or increase in plasma glucose > 20 mg/dL was 13.8 (5.6) minutes for G-pen, compared to 10 (3.6) minutes for Lilly Glucagon.

Therefore, it is evident that the pharmacodynamic response with G-Pen is slower by around 3-4 minutes compared to Lilly Glucagon. The difference in pharmacodynamic response was also analyzed by the statistical reviewer. She examined the rates of change in PG (or PG velocity) which demonstrate that the PG values of subjects on Lilly glucagon begin to accelerate earlier than subjects on G-Pen in both studies. The significance of this difference, given the differences in time to administration will be discussed in Section 7.2.1.

Table 22: Rate of change of Plasma Glucose, Study 301 and 303

BG velocity mg/dL/min Mean (95%CI)	Study 301		Study 303	
	G-Pen	Lilly glucagon	G-Pen	Lilly glucagon
BG>70mg/dL	1.97 (1.8,2.14)	2.56 (2.38, 2.75)	2.26 (2.1, 2.41)	3.0 (2.82,3.18)
Increase by 20mg/dL	1.83(1.67,1.99)	2.52 (2.31,2.73)	2.17 (2.01,2.32)	2.94 (2.76,3.13)

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Source: Statistical review, Table 19 & 20, Appendix-B.2

Reviewer's assessment:

The delay in glucose response can be communicated to healthcare professionals by including comparative response time in Section 14.0 of the PI. There may be select scenarios when this information is useful in emergency settings, such as when a second dose is considered by paramedics or ER personnel and IV access is problematic for dextrose administration- it may be preferable to administer the Lilly glucagon in this circumstance

Reviewer comment: Since this is an emergency use product for treatment of severe hypoglycemia, patients are instructed to administer oral glucose/carbohydrate after initial recovery, so duration and persistence of efficacy are not applicable for this application.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the post market setting, G-Pen will be used as emergency rescue product for the treatment of severe hypoglycemia in patients with diabetes mellitus who are unwilling or unable to take oral glucose due to impaired level of consciousness or seizures. As previously discussed in the review of the individual studies, it is not feasible to conduct a clinical study under conditions of actual use. The injectable glucagon products currently approved for this indication require reconstitution, which delays, and limits their use as caregivers may not be comfortable administering a product that requires reconstitution. The efficacy of G-Pen is delayed by 3-4 minutes compared to the currently marketed injectable glucagon. While time is very important in the context of a rescue product administration, the applicant of G-Pen is making the argument that this delay in efficacy matches a delay in administration for the approved glucagon products, which requires reconstitution. As evaluated by the applicant in study 303, preparation time for G-Pen for CRU staff was less than 30 seconds, compared to more than 90 seconds for Lilly Glucagon. It is certainly feasible that this difference would be of greater magnitude in real-world use. This argument seems reasonable, and the efficacy of G-Pen is supported overall by the development program based on glucose response.

7.2.2. Other Relevant Benefits

The G-pen offers the potential for greater ease of administration with lower potential for medication errors, which was discussed above in Section 7.2.1.

7.3. Integrated Assessment of Effectiveness

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The applicant completed two single dose cross-over studies comparing the efficacy and safety of G-Pen to Lilly Glucagon in adults with Type 1 DM. Study 301 was conducted as a double-blind study, while Study 303 had an open-label design with a modification to the hypoglycemia induction procedure. In addition, the applicant completed an uncontrolled sequential study evaluating G-Pen doses 0.5 and 1 mg in Pediatric patients with Type 1 DM aged 2 < 18 years of age.

As discussed in Sections 7.1.1, 6.1.2 and 6.2.2, G-Pen 1 mg did not satisfy the criterion for non-inferiority (NI) to Lilly Glucagon 1 mg based on analysis of failure scores for the primary endpoint (an increase in plasma glucose concentration from below 50 mg/dL to > 70 mg/dL within 30 minutes after receiving glucagon) for the mITT and pre-specified PP population in Study 301. The criterion was satisfied in Study 303. There were 4 patients who failed the NI criterion in Study 301. On review of the data, these subjects did experience a decrease in blood glucose post-dosing, consistent with excess insulin on board. These results also demonstrated a greater time lag for the glucagon response with G-Pen compared to Lilly Glucagon. The risks from this delay in effect should be mitigated by language in the indications section of the PI advising providers to instruct caregivers/patients to seek immediate emergency assistance after administration of G-Pen for severe hypoglycemia.

However, except for one subject who had an increase of 18 mg/dL, all others had an increase of over 20 mg/dL from their nadir glucose value post-dose by 30 minutes, and reached a blood glucose over 70 mg/dL by 45 min. The applicant proposed an alternative combined glucose response primary endpoint, which was an increase in plasma glucose concentration > 70 mg/dL or increase $\geq$ 20 mg/dL within the 0 to 30-minute period after study drug administration. As discussed in Sections 6.1.2 and 6.2.2, this endpoint was proposed after unblinded review of the study data by the applicant for Study 301 and as a prespecified secondary endpoint in Study 303. The NI criterion was satisfied by G-pen for this endpoint in both studies. Therefore, this endpoint can be considered in product labeling, since this endpoint is considered clinically relevant for reasons discussed in Sections 7.1.1 and 7.1.2 , and for consistency with other glucagon development programs.

Efficacy has to be interpreted predominantly based on whether the pharmacodynamic (blood glucose) results in the phase 2/3 studies is clinically acceptable, since evaluation under conditions of indicated use (hypoglycemia with impaired consciousness or seizures) is not feasible. Based on the glucose response with G-Pen observed in both phase 3 studies and the results for the combined glucose response endpoint, there is sufficient evidence of effectiveness.

Multiple secondary endpoints related to symptomatic relief of hypoglycemia were analyzed and included in the proposed PI. These will not be included in the final PI since (b) (4)

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(b) (4)

the results are not informative of the patient experience.

The applicant did compare treatments with regard to time (Minutes) to first plasma glucose > 70 mg/dL in the pooled analysis of studies 301 and 303. The mean (SD) time to achieve plasma glucose > 70 mg/dL or increase in plasma glucose > 20 mg/dL was 13.8 (5.6) minutes for G-pen, compared to 10 (3.6) minutes for Lilly Glucagon. Therefore, the efficacy response with G-Pen is delayed by 3-4 minutes compared to the currently marketed injectable glucagon. As evaluated by the applicant in study 303, preparation time for G-Pen for CRU staff was less than 30 seconds, compared to more than 90 seconds for Lilly Glucagon. It is certainly feasible that this difference would be of greater magnitude in real-world use, especially by non-medical personnel, like caregivers etc. An added consideration is relative ease of administration since reconstitution is not required and post-marketing reports of medication errors, including injection of diluent alone without the vial of powdered medication with the currently approved glucagon products for injection³⁷. However, the delay in glucose response can be communicated to healthcare professionals by including comparative response time in Section 14.0 of the PI.

In the uncontrolled Pediatric study 302 (see Section 6.3.2) the primary efficacy endpoint was the change from baseline in plasma glucose at 30 minutes. The study met the primary efficacy endpoint for all age groups, with change in plasma glucose from baseline of 81.4 mg/dL, 84.2 mg/dL, and 54.0 mg/dL for the 2 to <6 years old, 6 to <12 years old, and 12 to <18 years old groups, respectively. The median time to increase by ≥ 25 mg/dL from baseline in plasma glucose was 15 minutes in patients between 2 to <12 years old and 20 minutes in patients 12 to <18 years of age. A lower glucose response at 30 minutes and slower increase by ≥ 25 mg/dL in patients 12 to <18 years of age was observed with both the 0.5 mg and 1 mg dose. The study limitations included a lack of control group and applicability of the results to conditions of real use (severe hypoglycemia). However, all subjects demonstrated a robust pharmacodynamic (glucose) response to study drug. While the response to glucagon was slower and of a smaller magnitude in the 12 to <18-year old subjects, it still achieved the pre-specified endpoint, supporting evidence of effectiveness for this patient population and the applicant's proposed dose of 1.0 mg in subjects 12-18 years of age.

³⁷ Faster Use and Fewer Failures with Needle-Free Nasal Glucagon Versus Injectable Glucagon in Severe Hypoglycemia Rescue: A Simulation Study. Diabetes Technology & Therapeutics Volume 19, Number 7, 2017
CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

8. Review of Safety

8.1. Safety Review Approach

Of the six clinical studies conducted by the applicant, two were bioequivalence studies (XSGP-201 and 101). Of the remaining four studies, Study XSGP-202 was an uncontrolled Phase 2, open-label, cross-over pilot study in 7 subjects with Type 1 DM evaluating doses of G-Pen 0.5 mg and 1 mg. The primary objective of this study was to evaluate/establish the hypoglycemia induction technique for the phase 3 studies. Therefore, the main focus of my safety review was the Phase 3 integrated pool of all adults in Studies 301 and 303 and safety information for pediatrics from uncontrolled pediatric study XSGP-302.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Safety population in the individual studies was defined as all subjects randomized who received at least one dose of study drug, and the actual treatment received was used for all safety analyses. This was identical to the mITT population in Study 301 (G-Pen: 78 subjects, Lilly Glucagon: 79 subjects). In study 303, the mITT population consisted of 76 subjects who received G-pen, and 78 subjects who received Lilly Glucagon. Given the cross-over design, the number of subjects receiving each treatment does not represent unique subjects, but rather G-Pen or comparator administrations. Therefore, the adult Phase 3 Type 1 DM pool consisted of 154 subjects in the G-Pen sequence and 157 subjects in the Lilly sequence.

A total of 11 subjects aged 12-18 years received single doses of G-Pen 1 mg and 31 subjects received single doses of G-Pen 0.5 mg in pediatric Study XSGP-302.

8.2.2. Relevant characteristics of the safety population:

The demographics of the safety population in the individual studies is discussed in Sections 6.1.2, 6.2.2 and 6.3.2.

8.2.3. Adequacy of the safety database:

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The adult and pediatric safety database in this clinical program seems adequate for evaluation of common adverse events with administration of G-Pen. It is limited in scope for evaluation of rare events given the limited sample size. As mentioned earlier, the RLD (Lilly glucagon, NDA 020928) and GlucaGen (Novo Nordisk) only have PK/PD data in healthy volunteers included in the package insert. Available safety data included in the package insert is mainly from post-marketing data, known pharmacologic effects of glucagon and effects observed in patients with glucagonomas and other neuroendocrine tumors. Therefore, limited safety information is available even for the approved glucagon products. Given that this product is intended for short-term emergency use, the limited safety database is considered adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

From a safety perspective, there were no concerns with data integrity or quality.

8.3.2. Categorization of Adverse Events

Adverse events were coded by Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 system organ class (SOC) and preferred term. The pivotal phase 3 adult studies were single-dose cross-over studies, and patients aged 12-18 years crossed over to receive the 0.5 and 1 mg doses in Pediatric study 302. Therefore, the number of subjects receiving each treatment (with the exception of pediatric subjects < 12 years of age) does not represent unique subjects, but rather G-Pen or comparator administrations, G-Pen 1 mg or 0.5 mg

8.3.3. Routine Clinical Tests

The overall safety evaluation plan in the phase 3 clinical studies conducted with G-Pen included evaluation of adverse events and monitoring of clinical chemistry and hematology laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations at baseline and follow-up. Injection site reactions were assessed with standardized scales. This was acceptable.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in this clinical program.

8.4.2. Serious Adverse Events

There was one SAE in Study 202. The narrative is described below:

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Subject XSGP (b) (6) received 1 mg of investigational product (G-Pen 1 mg) and had a glucose of 221 mg/dL at 90 minutes. She resumed her insulin pump at basal rate and took a bolus dose prior to her meal. Following the same she experienced nausea and vomiting followed by an episode of vasovagal syncope around 2 hours following the glucagon injection. Her capillary blood glucose following the same was 108 mg/dL. Here nausea resolved in around 2 hours after observation.

Reviewer's Assessment: Association to study drug is also possible in addition to being procedure related, since the nausea/vomiting that triggered the vasovagal episode is a known adverse-effect of glucagon.

Study 301:

One patient with Type 1 DM in study 301 (b) (6) completed treatment with Lilly Glucagon 1 mg in a medically stable condition. She experienced a case of hypoglycemia the evening after discharge from the clinic. The subject woke up overnight and required external assistance. The subject was reportedly treated by an emergency medical technician with saline only. Glucose values are not reported. However, the subject continued in the study, returned to the clinic for Treatment 2 (G-Pen 1 mg), and completed the study

Reviewer's Assessment: This event did not have any temporal association to glucagon administration. Inadequate information is available to make an accurate assessment given the report that only saline was given. It is possible that the event was managed with oral glucose or carbohydrate.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The applicant reports no TEAEs that led to study treatment discontinuation in these studies.

8.4.4. Significant Adverse Events

Available safety data included in the package insert of approved glucagon products is mainly from post-marketing data, known pharmacologic effects of glucagon and effects observed in patients with glucagonomas and other neuroendocrine tumors. Potentially significant AEs observed with Glucagon include serious allergic hypersensitivity reactions, catecholamine release in patients with pheochromocytoma, lack of efficacy in patients with insulinoma, and lack of efficacy in patients with decreased hepatic glycogen.

In addition to the adverse events listed above, other events reported include hypertension and tachycardia (especially in patients taking beta-blockers), loss of glucose-raising effect in patients taking indomethacin and increased anti-coagulant effect of warfarin.

Reviewer's Comment: Except for one episode of tachycardia, the adverse events listed above were not observed in the clinical studies. However, given the limited safety database, they

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should be included in the Contraindications, Warning and Precautions, Adverse Reactions and Drug Interactions Sections of the PI, consistent with the previously approved products.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Phase 3 Adult studies (301 & 303):

Overall, 71 (46.1%) of G-Pen treated subjects reported AEs vs. 52 (33.1%) of Lilly Glucagon treated subjects (see table below). As expected, the most common G-Pen TEAEs were in the Gastrointestinal Disorders SOC, with a slightly higher incidence of nausea (29.9% versus 22.9%, respectively) and vomiting (16.2% versus 9.6%, respectively). Headaches were also numerically more frequent following G-pen treatment (G-pen: 8 [5.2%], Lilly:6 [3.8%]). All these events were reported as mild or moderate in severity. Injection site pain was reported in 2 (1.3%) of G-Pen treated subjects. However moderate to severe Injection site edema at 30 minutes or end-of visit, which was reported separately by the applicant was more frequent with G-Pen. This will be further discussed in section 8.5. Tachycardia (a known AE with glucagon) was reported in one patient (0.6%) during G-pen treatment.

Table 23: Treatment-Emergent Adverse Events Occurring in ≥ 2 G-Pen-Treated Subjects in the Adult Phase 3 Type 1 Diabetic Subjects Pool

System Organ Class Preferred Term	G-Pen Subject N=154 n (%)	Lilly Subject N=157 n (%)
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)
Local Tolerability		
Moderate to severe Injection site edema at 30 minutes	10 (6.4%)	0

Source: ISS Table 9.1.2 and Table 7.1.2

Similar findings were also observed in the pediatric study 302, which was uncontrolled. Hypoglycemia was reported as a common AE in multiple subjects in this study secondary to the

study procedure (see table below). Injection site discomfort was reported as an AE in 1 subject (3.2%) in the 0.5 mg dose and injection site reaction was reported in one subject (9.1%) in the 1.0 mg dose group. All TEAEs were mild or moderate in severity as assessed by the investigator.

Table 24: Treatment-Emergent Adverse Events Occurring in ≥ 2 G-Pen-Treated Subjects in Pediatric Study 302

System Organ Class Preferred Term	2.0-<6.0yr (0.5mg) Subject N=7, n (%)	6.0- <12.0yr (0.5mg) Subject N=13, n (%)	12.0- <18.0yr (0.5mg) Subject N=11 n (%)	All (0.5mg) Subject N=31, n (%)	12.0- <18.0yr (1.0mg) Subject N=11, n (%)
Gastrointestinal disorders	3 (42.9)	7 (53.8)	4 (36.4)	14 (45.2)	6 (54.5)
Nausea	3 (42.9)	7 (53.8)	4 (36.4)	14 (45.2)	4 (36.4)
Vomiting	1 (14.3)	3 (23.1)	0	4 (12.9)	2 (18.2)
Metabolism and nutrition disorders	2 (28.6)	8 (61.5)	3 (27.3)	13 (41.9)	3 (27.3)
Hyperglycemia	1 (14.3)	1 (7.7)	0	2 (6.5)	0
Hypoglycemia	2 (28.6)	7 (53.8)	3 (27.3)	12 (38.7)	3 (27.3)
Nervous system disorders	0	2 (15.4)	1 (9.1)	3 (9.7)	0
Dizziness	0	0	1 (9.1)	1 (3.2)	0
Headache	0	2 (15.4)	0	2 (6.5)	0
Local Tolerability					
Injection site edema at 30 minutes	3 (42.9)	8 (61.5)	5 (45.5)	-	5 (45.5)
Injection site discomfort at 30 minutes	1 (14.3)	6 (46.2)	2 (18.2)	-	2 (18.2)
Injection site erythema at 30 minutes	2 (28.6)	7 (53.8)	4 (36.4)	-	6 (54.5)

Source: ISS Table 12.1.2, CSR Tables 14.3.4.2, 14.3.5.2 and 14.3.6.2 for Study 302

8.4.6. Laboratory Findings

Scheduled laboratory tests were performed in the adult phase 3 studies. In Study XSGP-302, clinical chemistry laboratory evaluations were performed only for screening, without follow-up laboratory evaluations. Except for mean fasting glucose elevation at baseline, which is expected for the patient population, there were no relevant abnormalities in the clinical chemistry or hematology evaluations.

8.4.7. Vital Signs

Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP), were monitored in the clinical studies conducted with G-Pen. Comparisons were performed at various time in the clinical studies (e.g., 30, 60, 90, 120, and 180/240 minutes post drug injection), and evaluation shifts from baseline/screening to follow-up was performed. There were no significant differences between treatment groups or significant differences from

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baseline post-treatment. Similarly mean vital sign measurements were within normal limits in each age group in the pediatric study, and no clinically relevant changes in vital signs was observed.

8.4.8. QT

Not applicable, since this product is not an NME.

8.4.9. Electrocardiograms (ECGs)

ECGs were collected in the adult studies at screening and follow-up. There were no new abnormal ECG findings detected after treatment in any subjects in study 301. In study 303, two subjects (b) (6) were found to have marked sinus bradycardia during ECGs at the follow-up visit after receiving both G-Pen and Lilly glucagon, but neither was considered to be clinically significant by the investigator.

8.4.10. Immunogenicity

Antibodies were not evaluated in the clinical studies. However, as with all therapeutic peptides, there is the potential for immunogenicity and a statement reflective of the same should be included in the PI.

8.5. Analysis of Submission-Specific Safety Issues

The main significant safety issue that was identified during nonclinical studies with Xeris glucagon was injection site pain/reactions identified during local tolerance studies in rats, which appeared to be more severe after the recovery period in Xeris glucagon-treated rats when compared to Lilly glucagon-treated rats.

8.5.1. Injection Site Edema, Erythema and Pain

These events were analyzed separately by the applicant as Local Tolerability issues.

Injection site Edema:

This was assessed by the investigator based on the modified Draize scale for erythema and edema as shown below.

Table 25: Draize Scale for Edema and Erythema

Erythema Formation		Edema Formation	
Description	Score	Description	Score
No erythema	0	No edema	0
Very slight erythema Barely perceptible	1	Very slight edema Barely perceptible	1
Well defined erythema	2	Well defined edema	2
Moderate erythema	3	Moderate edema Raised approx. 1 mm	3
Severe erythema Beet redness to slight eschar formation	4	Severe edema Raised more than 1 mm and beyond exposure area	4

Source: Appendix 3, Protocol for study 301, V1.6 (March 16, 2017)

As shown in the table below, in contrast to Lilly glucagon, moderate to severe injection site edema at 30 minutes was present only in G-Pen treated subjects. Two patients had severe persistent edema at the end of the visit.

Table 26: Edema in Adult Phase 3 Type 1 Diabetic Subjects

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

¹ Subjects measured at 180 minutes, 240 minutes, or prior to exiting clinic.

Source: Table 18, Summary of Clinical Safety

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The applicant reported that severe edema was present only in two patients who received G-pen in the outer thigh or outer arm. However, three patients (1.9%) who received the injection in the abdomen also had moderate edema at 30 minutes.

Pediatric Study 302:

Analyses of edema by Draize scale was not done in Study 302, only the incidence of edema was reported in this study. No severe or serious AEs of erythema or edema were reported.

Incidence of edema by visit and age groups is shown in the table below. Up to 60% of patients had edema at 30 minutes. More subjects (31%) reported edema at 180 minutes in the 6-12 years group.

Table 27: Incidence of Edema After Administration of G-Pen by Age Group and by Treatment Dose, Study 302:

Age Group	G-Pen™ Dose	Incidence of Edema					
		10 minutes		30 minutes		180 minutes	
		n	%	n	%	n	%
2.0-<6.0 years (N=7)	0.5 mg	3	42.9	3	42.9	1	14.3
6.0-<12.0 years (N=13)	0.5 mg	9	69.2	8	61.5	4	30.8
12.0-<18.0 years (N=11)	1.0 mg	5	45.5	5	45.5	1	9.1
12.0-<18.0 years (N=11)	0.5 mg	6	54.5	5	45.5	1	9.1

Source: table 14.3.6.2, CSR for Study 302.

Reviewer's Assessment: Since this is not a serious or severe AE, it can be included in the Adverse reactions section of the PI.

Injection site Erythema:

There were no significant differences in injection site erythema overall (see table below), as well as based on injection site between G-Pen and Lilly glucagon treatment groups. Injection site erythema had resolved in most subjects by the end of the visit.

Table 28: Erythema: Adult Type 1 Diabetic Subjects

Time	Edema	G-Pen N=161 n (%)	Lilly N=157 n (%)
10 minutes	None Very slight Well defined Moderate Severe	87 (54.0) 58 (36.0) 15 (9.3) 1 (0.6) 0	86 (54.8) 54 (34.4) 16 (10.2) 1 (0.6) 0
30 minutes	None Very slight Well defined Moderate Severe	95 (59.0) 51 (31.7) 15 (9.3) 0 0	96 (61.1) 46 (29.3) 14 (8.9) 0 0
End of Visit ¹	None Very slight Well defined Moderate Severe	93 (57.8) 3 (1.9) 4 (2.5) 0 0	54 (34.4) 5 (3.2) 2 (1.3) 0 0

Note: For subjects with multiple values for the same treatment and time point, the maximum value was used

¹ Subjects measured at 180 minutes, 240 minutes, or prior to exiting the clinic.

Source: Table 20, Summary of Clinical safety.

Pediatric Study 302:

Similar to edema, analyses by Draize scale was not done for erythema, only incidence was reported in the CSR. Erythema had resolved (except for 1 subject) by 180 minutes. The incidence at 30 minutes was similar to the incidence of edema (see table below).

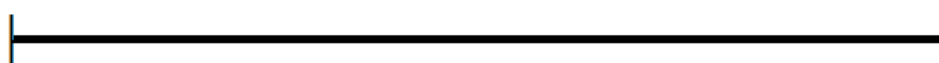
Table 29: Incidence of Erythema After Administration of G-Pen by Age Group and by Treatment Dose for Subjects Aged 2.0-<18.0 , Study 302

		Incidence of Erythema					
		10 minutes		30 minutes		180 minutes	
Age Group	G-Pen TM Dose	n	%	n	%	n	%
2.0-<6.0 years (N=7)	0.5 mg	4	57.1	2	28.6	0	0.0
6.0-<12.0 years (N=13)	0.5 mg	8	61.5	7	53.8	0	0.0
12.0-<18.0 years (N=11)	1.0 mg	5	45.5	6	54.5	1	9.1
12.0-<18.0 years (N=11)	0.5 mg	5	45.5	4	36.4	0	0.0

Source: Table 14.3.5.2, CSR for study 302

Injection site Discomfort:

Injection site discomfort was also assessed by a visual analog Scale (VAS). The subject completed the VAS by drawing a single vertical line through the scale corresponding to the perceived intensity (severity) of discomfort according to the instructions provided in the questionnaire. The goal was for the subject to report the amount of discomfort, if any, remaining at each time point, as opposed to reporting the transient pain associated with needle insertion. If a subject was unable to physically complete the questionnaire, the subject will indicate the point on the VAS corresponding to their level of discomfort, and study staff would enter a vertical line at that point. Documentation will be provided on each completed questionnaire as to who completed the form.



No Discomfort

Worst Possible Discomfort

They also had to describe the discomfort as pain (throbbing, soreness, muscle ache); itching; tingling, twitching or numbness and irritation.

Adult Phase 3 Type 1 DM Subjects:

The mean pain score was numerically higher for G-Pen at all time points, specifically at 10 minutes. Pain scores were low by the End-of treatment visit. However, standard deviations reported in this scale were very wide, indicative of wide variability in the results.

Table 30: Pain score by VAS, Adult Phase 3 Type 1 Diabetic Subjects

Time Point	G-Pen (N=154)	Lilly Glucagon (N=157)
10 mins post-dose Mean (SD)	19.4 (23.7)	6.1 (12.4)
30 mins post-dose Mean (SD)	9.7 (18.5)	1.3 (5.1)
End- of Visit (180 or 240 mins post-dose), Mean (SD)	5.1 (9.45)	1.6 (7.5)

Source: ISS table 6.1.2,

Pediatric Study 302:

Injection site discomfort was evaluated via the 10-point Faces Pain Scale–Revised (FPS-R) score, at 10, 30, and 180 minutes post injection in the Phase 3 Pediatric Subjects pool. Similar to the adult subjects, the maximum mean pain score was reported at 10 minutes. A single subject in 2-6 years age group at 180 minutes reported continued discomfort with a value of four (see table below). Six subjects in the 6-12 years group had a score reported at 180 minutes. These results are difficult to interpret given the limitations of the patient population (specifically the lower age groups) and the uncontrolled study design.

Table 31: Faces Pain Scale - Revised (FPS-R) Score by Age Group and by Treatment Dose for Subjects Aged 2.0-<18.0 Study 302

Age	G-Pen Dose	Statistics	FPS-R Score		
			10 minutes	30 minutes	180 minutes
2.0-<6.0 years	0.5 mg	N	7	7	1
		Mean (SD)	2.6 (1.9)	0.6 (1.5)	4.0 (NA)
		Median	2	0	4
	1.0 mg	N	13	13	6
		Mean (SD)	3.1 (3.3)	1.2 (1.5)	0.3 (0.8)
		Median	2	0	0
	1.0 mg	N	11	11	2
		Mean (SD)	1.6 (1.7)	0.5 (1.3)	0
		Median	2	0	0
	0.5 mg	N	11	11	2
		Mean (SD)	1.1 (2.1)	0.5 (2.3)	0
		Median	0	0	0

Source: Table 14.3.4.1, CSR for study 302.

Reviewer's Assessment: Similar to injection site edema, the results from the pooled adult data can be included in the Adverse reactions section of the PI.

8.6. Safety Analyses by Demographic Subgroups

The applicant performed an analysis of safety in subgroups based upon: sex, race, ethnicity, age, body mass, and disease duration of Type 1 DM.

Females had a higher incidence of TEAEs in general with G-Pen and Lilly glucagon compared to males (G-pen: 56.9% vs. 38.2 %; Lilly glucagon: 44.3% vs. 24.1%). Female subjects had a higher incidence of headache (11.1%) versus male subjects (2.2%), and a higher incidence of nausea (34.7%) versus male subjects for both products (G-pen: 34.8% vs. 26.1 %; Lilly glucagon: 32.9% vs. 14.9%). The incidence of vomiting was comparable with G-pen among females and males; while a lower incidence was reported in females vs. males with Lilly glucagon (G-pen: 18.2% vs. 14.8 %; Lilly glucagon: 5.7% vs. 12.6%, respectively).

Subjects ≤ 80 kg experienced a greater frequency of TEAEs compared to subjects > 80 kg with a greater difference observed with G-Pen vs. Lilly glucagon (G-pen: 57.0% vs. 34.6 %; Lilly glucagon: 36.5% vs. 31.6%). This pattern was observed with the incidence of nausea (G-pen: 35.6% vs. 23.4 %; Lilly glucagon: 24.3% vs. 22.8%), and headache (G-pen: 8.2% vs. 2.6 %; Lilly glucagon: 6.8% vs. 1.3%) .

No apparent differences were noted in the distribution of TEAEs in subgroups compared to the entire safety population.

The small number of non-White subjects (10.4%), and subjects > 65 years of age (9.7%) makes interpretation these subgroup results by race, ethnicity or age difficult. Similarly, the sample size for the pediatric population was too small to make any meaningful sub-group comparisons.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Long term studies in animals to evaluate carcinogenic potential have not been performed. This is acceptable, since this is not a product intended for chronic use.

8.8.2. Human Reproduction and Pregnancy

Refer to the Division of pediatric and Maternal health (DPMH) review and labeling recommendations dated April 10, 2019.

There are limited human pregnancy outcome data for glucagon in the published literature. There have been no reports of cases related to pregnancy, lactation, or effects on fertility reported to the Applicant or collected during clinical studies of G-Pen. The findings in animal studies with animal-sourced glucagon did not indicate a risk to the fetus. There is also very little human data available on the effect of glucagon on fertility.

There are no data on the presence of glucagon in animal or human milk. The high molecular weight (~3483 Daltons) would be expected to limit transfer of the drug into breastmilk. The very short half-life (8-32 minutes) would also limit any absorption of the product from the infant's gut.

Reviewer's Comment: Since this a single-use product for a potentially life-threatening condition, the benefits would outweigh any associated risk to the mother or fetus.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Pediatric Assessment was included with the submission. There were no assessments of growth effects, which is acceptable since this is a single-use product for emergency treatment of severe hypoglycemia.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There appears to be no potential for overdosing this single use product. No studies to assess the abuse potential or effects of withdrawal/rebound of G-Pen have been conducted. G-Pen is not likely to be abused since glucagon does not produce dependence effects.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable, since G-pen has not been approved for marketing in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

Refer to Section 7.2.1 for considerations for benefit in post-market setting. As mentioned in Section 2.2, there are reports of medication errors with the approved glucagon products from injection of the diluent alone without the glucagon powder. Potential for medication errors would theoretically be less with G-Pen. In addition to the rarer serious adverse events for all glucagon products (discussed in Section 8.4.4), the main concern is delayed recovery from hypoglycemia compared to the approved injectable products. This can be addressed by product labelling (discussed in Section 11)

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were raised by other disciplines.

8.10. Integrated Assessment of Safety

The adult Phase 3 Type 1 DM pool consisted of 154 patients in the G-Pen sequence and 157 patients in the Lilly sequence. A total of 11 subjects aged 12-18 years received single doses of G-Pen 1 mg and 31 subjects received single doses of G-Pen 0.5 mg in pediatric Study XSGP-302. The adult and pediatric safety database in this clinical program seems adequate for evaluation of common adverse events with administration of G-Pen.

There were no deaths in the clinical program. There was one SAE of vasovagal syncope two following glucagon administration in phase 2 study 202 which was attributed to study procedures. There were no reported discontinuations due to adverse events.

As expected, the most common G-Pen TEAEs were in the Gastrointestinal Disorders SOC, with a slightly higher incidence of nausea (29.9% versus 22.9%, respectively) and vomiting (16.2% versus 9.6%, respectively) compared to Lilly glucagon treatment. Headaches were also numerically more frequent following G-pen treatment (G-pen 8 [5.2%], Lilly-6 [3.8%]). All these events were reported as mild or moderate in severity.

Injection site pain was reported as an AE in 2 (1.3%) of G-Pen treated subjects. However, in the investigator reported assessment of local tolerability, moderate and severe injection site edema at 30 minutes was reported in 5.2% and 1.3% of G-Pen treated subjects respectively compared with none in the Lilly glucagon treatment sequence. Similarly, the mean pain score was higher with G-pen compared with Lilly glucagon at 10 minutes. However, by 30 minutes, the pain scores were zero in both treatment groups. These AEs can be included in the adverse reactions section of the PI.

Overall, except for a numerically higher incidence of nausea/vomiting and injection site edema/pain, the common adverse event profile of G-Pen was consistent with approved glucagon products.

The adverse event profile in the pediatric studies was similar to the AEs observed in the phase 3 study. No new safety issues of concern were observed.

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee conducted for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling negotiations with the applicant are ongoing at this point. Major changes will be as follows:

- Mitigate the risk of a delay in treatment effect by advising providers to instruct caregivers/patients to seek immediate emergency assistance after administration of G-Pen for severe hypoglycemia. This would be consistent with the PI of approved products
- The primary endpoints in Section 14 should be the alternative composite endpoint (i.e.

number (%) of patients attaining a plasma glucose of over 70 mg/dL or an increase in plasma glucose of over 20 mg/dL in 30 minutes overall and for individual components).

- Include information on mean time to achieve plasma glucose > 70 mg/dL or increase in plasma glucose > 20 mg/dL for G-Pen vs. Lilly glucagon in section 14 (see section 7.1.5 and 7.3).
- Include information on the incidence of injection site edema.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Since this is an emergency use product for severe hypoglycemia, the main safety concerns identified are a comparative delay in effect (i.e. increase in blood glucose) for G-pen compared with Lilly Glucagon, and adequate training/education for use and effects of glucagon by caregivers and non-medical personnel in contact with the patient. It was felt that this can be adequately addressed by product labeling instructing providers to educate/train caregivers and patients prescribed G-Pen about the proper use of the product and effects; and to immediately seek emergency assistance after administering G-pen. Therefore, it was determined that a REMS was not necessary.

12. Postmarketing Requirements and Commitments

There were no clinical issues identified that should be addressed by a post-marketing PMR or PMC.

13. Appendices

13.1. References

Relevant references have been included as footnotes in each section.

13.2. Financial Disclosure

Clinical Review
 {Suchitra Balakrishnan, MD, Ph.D. }
 {NDA212097}
 {G-voke HypoPen and PFS, Glucagon injection}

The applicant provided a list of all principal investigators and sub-investigators who participated in the six clinical trials of G-Pen sponsored by Xeris. The Applicant certified that it has a completed financial disclosure form on file for all listed investigators, none of whom reported disclosable financial arrangements or information

Covered Clinical Study (Name and/or Number): XSGP301 and 303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>23 (Principal Investigator)</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>none reported</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>none reported</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NA Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

SUCHITRA M BALAKRISHNAN
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08/30/2019 10:19:11 AM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2018-301
IND/NDA/BLA Number/ Referenced IND for NDA/BLA:	NDA 212097 / ref IND 115091
Sponsor/Applicant:	Xeris Pharmaceuticals, Inc.
Established Name/Trade Name:	Glucagon injection
Indication:	Treatment of severe hypoglycemia
Meeting Type/Deliverable:	Internal review and advice to the division
Review Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Reviewer	Suchitra Balakrishnan
Clinical Team Leader (TL)	Mitra Rauschecker
Review Division Project Manager:	Liz Godwin
COA Reviewer:	Susan Pretko
COA TL:	Wen-Hung Chen
COA Associate Director:	Elektra Papadopoulos
Date Consult Request Received:	10/09/2018
Date COA Review Completed:	05/07/2019

Please check all that apply:

- ☐ Rare Disease/Orphan Designation
☐ Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 212097 for glucagon injection. The sponsor has completed phase 3 clinical trials of their drug development program and has submitted an application for regulatory approval. The proposed indication is treatment of severe hypoglycemia .

The applicant proposes description in the label of the following patient-reported outcome (PRO) obtained in two non-inferiority, randomized, controlled, double-blinded, 2-treatment, 2-way crossover comparative efficacy and safety phase 3 studies in subjects, age 18-75 years, with Type 1 diabetes (T1D).

Table 1. COA Included in the Phase 3 studies, study 301 and 303

COA Name (COA Type)	Concept(s)	Endpoint Position ¹	Copy of COA
Hypoglycemia Symptom Questionnaire (HSQ; PRO)	Symptoms of hypoglycemia	Secondary	Appendix 1

This submission included an NDA package. The Division seeks COA Staff input on clinical utility of this symptom questionnaire for assessment of efficacy in the treatment of hypoglycemia.

¹ Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

The review concludes that the proposed HSQ is not fit-for-purpose² for the intended context of use (see Section 3 of this review) to support regulatory labeling. A brief summary of the review conclusions is below.

- The HSQ appears to have face validity in term of including symptoms that are related to hypoglycemia events. However, it is inappropriate for use as a PRO measure in the context of induced hypoglycemia to assess symptoms as patients in a state of or recovering from hypoglycemia would likely not be able to provide reliable ratings of their symptoms either physically or verbally.
- The HSQ is intended to be a PRO and that only the patients are able to respond to the questions about the symptoms. The instruction for completing the HSQ for this study was unclear regarding the situation(s) when the site personnel should complete the questions for the patients. As a result, the majority of the HSQ was completed by the site personnel which makes it difficult to conclude that the HSQ data showed that the patients experienced resolution of hypoglycemia symptoms. The instruction, *"If a subject is unable to physically complete the questionnaire"*, is insufficient as "unable to physically complete" is too vague and should be further defined and clarified.
- The HSQ data may be more appropriate to inform drug safety instead of efficacy in the intended context of use for this NDA submission.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Background:

- Regulatory Background
The sponsor submitted a New Drug Application (NDA) for G-Pen (glucagon injection) under the 505(b)(2) application pathway and is relying on FDA's previous findings of safety and effectiveness for Glucagon (glucagon injection) (NDA 020928, Eli Lilly & Co.).
- Previous COA Reviews
There are no previous COA reviews for the reference IND.
- Disease Background
Hypoglycemia in diabetes is defined as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm", and manifests clinically as diaphoresis, pallor, nausea, palpitations, tremor, anxiety, cognitive impairment, behavioral changes and psychomotor abnormalities, and loss of consciousness, seizure, and coma in severe hypoglycemia
- Investigational Product

²Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; <https://www.ncbi.nlm.nih.gov/books/NBK338448/>)

Glucagon is a peptide secreted by the alpha cells of the islets of Langerhan's in the pancreas, and functions as an anti-hypoglycemic agent and a gastrointestinal motility inhibitor. Administration of glucagon with current products (i.e. Lilly Glucagon for Injection, and Novo GlucaGen®) is a nine-step process including assembly of the kit, aqueous reconstitution of the powdered glucagon, and manual administration of the dose.

G-Pen™ is a glucagon rescue pen that is simple and ready-to-use for episodes of severe hypoglycemia. It will be offered in two pre-filled syringes containing 0.5 mg for pediatric patients and 1 mg for patients 12 years and older. The sponsor has described that the simplified administration process will hasten recovery from hypoglycemia.

- Other materials reviewed:
 - Xeris submission, received 04/18/2019, SDN 0028 (29) containing HSQ Supplemental tables (IR Response).
 - Xeris submission, received 02/15/2019, SDN 0020 (21) containing HSQ Supplemental tables (IR Response).
 - Xeris submission, received 12/28/2018, SDN 0014 (15) containing the draft label.
 - Xeris submission, received 08/10/2018, SDN 0000 (1) containing the following:
 - Phase 3 study protocols: PROTOCOL XSGP-301 and PROTOCOL XSGP-303.
 - Integrated Summary of Efficacy (ISE) data tables.
 - Statistical Analysis Plans for the Summary of Clinical Efficacy (Section 2.7.3 ISE)

2 FIT-FOR-PURPOSE SUMMARY

Table 2. Fit-for-purpose assessment (based on available evidence)

COA Name(s)	Attribute sufficiently established ³	Supported by:	Location of Supporting Materials
Hypoglycemia Symptom Questionnaire (HSQ)	☐ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☒ No	☐ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☐ Evidence of content validity ☒ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☐ COA well-defined and concept is able to be accurately communicated ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	Study 301 Protocol, Appendix 1

Reviewer's Comment(s):

³ See Sections 5 and 6 of this COA review for more detailed information.

Refer to the reviewer's comments in Section 7. Content Validity, for more detailed comments on the content validity of the HSQ. Although the HSQ appears to have face validity, concerns with how the HSQ was administered in the study and whether it can appropriately and reliably capture patient-reported symptoms leads this reviewer to believe that it is not fit for purpose in the intended context of use.

Given concern that patients in a hypoglycemic state may not be able to report symptoms of hypoglycemia in a reliable and interpretable way, this reviewer believes that a clinician-reported outcome (ClinRO) may be more appropriate to assess hypoglycemic symptoms. In addition, such data may be more appropriate for use to inform drug safety in the intended context of use for this NDA submission.

3 CONTEXT OF USE

The sponsor completed two Phase 3 studies (studies 301 and 303) to demonstrate efficacy and safety of their product in adult patients with Type 1 Diabetes Mellitus (T1D).

3.1 Clinical Trial Population

The clinical trial population for Studies 301 and 303 and were adult patients aged 18-75 years, inclusive, diagnosed with T1D for at least 24 months. Study 301 was conducted in 8 sites in North America and study 303 was conducted in 6 sites in North America.

A complete list of the inclusion and exclusion criteria can be found in the clinical trial protocols.

3.2 Clinical Trial Design

Tables 3 and 4 describe the study designs for studies 301 and 303.

Table 3. Clinical Trial Design for Study 301

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☐ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☒ Cross-over ☐ Multinational ☒ Non-inferiority	2 to 15 weeks	Yes

Table 4. Clinical Trial Design for Study 303

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm	12 to 65 days	Yes

Trial Phase	Trial Design	Trial Duration	Registration Intent
	☐ Open label ☐ Double-blind ☒ Randomized ☐ Placebo-/Vehicle-controlled ☒ Active comparator-controlled ☒ Cross-over ☐ Multinational ☒ Non-inferiority		

Refer to the clinical study protocols for more details on the clinical trial design.

Reviewer's Comment(s):

The randomized treatment sequence is shown below (Table 3 from the study 301 and 303 protocol). Two episodes of insulin-induced hypoglycemia (plasma glucose < 50.0 mg/dL) were induced in random order and subjects received 1mg G-Pen™ during 1 episode and 1mg of the comparator product (Lilly Glucagon) during the other episode. Glucagon was administered at least 5 minutes after the initial reading < 50.0 mg/dL. Blood glucose levels were monitored for 90 minutes post-dosing in study 301 and for 180 minutes post-dosing in study 303.

Group	Dose 1	Dose 2
1	G-Pen™ 1 mg	Lilly 1 mg
2	Lilly 1 mg	G-Pen™ 1 mg

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 5 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for the phase 3 studies.

Table 5. Endpoint Position, Definition, and Assessment Schedule for Study 301 and Study 303

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Primary (COA and/or biomarker)	Plasma glucose	Failure to recover from hypoglycemia	Failure to recover from hypoglycemia (return to plasma glucose > 70 mg/dL) throughout the 0 to 30-minute period from the administration of study drug	☒ Other: Every 5 minutes following administration of glucagon

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary	Hypoglycemia Symptom Questionnaire (HSQ; PRO)	Symptoms of hypoglycemia	Neuroglycopenic symptoms, Autonomic symptoms, and Overall Assessment of Hypoglycemia*	☒ Other: Every 5 minutes following administration of glucagon

* Refer to the reviewer's comments below for discrepancies in how the secondary endpoint based on the HSQ was defined.

Reviewer's Comment(s):

Per the study protocol for studies 301 and 303, the HSQ was administered to rate severity of hypoglycemia symptoms at the following time points:

- Just before the IV bolus push dose of insulin is given at the start of the hypoglycemia induction procedure.
- Every time blood is drawn for evaluation of plasma glucose concentration during the induction procedure.
- Just before study drug is administered.
- Every 5±2 minutes after glucagon is administered, until all symptoms have abated (i.e., all symptoms have score = 1) or 45 minutes post-dosing, whichever occurs first.

For study 303, HSQ was administered until all symptoms abated or 90 minutes post-dosing, whichever occurred first. The HSQ was also administered every 30 minutes (coinciding with plasma glucose measurements) between 90-180 minutes post study drug dosing, or until all symptoms abated (i.e., all symptoms have score = 1).

Based on this information, subjects should have a score of 1 for all hypoglycemia symptoms to consider hypoglycemia symptoms abated. However, the ISE SAP only refers to the symptoms in the Neuroglycopenic Symptom domain and describes symptom relief for a subject as a return to an aggregate score that was no more than one unit just above minimal aggregate score prior to receiving glucagon.

3.4 Labeling or promotional claim(s) based on the COA

Table 3 below from the draft label submitted by the sponsor shows the specific targeted COA-related labeling claims, for section 14 of the label.

Table 3: Summary of Efficacy Response Rates of PRODUCT NAME and GEK				
Clinical Study Endpoint	Response Rate-Study A		Response Rate-Study B	
	PRODUCT NAME	GEK	PRODUCT NAME	GEK
Subjects successfully rescued from induced hypoglycemia without other rescue therapy (e.g., intravenous dextrose).	100% (78/78)	100% (79/79)	100% (76/76)	100% (78/78)
Resolution of hypoglycemia symptoms	100% (78/78)	100% (79/79)	100% (76/76)	100% (78/78)
Global feeling of hypoglycemia improvement pre/post injection	100% (77/77)	100% (79/79)	100% (73/73)	100% (76/76)
Plasma glucose of >70 mg/dL or resolution of all induced neuroglycopenic symptoms within 30 minutes post injection	100% (78/78)	100% (79/79)	100% (76/76)	100% (78/78)
Plasma glucose of >70 mg/dL or $\geq$ 20 mg/dl increase by 30 minutes post-injection	Intent-to-treat 97.4% (76/78)	Intent-to-treat 100% (79/79)	Intent-to-treat 100% (76/76)	Intent-to-treat 100% (78/78)
	Per-protocol 97.4% (75/77)	Per-protocol 100% (78/78)	Per-protocol 100% (73/73)	Per-protocol 100% (73/73)
Sustained glucose elevation from [0-90] minutes post-injection.	100% (78/78)	100% (79/79)	100% (76/76)	100% (78/78)
Mean time to initial symptom relief				
- Autonomic	Not evaluated	Not evaluated	9.9 min	9.8 min
- Neuroglycopenic	Not evaluated	Not evaluated	10.3 min	9.9 min
Mean time to complete symptom resolution				
- Autonomic	15.4 min	14.2 min	13.8 min	12.0 min
- Neuroglycopenic	16.3 min	13.9 min	14.2 min	12.2 min

Reviewer's Comment(s):

Per discussion at the internal labeling meeting on 04/03/2019, the following issues were raised regarding Table 3:

- 1. No timepoints are included in the table; therefore, interpretation of the data is unclear.***
- 2. This reviewer does not agree with the sponsor's claims that 100% of subjects experienced resolution of hypoglycemia symptoms, nor that 100% of subjects experienced a global feeling of hypoglycemia symptom improvement, based on the following:***
 - a. The pooled analysis of data from studies 301 and 303 (table 3.5.1 from the ISE, below) showed that not all subjects reported neuroglycopenic symptom relief 30-minutes post-dose.***

Table 3.5.1 Number of Subjects with Neuroglycopenic Symptom Relief Within 30 Minutes: Adult Phase 3 Type 1 Diabetic Subjects Modified Intent-to-Treat Population		
Pooled Analysis (301, 303)		
Time Point	G-Pen (N=154)	Lilly (N=157)
Within 30 mins post-dose	131 (85.1)	129 (82.2)

Note that the information provided describes between-group differences rather than within-patient clinically meaningful change.

4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

Table 5. Concepts of Interest for COAs Included in Studies 301 and 303

COA name	Concept(s)
Hypoglycemia Symptom Questionnaire (HSQ)	Symptoms of hypoglycemia

The conceptual framework for the HSQ is shown in Table 6.

Table 6. Conceptual Framework for the HSQ

Item	Domain (if applicable)	General Concept
Dizziness	Neuroglycopenic symptoms	Symptoms of hypoglycemia
Blurred Vision		
Difficulty in thinking		
Faintness		
Sweating	Autonomic symptoms	
Tremor		
Palpitations		
Feeling of nervousness		
Overall Assessment of Hypoglycemia	Overall feeling of hypoglycemia	

5 CLINICAL OUTCOME ASSESSMENT(S)

Hypoglycemia Symptom Questionnaire (HSQ)

The HSQ is intended to measure hypoglycemia symptom relief from just after the decision to dose with glucagon to 90 minutes (study 301) or 180 minutes (study 303) post-dose. The HSQ has 8 items that each assess the current intensity (severity) of hypoglycemic symptoms on a scale of 1-6, with a minimum score of “1” indicating the symptom was absent and a maximum score of “6” indicating the symptom was severe. A final item assesses overall feelings of hypoglycemia and asks, “Do you currently feel hypoglycemic?” Responses are recorded as “yes” or “no”.

Reviewer’s Comment(s)

Based on the HSQ instructions, the subject should complete the HSQ. However, if a subject is unable to physically complete the questionnaire, the subject will provide verbal responses, which will be recorded on the questionnaire by study staff. Documentation will be provided on each completed questionnaire as to who completed the form. Refer to the reviewer’s comments in section 7 on who completed the HSQ in the clinical trials.

6 SCORING ALGORITHM

HSQ

The HSQ has 4 items in the Neuroglycopenic Symptoms domain and 4 items in the Autonomic Symptoms domain. Each item is scored according to severity, where higher scores reflect a worse severity. The possible score range for each item is 1-6 and for each domain is 4-24. An average score may be calculated for each domain, and a total average score may be calculated by combining the scores from both domains, producing a possible score range of 4-24. The item on “Overall Assessment of Hypoglycemia” captures the response as a categorical variable and thus is meant to be assessed descriptively.

Reviewer’s comment(s):

The SAP for Studies 301 and 303 stated that the average Neuroglycopenic, Autonomic and Total Symptom scores (ANS, AAS and ATS, respectively) would be described descriptively. The “Overall Assessment of Hypoglycemia” would be treated as a categorical variable, and the time to first reporting of “no” for the global hypoglycemia questionnaire would be calculated and compared between treatment groups. However, the sponsor only included the Neuroglycopenic domain in the ISE SAP.

Per the ISE SAP, only the number of subjects experiencing relief from neuroglycopenic symptoms within 30 minutes of the injection of study medication was assessed. Symptom relief of hypoglycemia for a subject was defined as a return to an aggregate score that was no more than one unit above minimal aggregate score prior to receiving glucagon.

7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒ Copy of instrument
- ☐ Literature review and/or publications
- ☐ Documentation of expert input
- ☐ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☐ Synopsis of qualitative findings
- ☐ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- ☐ Quantitative summary report with evidence to support item retention and scoring
- ☐ Transcripts (if available)

Table 7 documents the adequacy of the content of the HSQ.

Table 7. Review of Content Validity for the HSQ.

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☐ Literature ☒ Clinical input e.g. discussion with	Internal Meetings

		clinical reviewer	discussion with the medical officer
Content validity	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☐ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☐ Target sample for qualitative research is appropriate. ☐ Studied sample for qualitative research adequately represents the target patient population ☐ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☐ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☐ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☐ Other (see Reviewer's comments)	Supporting evidence was not provided by the applicant

Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.

Reviewer's comment(s):

Based on discussion with the medical officer, the content of the HSQ appears appropriate. However, patients in a state of hypoglycemia may not be able to provide valid and reliable responses due to neuroglycopenic symptoms. Although the HSQ instructions indicate that site-personnel will record subject verbal responses if the subject is unable to physically complete the questionnaire, it is unclear whether subjects will be able to reliably rate their symptoms. In addition, qualitative evidence to support the content of the HSQ (including item stems, response options, and information to justify scoring) was not submitted.

On January 31, 2019 an IR was sent to the sponsor for documentation to support the content validity of the HSQ. The exact language in the IR can be found below.

1. Submit descriptive statistics for individual items of the hypoglycemia symptom questionnaire (HSQ) for studies 301 and 303. Separate this data by patient response and site personnel response. Include frequencies of item responses, floor and ceiling effects, and percentage of missing data. Include this information for each time the HSQ is administered.
2. Submit the proportion of HSQ responses that were reported by the patient or by study personnel. Include this information for each time the HSQ is administered.
3. Submit evidence to support the development history, content validity, and measurement properties of the HSQ. Include evidence that patients can reliably respond to the overall assessment of hypoglycemia, “Do you currently feel hypoglycemic?”
4. Submit screenshots of the hypoglycemia symptom questionnaire as it was administered to patients.
5. Submit information on training methods and/or training materials that were provided regarding the HSQ in your phase 3 studies.

The sponsor provided a response on February 15, 2019, that addressed items 1 and 2. Refer to the reviewer’s comments in section 9 for more information. However, the sponsor did not provide information to address items 3, 4, and 5. Therefore, this reviewer is unable to determine that the HSQ has content validity. It is unclear whether subjects are able to respond to the HSQ and following discussion with the division, some patients may still experience symptoms of hypoglycemia with plasma glucose levels of 80. In addition, without information on the training methods/materials, this reviewer does not have confidence that the HSQ was administered as described by the sponsor. This reviewer does not agree that the HSQ is fit for regulatory purposes in the stated context of use.

8 OTHER MEASUREMENT PROPERTIES

The sponsor did not submit a quantitative analysis plan, nor a summary report with evidence to support reliability, construct validity, ability to detect change, and scoring.

Reviewer’s comment(s):

Due to insufficient evidence to support the measurement properties of the HSQ, this reviewer does not agree that the HSQ is well-defined and reliable.

9 INTERPRETATION OF SCORES

The applicant did not provide documentation to support the adequacy of the score interpretability of the HSQ (e.g., anchor-based analyses, qualitative support for meaningful change, etc.)

D. APPENDICES

Appendix 1. Hypoglycemia Symptom Questionnaire

Appendix 1. Hypoglycemia Symptom Questionnaire (HSQ)

Investigative Site Instructions: The subject should complete the Hypoglycemia Symptom Questionnaire at the following time points:

- Just before the IV bolus push dose of insulin is given at the start of the hypoglycemia induction procedure.
- Every time blood is drawn for evaluation of plasma glucose concentration during the induction procedure.
- Just before study drug is administered.
- Every 5±2 minutes after glucagon is administered, until all symptoms have abated (i.e., all symptoms have score = 1) or 45 minutes post-dosing, whichever occurs first.

Note: If a subject is unable to physically complete the questionnaire, the subject will provide verbal responses, which will be recorded on the questionnaire by study staff. Documentation will be provided on each completed questionnaire as to who completed the form.

Subject Instructions: Please rate the current intensity (severity) of each of the following symptoms on a scale of 1-6, with a minimum score of “1” meaning the symptom was absent and a maximum score of “6” meaning the symptom was severe. For the final question, please answer “yes” or “no.”

Neuroglycopenic Symptoms	Severity Score (1-6)
Dizziness	
Blurred vision	
Difficulty in thinking	
Faintness	
Autonomic Symptoms	Severity Score (1-6)
Sweating	
Tremor	
Palpitations	
Feeling of nervousness	
Overall Assessment of Hypoglycemia	Yes/No
Do you currently feel hypoglycemic?	

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/

SUSAN M PRETKO
05/21/2019 09:38:24 AM

WEN-HUNG CHEN
05/21/2019 09:50:02 AM

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