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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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Applicant's letter date:	08/09/2018
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Product:	G-Pen (Glucagon injection)
Indication:	Treatment of severe hypoglycemia (insulin coma or insulin reaction)
Applicant:	Xeris Pharmaceuticals
Review Division:	Division of Metabolism and Endocrinology
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1 Executive Summary

1.1 Introduction

Xeris Pharmaceuticals, Inc. seeks to market glucagon solution for injection for the treatment of severe hypoglycemia. Xeris Pharmaceuticals' formulation is stable and can be pre-loaded into syringes, unlike previous formulations that require reconstitution before administration.

Xeris glucagon drug substance is produced by solid-phase peptide synthesis (SPPS) and conserves the natural glucagon peptide sequence. Xeris is pursuing the 505(b)(2) regulatory pathway and is relying on safety information for Lilly glucagon (NDA 20928).

1.2 Brief Discussion of Nonclinical Findings

Toxicology, pharmacokinetic and local tolerance studies were performed to compare profiles for Xeris (G-Pen test article) and Lilly (comparator) glucagon and to qualify potential impurities after deliberate degradation designed to simulate the product at the end of its shelf life. Both acute and sub-chronic studies in rats indicate that Xeris and Lilly glucagon were well tolerated and had similar toxicity profiles. A chronic 14 day repeat dose study in rats resulted in minimal to marked, reversible injection site reactions that appeared to be more severe after the recovery period in high dose (HD) Xeris glucagon-treated rats 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). Impurities present in deliberately degraded Xeris glucagon did not have a profound effect on the toxicological profile of G-Pen, as the majority of observations seen after repeated daily administration had been observed previously.

Despite large inter-animal variability, single and repeated administration of Xeris G-Pen tended to have higher C_{max} (fold increase ranged between 1.1 and 2.0x) and AUC_{0-t} (fold change ranged between 1.1 and 3.1X) values when compared to Lilly Glucagon. However, the increased systemic exposure did not result in remarkable differences in the toxicology profile or pharmacodynamic response (as measured by the increase in glucose levels) between the two formulations. A unique finding in the liver after treatment with Xeris glucagon (increased liver weights and liver weight ratios that correlated with minimal to moderate glycogen-type vacuolation and minimal to mild subcapsular necrosis) has been previously reported after exposure to glucagon (Arstila and Trump 1968) and is not thought to occur due to formulation differences.

In conclusion, nonclinical data support approval of Xeris Glucagon. Changes in Labeling for Sections 8 and 13 are indicated below.

1.3 Recommendations

None.

1.3.1 Approvability

Pharmacology/Toxicology recommends the approval of G-Pen.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In a rat reproduction study, no embryofetal toxicity was observed with glucagon administered by injection during the period of organogenesis at doses representing up to 40 times the human dose, based on body surface area (mg/m^2) (see *Data*).

Animal data

In pregnant rats given animal sourced glucagon twice-daily by injection at doses up to 2 mg/kg (up to 40 times the human dose based on body surface area extrapolation, mg/m^2) during the period of organogenesis, there was no evidence of increased malformations or embryofetal lethality.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals to evaluate carcinogenic potential have not been performed. Recombinant glucagon was positive in the bacterial Ames assay. It was determined that an increase in colony counts was related to technical difficulties in running this assay with peptides. Studies in rats have shown that glucagon does not cause impaired fertility.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional) 16941-32-5

Generic Name: Glucagon, Glucagon (1-29) (human)

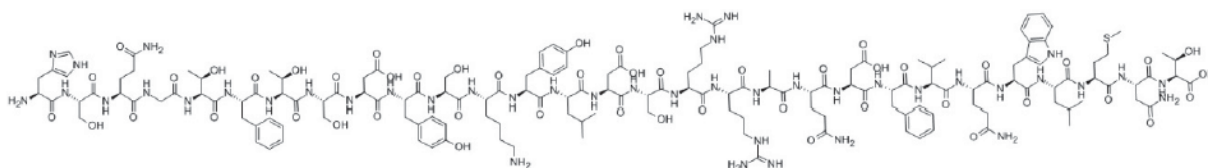
Code Name: G-Pen

Chemical Name: Glucagon

Molecular Formula/Molecular Weight: C₁₅₃H₂₂₅N₄₃O₄₉S/3482.8 g/mol

Structure or Biochemical Description: Glucagon is a 29 amino acid (non-steroidal) hormone. Glucagon drug substance used in the G-Pen (glucagon injection) drug product is produced under Solid Phase Peptide Synthesis.

NH₂-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-COOH.



Pharmacologic Class: Anti-hypoglycemic agent and gastrointestinal motility inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

	Product Name	Sponsor	Indication	Status
INDs				
115091	Glucagon	Xeris Pharmaceuticals	Treatment of hypoglycemia	Active

(b) (4)

(b) (4)				
NDAs				
20928	Glucagon	Eli Lilly and Co	Treatment for severe hypoglycemia	Approved
20918	Glucagen (Glucagon)	Novo Nordisk Pharmaceuticals	Treatment for severe hypoglycemia	Approved
DMFs				
(b) (4)				
(b) (4)	Glucagon	Bachem AG	N/A	Active

2.3 Drug Formulation

Table 1: Quantitative Composition of G-Pen Formulation 1 mg and 0.5 mg

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

¹ Overfill to guarantee label claim

Table copied from the Sponsor's submission.

2.4 Comments on Novel Excipients

The acute subcutaneous use of (b) (4) mg DMSO and (b) (4) mg trehalose has been qualified in the nonclinical studies conducted.

2.5 Comments on Impurities/Degradants of Concern

Glucagon used in G-Pen is manufactured by Bachem AG (DMF (b) (4)) and is cGMP-grade. All impurities listed in the Bachem Type II DMF for glucagon are within the ICH Q3A identification and qualification thresholds. In contrast to Bachem, which uses solid

phase peptide synthesis to manufacture glucagon, Eli Lilly (NDA 20928) isolate recombinant glucagon from cultures. Therefore, the Bachem glucagon peptide includes

(b) (4)

All identified process-related substances/degradation products were below the 0.15% threshold described in the ICH Q3A guidance.

Degradants

Potential degradants in the G-Pen formulation included peptide fragments that were not expected to have altered activity or altered toxicity from the parent peptide.

Extractables and Leachables

Three leachable compounds were detected in the glucagon drug product under accelerated stability conditions that were not listed in the internal Inactive Ingredient Database and exceeded the threshold in the ICH Q3A guidance.

(b) (4)

¹ <https://echa.europa.eu/registration-dossier/-/registered-dossier/13491/7/9/1>

findings are common after exposure to glucagon and are not thought to be due to exposure. (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The product will be administered subcutaneously to treat insulin coma or insulin reaction resulting from severe hypoglycemia as a subcutaneous injection on an as-needed basis.

Adults and adolescents ≥ 12 years: 1 mg (0.2 mL),

Children < 12 years that weigh < 45 kg (100 lbs): 0.5 mg (0.1 mL),

Children < 12 years that weigh ≥ 45 kg (100 lbs): 1 mg

Glucagon is contraindicated in patients with known hypersensitivity to glucagon or any other constituents in the product, pheochromocytoma or insulinoma.

2.7 Regulatory Background

IND 115091 for the development of G-Pen (glucagon injection) as a single-use disposable rescue injection for treatment of severe hypoglycemia in patients with diabetes was submitted to the FDA on January 7, 2013.

At the End of Phase 2 Meeting on July 28, 2014, FDA indicated that the nonclinical studies provided were sufficient to support the acute subcutaneous use of G-Pen for a 505(b)(2) NDA and to support the use of DMSO and trehalose excipients at the proposed levels.

On April 29, 2015, PeRC concurred with an initial Pediatric Study Plan (iPSP) to waive treatment for patients less than 2 years of age. An iPSP was agreed upon on March 27, 2015 and Xeris completed a study to examine the pharmacodynamics of age-appropriate doses of G-Pen in pediatric patients aged 2-17 years.

Following a meeting to discuss CMC development of the G-Pen (February 10, 2016), Xeris provided long-term stressed stability data for G-PEN in commercial prototype (syringe) cartridges. The study was performed in rats with deliberately degraded product (designed to simulate the product at the end of its shelf-life) to qualify potential impurities in the test article (Study #: TX17-GPEN01).

The formulation of G-Pen was modified between Phase 2 and Phase 3 clinical trials (b) (4)

On August 10, 2018, Xeris submitted an NDA for G-Pen using the 505(b)(2) regulatory pathway that included reference to Bachem glucagon DMF # (b) (4) for glucagon pharma grade and relied on safety information from Lilly glucagon (NDA 20928). Toxicology, pharmacokinetic and local tolerance studies were performed to compare profiles for Xeris and Lilly glucagon, qualify potential impurities after deliberate degradation and determine the local tolerance of G-Pen.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacokinetics
Pharmacokinetics of Xeris Test Article Following Administration to Male Sprague-Dawley Rats (20108166)
Toxicology
A 14-Day Toxicity Study of Glucagon and Potential Impurities by Subcutaneous Administration in Sprague-Dawley Rats (TX17-GPEN01)
A single Dose Local Tolerance Study of G-Pen™ by Subcutaneous Injection in Rabbits (TX16-GPEN-01)

3.2 Studies Not Reviewed

The following studies were previously reviewed under IND 115091 and are summarized in the General Toxicology section.

Toxicology
Pharmacokinetics and Fourteen-Day Subcutaneous Toxicity Study with Glucagon in Rats (CB12-5015-R-TX)
A 14-Day Subcutaneous Study of Xeris' Concentrated, Non-Aqueous Solution of Glucagon in Rats with a 2-Week Recovery Period Administration in Sprague-Dawley Rats (XSGPE-TX02)

3.3 Previous Reviews Referenced

IND 115091, Robert Maher, 01/16/2013, REV-NONCLINICAL-21 (Primary review)

IND 115091, Robert Maher, 09/24/2013, REV-NONCLINICAL-21 (Primary review)

4 Pharmacology

4.1 Primary Pharmacology

Glucagon acts as an anti-hypoglycemic agent by stimulating glycogenolysis and gluconeogenesis. A single subcutaneous administration of Xeris glucagon (0.24 – 2 mg/kg) produced increases in mean blood glucose concentrations that were comparable to Lilly glucagon. Increases in mean blood glucose concentrations did not occur in a dose-dependent manner. Generally, all concentrations of Xeris and Lilly glucagon resulted in similar mean blood glucose concentration time curves after a single dose indicating that both glucagon formulations may have been studied at saturating doses.

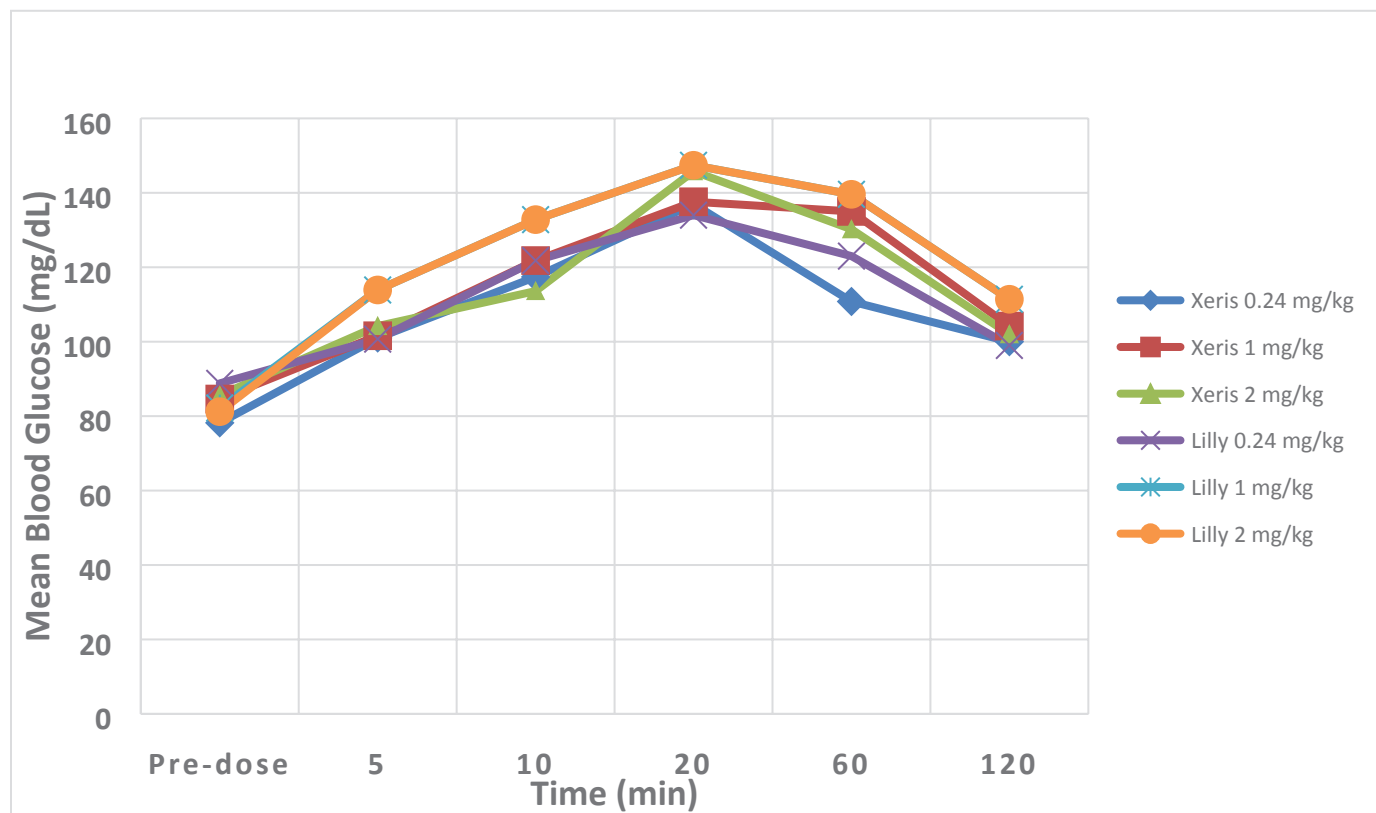
Figure 1: Blood Glucose Time Course for Males on Day 1 (Study # XSGPE-TX02)

Figure prepared by Elena Braithwaite.

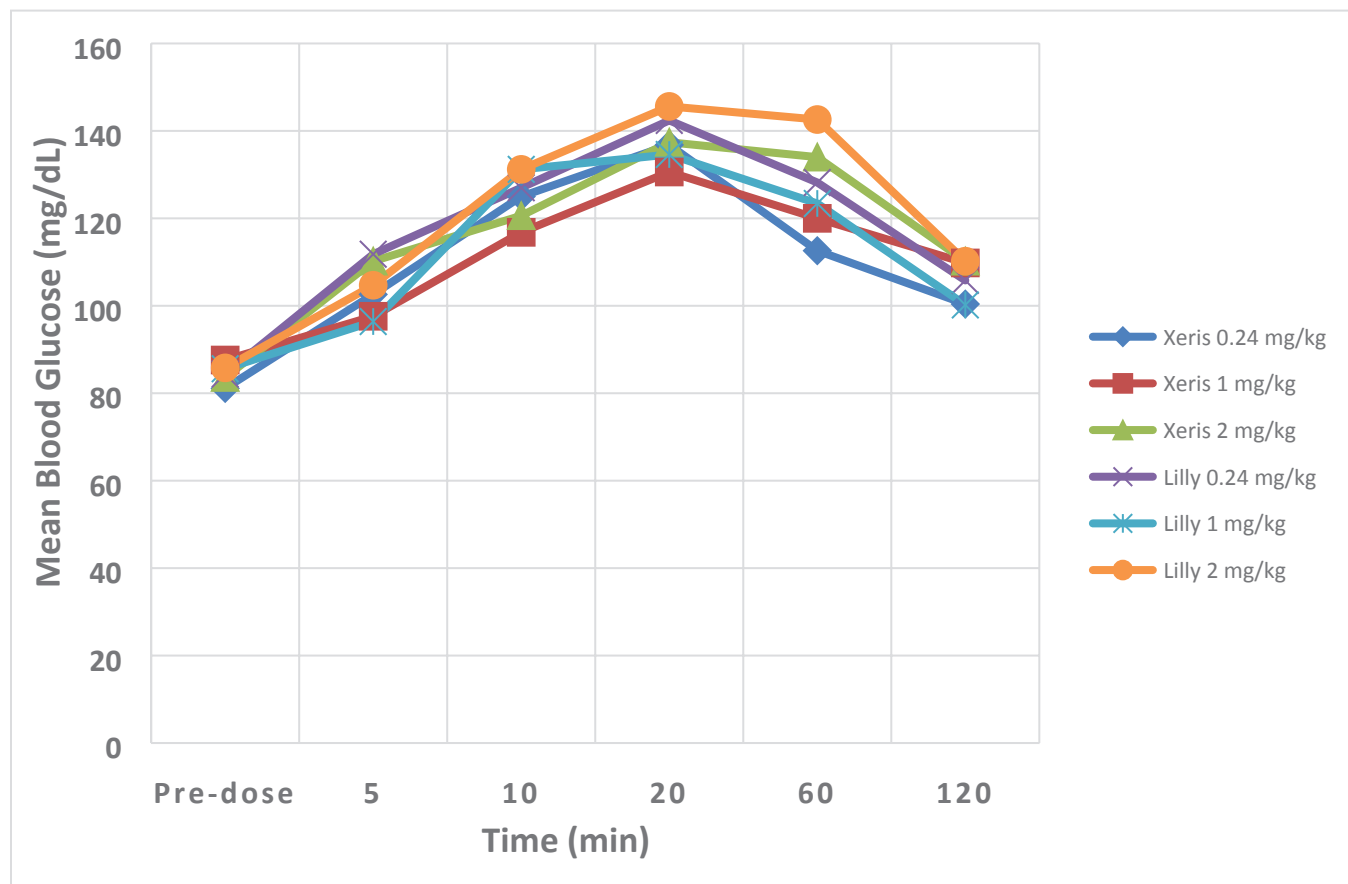
Figure 2: Blood Glucose Time Course for Females on Day 1 (Study # XSGPE-TX02)

Figure prepared by Elena Braithwaite. Blood was collected from toxicokinetic rats administered 0.24, 1, or 2 mg/kg Xeris or Lilly glucagon by subcutaneous injection and blood glucose concentrations were monitored.

Table 2: Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Xeris Glucagon on Day 14

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC _(0-t) (pg•min/mL)	AUC _(0-t) /D (pg•min/mL/mg/dose)	T _{1/2} (min)	R _{AUC} ^a
0.24	Female	10.0	31,200 $\pm$ 2840	130,000	898,000 $\pm$ 77,500	3,740,000	13.3	1.51
	Male	10.0	35,100 $\pm$ 3240	146,000	1,180,000 $\pm$ 223,000	4,920,000	13.6	2.04
1	Female	20.0	59,300 $\pm$ 9010	59,300	2,600,000 $\pm$ 220,000	2,600,000	14.5	0.945
	Male	10.0	69,300 $\pm$ 13,400	69,300	1,860,000 $\pm$ 153,000	1,860,000	14.8	0.970
2	Female	10.0	90,700 $\pm$ 21,900	45,400	4,220,000 $\pm$ 512,000	2,110,000	29.3	1.12
	Male	10.0	83,000 $\pm$ 19,900	41,500	3,430,000 $\pm$ 313,000	1,720,000	23.0	1.10

^aR_{AUC} = Day 14 AUC_(0-t)/ Day 1 AUC_(0-t).

Table 3: Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Lilly Glucagon on Day 14

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC _(0-t) (pg•min/mL)	AUC _{(0-t)/D} (pg•min/mL/mg/dose)	T _{1/2} (min)	R _{AUC} ^a	AUC _(0-t) Ratio Xeris/Lilly
0.24	Female	10.0	19,600 $\pm$ 3050	81,500	296,000 $\pm$ 29,500	1,230,000	21.5	0.885	3.03
	Male	5.00	24,100 $\pm$ 5080	100,000	383,000 $\pm$ 49,200	1,600,000	NC	0.924	3.08
1	Female	10.0	44,900 $\pm$ 2230	44,900	1,650,000 $\pm$ 217,000	1,650,000	15.4	0.823	1.58
	Male	10.0	34,900 $\pm$ 4580	34,900	1,130,000 $\pm$ 94,000	1,130,000	17.0	0.792	1.65
2	Female	10.0	85,500 $\pm$ 17,700	42,700	2,830,000 $\pm$ 343,000	1,410,000	16.4	1.10	1.49
	Male	10.0	44,300 $\pm$ 10,500	22,100	1,980,000 $\pm$ 286,000	988,000	21.3	0.719	1.73

^aR_{AUC} = Day 14 AUC_(0-t)/ Day 1 AUC_(0-t).

Tables copied from the Sponsor's submission (Tables 2.2 and 2.4 from Study #: XSGPE-TX02). Blood was collected from toxicokinetic rats administered 0.24, 1, or 2 mg/kg Xeris or Lilly glucagon by subcutaneous injection. Glucagon concentrations in plasma were evaluated using a radioimmunoassay.

4.2 Secondary Pharmacology

No secondary pharmacology studies were conducted.

4.3 Safety Pharmacology

No safety pharmacology studies were conducted.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

At similar doses, systemic exposure to Xeris glucagon was typically greater in comparison to Lilly glucagon (the comparator) as measured by C_{max} and AUC_(0-t) values. T_{max} and T_{1/2} values between the two products were similar.

The TK profile of Phase 3 formulation, without (b) (4), was similar to that of Phase 2 formulation containing (b) (4).

Table 4: Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following Subcutaneously Administered Xeris Glucagon on Day 1

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC _(0-t) (pg•min/mL)	AUC _{(0-t)/D} (pg•min/mL/mg/dose)	T _{1/2} (min)
0.24	Female	10.0	35,400 $\pm$ 5220	147,000	596,000 $\pm$ 72,700	2,490,000	13.8
	Male	10.0	31,900 $\pm$ 8670	133,000	578,000 $\pm$ 76,000	2,410,000	13.7
1	Female	10.0	105,000 $\pm$ 27,900	105,000	2,750,000 $\pm$ 184,000	2,750,000	12.2
	Male	10.0	63,100 $\pm$ 5150	63,100	1,910,000 $\pm$ 201,000	1,910,000	13.2
2	Female	20.0	85,500 $\pm$ 11,700	42,700	3,780,000 $\pm$ 365,000	1,890,000	14.6
	Male	10.0	83,200 $\pm$ 9980	41,600	3,110,000 $\pm$ 185,000	1,550,000	16.8

Table copied from the Sponsor's submission (Table 2.1).

Table 5: Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following Subcutaneously Administered Lilly Glucagon on Day 1

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC ₍₀₋₄₎ (pg•min/mL)	AUC ₍₀₋₄₎ /D (pg•min/mL/mg/dose)	T _{1/2} (min)	AUC ₍₀₋₄₎ Ratio Xeris/Lilly
0.24	Female	10.0	16,600 $\pm$ 3160	69,100	334,000 $\pm$ 44,300	1,390,000	15.1	1.78
	Male	10.0	22,800 $\pm$ 1950	95,100	415,000 $\pm$ 27,300	1,730,000	13.9	1.39
1	Female	10.0	60,400 $\pm$ 14,300	60,400	2,010,000 $\pm$ 180,000	2,010,000	14.9	1.37
	Male	5.00	50,800 $\pm$ 10,300	50,800	1,430,000 $\pm$ 156,000	1,430,000	13.7	1.34
2	Female	10.0	89,700 $\pm$ 19,400	44,800	2,570,000 $\pm$ 424,000	1,280,000	13.8	1.47
	Male	10.0	84,000 $\pm$ 32,300	42,000	2,750,000 $\pm$ 474,000	1,370,000	14.3	1.13

Table copied from the Sponsor's submission (Table 2.3).

Pharmacokinetics of Xeris Test Article Following Administration to Male Sprague-Dawley Rats

Objective:

To determine if any meaningful differences in the pharmacokinetic profile exist between the Phase 3 (new) clinical formulation (does not contain (b) (4) and utilizes sulfuric acid (u) (4) the Phase 2 (old) formulation.

Study No: 20108166

Study Report location: 4.2.2.3., SDN: 1, EDR: 0000

GLP compliance: N

Drug, lot # and purity:

Original Glucagon Formulation, Lot#: FFM-16-037-F-4, 100% pure

New Glucagon Formulation, Lot #: FFM16-038-F-3, 100% pure

(b) (4):CD(SD) Rats (♂)

Doses/frequency: 1 mg/kg / single dose

Administration: Subcutaneous

Age: Not specified

Weight: ~250 g

Vehicle: Not specified

Main: 5/group

Clinical Signs

Observations were recorded after dosing and at each sample collection time point

No clinical observations were noted.

Toxicokinetics

Serial blood samples were collected from all study animals at detailed time points.

Both formulations had similar pharmacokinetic curves.

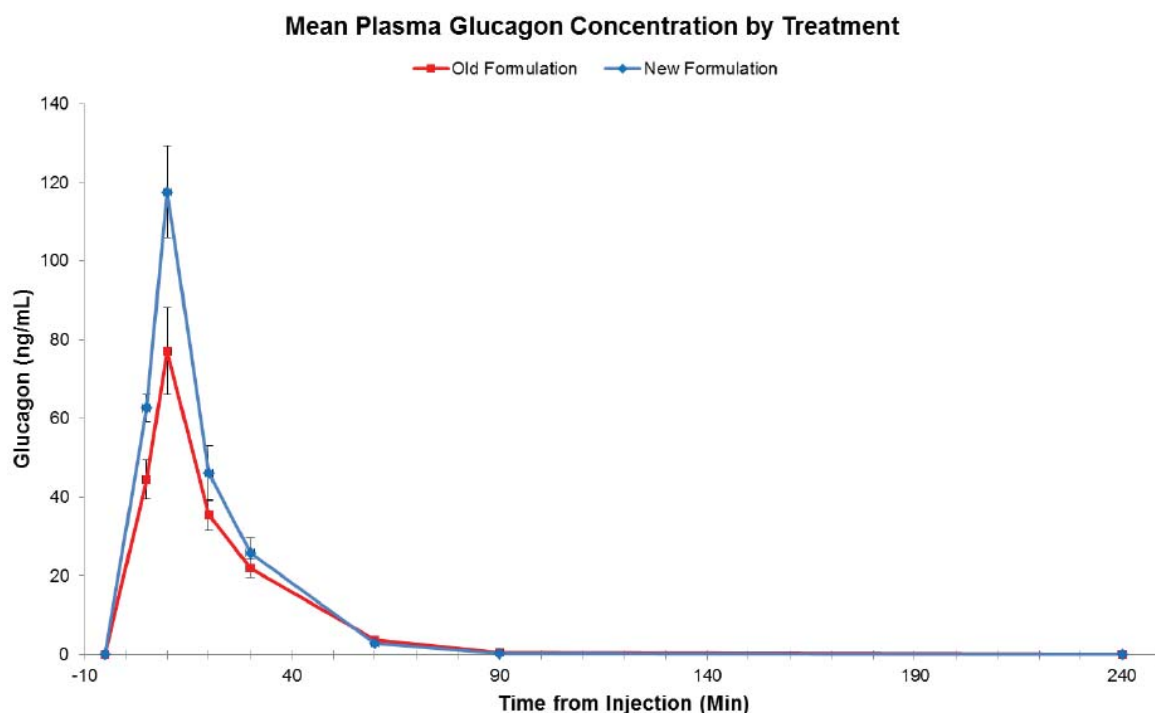
Figure 3: Comparative Glucagon AUC between Old and New Formulations of G-Pen™

Figure reproduced from the Sponsor's submission (Figure 1).

6 General Toxicology

The nonclinical program for Xeris glucagon was designed to evaluate the toxicology profile, pharmacokinetic profile, glucose response and local tolerance of Xeris glucagon when administered subcutaneously. Xeris Pharmaceuticals also compared their formulation to similar doses of Lilly glucagon (the reference product) and investigated the potential toxicity of any impurities that may develop over the shelf-life of the product.

6.2 Repeat-Dose Toxicity

Study title: A 14-Day Subcutaneous Study of Xeris Concentrated, Non-Aqueous Solution of Glucagon in Rats with a 2-Week Recovery Period and Satellite Toxicokinetic Evaluation (XSGPE-TX02)

In this 14-day repeat dose toxicity study, rats were treated with 0, 0.24, 1, or 2 mg/kg/day Xeris or Lilly glucagon.

- Both Xeris and Lilly glucagon were well tolerated and the NOAEL for both products was the highest dose examined (2 mg/kg).
- In general, the incidence and severity of injection site reactions were slightly higher in Xeris-treated rats when compared to Lilly-treated rats. The most common injection site reactions included minimal to marked necrosis, fibrosis, hemorrhage, muscle degeneration/atrophy/regeneration in the panniculus, epidermis squamous hyperplasia or serocellular crust.
- During a glucose extension study, rats treated repeatedly with 0.24, 1, or 2 mg/kg/day Xeris or Lilly glucagon had comparable increases in blood glucose levels even though Xeris glucagon tended to have AUC_(0-t) values up to 2-fold higher than Lilly glucagon.

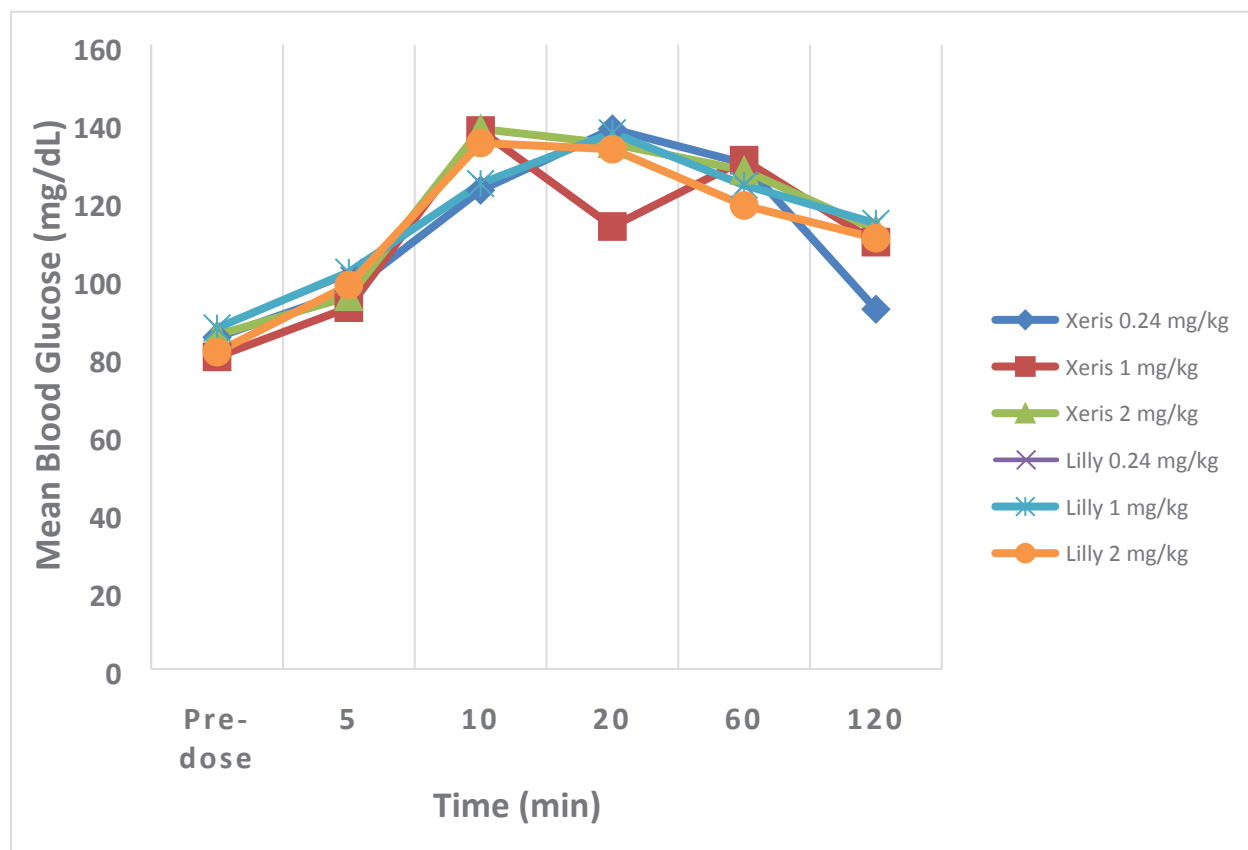
Figure 4: Blood Glucose Time Course for Males on Day 14

Figure prepared by Elena Braithwaite.

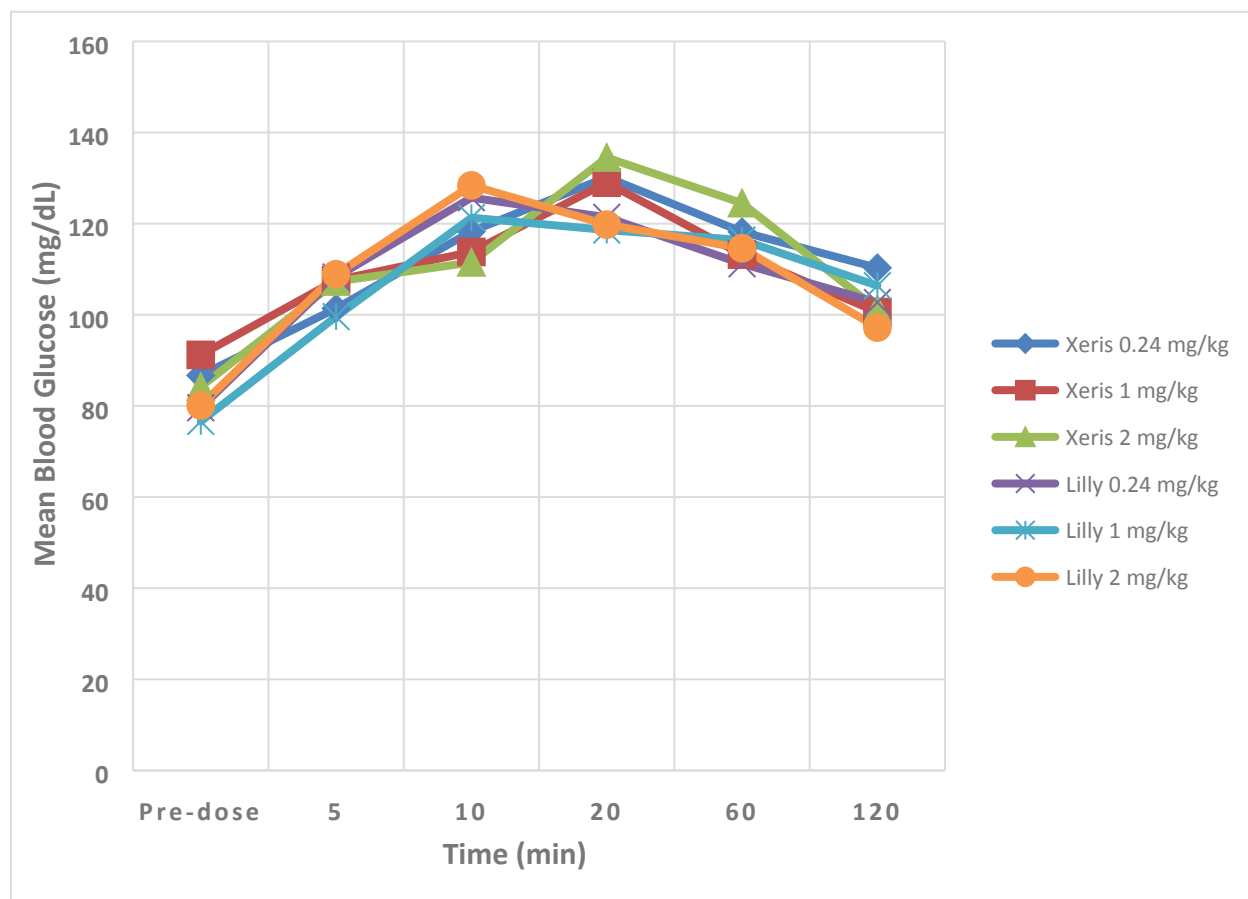
Figure 5: Blood Glucose Time Course for Females on Day 14

Figure prepared by Elena Braithwaite.

Table 6: Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following Subcutaneously Administered Xeris Glucagon on Day 14

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC _(0-t) (pg•min/mL)	AUC _{(0-t)/D} (pg•min/mL/mg/dose)	T _{1/2} (min)	R _{AUC} ^a
0.24	Female	10.0	31,200 $\pm$ 2840	130,000	898,000 $\pm$ 77,500	3,740,000	13.3	1.51
	Male	10.0	35,100 $\pm$ 3240	146,000	1,180,000 $\pm$ 223,000	4,920,000	13.6	2.04
1	Female	20.0	59,300 $\pm$ 9010	59,300	2,600,000 $\pm$ 220,000	2,600,000	14.5	0.945
	Male	10.0	69,300 $\pm$ 13,400	69,300	1,860,000 $\pm$ 153,000	1,860,000	14.8	0.970
2	Female	10.0	90,700 $\pm$ 21,900	45,400	4,220,000 $\pm$ 512,000	2,110,000	29.3	1.12
	Male	10.0	83,000 $\pm$ 19,900	41,500	3,430,000 $\pm$ 313,000	1,720,000	23.0	1.10

^aR_{AUC} = Day 14 AUC_(0-t) / Day 1 AUC_(0-t).

Table copied from the Sponsor's submission (Table 2.2)

Table 7: Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following Subcutaneously Administered Lilly Glucagon on Day 14

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC ₍₀₋₄₎ (pg•min/mL)	AUC ₍₀₋₄₎ /D (pg•min/mL/mg/dose)	T _{1/2} (min)	R _{AUC} ^a	AUC ₍₀₋₄₎ Ratio Xeris/Lilly
0.24	Female	10.0	19,600 $\pm$ 3050	81,500	296,000 $\pm$ 29,500	1,230,000	21.5	0.885	3.03
	Male	5.00	24,100 $\pm$ 5080	100,000	383,000 $\pm$ 49,200	1,600,000	NC	0.924	3.08
1	Female	10.0	44,900 $\pm$ 2230	44,900	1,650,000 $\pm$ 217,000	1,650,000	15.4	0.823	1.58
	Male	10.0	34,900 $\pm$ 4580	34,900	1,130,000 $\pm$ 94,000	1,130,000	17.0	0.792	1.65
2	Female	10.0	85,500 $\pm$ 17,700	42,700	2,830,000 $\pm$ 343,000	1,410,000	16.4	1.10	1.49
	Male	10.0	44,300 $\pm$ 10,500	22,100	1,980,000 $\pm$ 286,000	988,000	21.3	0.719	1.73

^aR_{AUC} = Day 14 AUC₍₀₋₄₎/ Day 1 AUC₍₀₋₄₎.

Table copied from the Sponsor's submission (Table 2.4)

Study title: A 14-Day Toxicity Study of Glucagon and Potential Impurities by Subcutaneous Administration in Sprague-Dawley Rats

Study no.: TX17-GPEN01
 Study report location: SDN: 56, eCTD: 0050, 4.2.3.2
 Conducting laboratory and location: (b) (4)

Date of study initiation: May 4, 2017
 GLP compliance: Y
 QA statement: Y
 Drug, lot #, and % purity: Test Article: Glucagon, also known as XRS0102, Batch (Lot) #: MD-XP0001-95 (Total degradation products were no more than (b) (4) %) Control Article: XRS0102-V, Batch (Lot) #: MD-XP0001-114

Key Study Findings

- The toxicological profile of the forcibly degraded glucagon was similar to that of glucagon. The NOAEL was 2 mg/kg/day Xeris glucagon based on a lack of adverse findings (19-fold higher than the MRHD based on BSA).
- Consistent with previous studies, statistically significant increases in liver weights and liver weight ratios (liver:brain and liver:body weight), increased incidence of minimal to moderate glycogen-type vacuolation, and slightly increased incidences of minimal to mild subcapsular necrosis were observed. Liver findings tended to be more severe in male rats when compared to females.

Methods

Doses: 0, 1, or 2 mg/kg/day
 Frequency of dosing: Daily
 Route of administration: Subcutaneous
 Dose volume: 0.4 mL/kg for Control article and 2 mg/kg/day glucagon, 0.2 mL/kg for 0.2 mg/kg/day glucagon
 Formulation/Vehicle: Contained trehalose dehydrate, sulfuric acid and DMSO but concentrations were not specified
 Species/Strain: Rat/Sprague Dawley
 Number/Sex/Group: 10/sex/group
 Age: 8 weeks old
 Weight: ♂: between 234 and 276 g, ♀: between 181 and 218 g
 Satellite groups: None
 Unique study design:

Group No.	Test Material	Dose Level (mg/kg/day)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	No. of Animals	
					Main Study ^a	
					Males	Females
1	Control Article	0	0.4	0	10	10
2	Glucagon	1	0.2	5	10	10
3	Glucagon	2	0.4	5	10	10

^a Animals underwent terminal procedures on Day 15.

Deviation from study protocol: On Day 12, during dosing of ♂# 3002, the dosing syringe came detached from the needle and the exact volume administered could not be determined.

Observations and Results

Mortality

Animals were observed for general health, mortality and morbidity twice daily.

All animals survived until scheduled necropsy.

Clinical Signs

Cage-side observations were performed twice daily and detailed clinical observations were performed weekly.

Unremarkable

Body Weights

Animals were weighed twice weekly.

Unremarkable.

Feed Consumption

Food consumption was measured weekly.

Unremarkable. A large decrease in body weight was observed in females administered 2 mg/kg/day during days -1 to 7; but, the animals regained their weight during days 7-14.

Ophthalmoscopy

Ophthalmic examinations were performed during pre-treatment and on Day 13. Rats underwent funduscopy (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations.

Unremarkable.

Hematology

Terminal blood was collected on Day 15 while the rats were under deep anesthesia induced by isoflurane inhalation.

No biologically meaningful differences in hematology parameters were observed between the deliberately degraded Xeris glucagon, freshly prepared Xeris glucagon and Lilly glucagon.

Coagulation

No biologically meaningful differences in coagulation parameters were observed between the deliberately degraded Xeris glucagon, freshly prepared Xeris glucagon and Lilly glucagon.

Clinical Chemistry

Serum was analyzed for clinical chemistry parameters on Day 15.

No biologically meaningful differences in clinical chemistry parameters were observed between the deliberately degraded Xeris glucagon, freshly prepared Xeris glucagon and Lilly glucagon.

Urinalysis

Urine was collected from animals placed in metabolism cages.

Glucagon-treated male rats experienced decreased urine volumes when compared to controls while females showed the opposite with increases in urine volumes when compared to controls.

Table 8: Glucagon-related Urinalysis Changes in Rats on Day 15

	Male			Female		
Mg/kg/day	0	1	2	0	1	2
Volume (mL)	23.73	16.18 (↓32)	15.04 (↓37)	12.23	14.67 (↑20)	19.48 (↑59)

Gross Pathology

Main study animals were subjected to complete necropsy.

Unremarkable.

Organ Weights

Organs were weighed at scheduled euthanasia.

Statistically significant increases in liver weights and liver weight ratios were observed in all glucagon-treated rats. Increases in liver weights were similar to a previous 14-day repeat dose toxicity study comparing Xeris and Lilly glucagon.

Table 9: Summary of Noteworthy Organ Weight and Organ Weight Ratios on Day 15

		Males			Females		
Mg/kg/day		0	1	2	0	1	2
Liver							
	Absolute	10.03	12.88c (↑28)	12.51c (↑25)	6.69	7.56a (↑13)	7.73a (↑15)
	: body wt	3.09	4.056b (↑31)	4.17e (↑35)	3.15	3.63b (↑15)	3.75e (↑19)
	:brain wt	512.46	669.24e (↑31)	636.82b (↑24)	359.25	414.43a (↑15)	426.76b (↑19)

Table prepared by Elena Braithwaite. Numbers in bold were significantly different from the control group: a=p≤0.05, b=p≤0.01, c=p≤0.001 (Dunn), d=p≤0.05, e=p≤0.01 f=p≤0.001 (Dunnett)

Histopathology

Adequate Battery Y

Peer Review N

Histological Findings

Representative samples of tissues were preserved in 10% neutral buffered formalin. Histopathological evaluation was performed by a board-certified veterinary pathologist.

Increased incidences of minimal to moderate glycogen-type vacuolation was observed in glucagon-treated male rats. Although liver vacuolation was not observed in previous studies conducted with Xeris and Lilly glucagon, increased liver weights and vacuolation without additional histopathological changes has been observed previously when rats are exposed to glucagon analogs.

Table 10: Summary of Microscopic Findings in Rats at Terminal Euthanasia

		Male			Female		
mg/kg/day		0	1	2	0	1	2
Liver							
Vacuolation, glycogen-type	Minimal	0	2	2	0	1	1
	Mild	0	7	3	0	0	0
	Moderate	0	1	1	0	0	0

Table prepared by Elena Braithwaite.

Toxicokinetics

Not performed.

Dosing Solution Analysis

Not performed.

7 Genetic Toxicology

The mutagenic potential of Xeris glucagon was not evaluated.

8 Carcinogenicity

Long term studies to evaluate the carcinogenic potential of Xeris glucagon in animals have not been performed.

9 Reproductive and Developmental Toxicology

Studies to evaluate reproductive and developmental toxicity associated with exposure to Xeris glucagon in animals have not been performed.

10 Special Toxicology Studies

Study title: A Single Dose Local Tolerance Study of G-Pen™ by Subcutaneous Injection in Rabbits

Study no.:	TX16-GPEN-01
Study report location:	4.2.3.6., SDN: 1, eCTD: 0000
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 31, 2016
GLP compliance:	Y
QA statement:	Y
Drug, lot #, and % purity:	G-Pen™: Batch (Lot) #: GCG- (b) (4) -01, purity was not specified. Control article: 0.9% Sodium chloride for injection, USP, Batch (Lot) #: 62-072-JT G-Pen™ vehicle: Batch (Lot) #: GCG- (b) (4) -V-01

Key Study Findings

- Minimal to mild inflammation and degeneration/necrosis was observed at injection site #1 on Day 3 and decreased in incidence and severity on Day 14 indicating reversibility.

Methods

Doses: 1 mg G-Pen™
 Frequency of dosing: Once
 Route of administration: Subcutaneous
 Dose volume: 225 µL
 Formulation/Vehicle: Not specified. Inactive ingredients listed included trehalose dehydrate, sulfuric acid, and DMSO
 Species/Strain: Rabbits/New Zealand White
 Number/Sex/Group: 3 ♂/group
 Age: 13 to 24 weeks
 Weight: 2.5 to 4.5 kg
 Satellite groups: None
 Unique study design: Rabbits were dosed on Day 1. Necropsy and tissue collection were performed on Euthanasia Day 3 or 14.
 Deviation from study protocol: None of the deviations impacted the integrity or interpretation of study results.

Table 11: Summary of Local Tolerance Study Design

Group No.	Injection Site	Test Material	Dose Level (mg) ^a	Dose Volume (µL)	Number of Males
1	1	Control Article ^b	0	225	6
	2	Vehicle ^c	0	225	
2	1	G-Pen™	1	225	6
	2	Vehicle ^c	0	225	

^a Administered via 250 µL (b) (4) glass syringe, model (b) (4)

^b 0.9% Sodium Chloride for Injection, USP.

^c G-Pen™ vehicle.

Observations and Results

Mortality

Animals were assessed for clinical observation twice daily.

No unscheduled euthanasia.

Clinical Signs

Cage side observations were performed once daily and detailed clinical observations were performed once weekly.

Unremarkable.

Body Weights

Body weight was measured once weekly.

Changes in body weight and body weight gain were unremarkable.

Feed Consumption

Quantitatively measured throughout the study.

Unremarkable.

Gross Pathology

Main study animals were subjected to a complete necropsy examination.

Unremarkable.

Histopathology

Adequate Battery: Y

Peer Review: N

Histological Findings

Injection sites were collected from all animals and preserved mounted and stained.

On Day 3, an increased incidence of minimal to mild inflammation and degeneration/necrosis was observed at injection site #1.

Microscopic findings observed on Day 3 after 1 mg subcutaneous G-Pen administration included mild subcutaneous mixed cell inflammation characterized by infiltration with variable numbers of heterophils, plasma cells, macrophages, and lymphocytes mixed with variable amounts of necrotic cellular debris. A few injection sites also developed minimal hemorrhage sites. On Day 14, inflammation decreased in incidence and severity and one rabbit had a mild neutrophil crust (#5707).

Table 12: Intergroup Comparison of Noteworthy Histopathology Findings

		Mg Glucagon	
		0	1
Day 3			
Site Injection, 1	# examined	3	3
Inflammation, mixed cell; subcutaneous tissue	Mild	0	2
Degeneration/necrosis; myofiber; subcutaneous tissue	Minimal	0	2
Day 14			
Site Injection, 1	# examined	3	3
Infiltration, eosinophilic, subcutaneous tissue	Minimal	0	1
Crust; neutrophil	Mild	0	1

Table prepared by Elena Braithwaite.

Special Evaluation

Dermal Scoring

Daily, detailed observations were performed according to Draize

Unremarkable.

Dosing Solution Analysis

Analysis of concentration and homogeneity was not performed.

11 Integrated Summary and Safety Evaluation

Glucagon binds to specific cell surface receptors, activates adenylate cyclase and initiates a cascade that promotes glycogenolysis and stimulates gluconeogenesis. These two processes result in active liver phosphorylase breaking down glycogen into usable glucose. Currently marketed forms of glucagon require reconstitution of lyophilized product in a 9-step process, prior to injection.

Xeris Pharmaceuticals has developed a sterile, ready-to-use, stable, liquid formulation of (b) (4) glucagon that is administered subcutaneously via a pre-filled syringe for treatment of severe hypoglycemia in patients with diabetes. The Sponsor has submitted this IND under the 505(b)(2) pathway and relies on safety information for Eli Lilly glucagon (NDA 20928). While recombinant glucagon is isolated from culture in the referenced NDA, Xeris Pharmaceuticals plans to use glucagon manufactured by solid phase peptide synthesis (DMF # (b) (4)). Additionally, the formulation of G-Pen was modified between Phase 2 and Phase 3 clinical trials (b) (4)

(b) (4)

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

To evaluate the toxicity and pharmacokinetic profiles of Xeris glucagon in comparison with Lilly glucagon, repeat dose toxicity studies were performed in rats. Xeris and Lilly glucagon were well tolerated and had similar toxicity profiles. In sub-chronic studies in rats and rabbits, minimal to marked, reversible injection site reactions were the most common observation (scabs, inflammation, necrosis, atrophy or hemorrhage in the dermis and panniculus). Injection site reactions appeared to be more severe after the recovery period in HD Xeris glucagon-treated rats when compared to Lilly glucagon-treated rats [low incidences of minimal to mild inflammation and fibrosis of the dermis and panniculus persisted (typically more prominent in males), minimal squamous hyperplasia in the epidermis (males only), minimal to severe Telogen follicles (males and females)]. The Sponsor attributed the injection site reactions to DMSO present in the Xeris glucagon formulation.

In addition to injection site reactions, rats also experienced partially reversible increases in liver weights and liver weight ratios, an increased incidence of minimal to moderate glycogen-type vacuolation, and slightly increased incidences of minimal to mild subcapsular necrosis. These findings have been observed previously after exposure to glucagon (Arstila and Trump 1968). Impurities present in Xeris glucagon formulations designed to mimic the end of the self-life for this product did not have a profound effect on the toxicological profile.

The pharmacokinetic profiles of Xeris and Lilly glucagon were also similar. Both products effectively increased blood glucose concentrations to comparable levels for the doses examined after acute exposure (blood glucose levels did not increase with increasing doses of Xeris or Lilly glucagon, possibly indicating that saturating pharmacodynamic doses were examined). Although systemic exposure to glucagon (as determined by AUC values) was highly variable between individuals after acute or sub-chronic subcutaneous administration, Xeris glucagon tended to have higher AUC values when compared to Lilly glucagon after chronic administration ($AUC_{(0-t)}$ ratios ranged from 1.13 to 1.78 on Day 1 and from 1.49 to 3.08 on Day 14).

In order to support the formulation change between Phase 2 and Phase 3 clinical trials, the pharmacokinetic profile of two different formulations of glucagon was evaluated in a single dose pharmacokinetic study performed in Sprague Dawley rats. This bridging study showed that “old” (b) (4) and “new” (b) (4)

(b) (4) formulations of glucagon had similar pharmacokinetic profiles. Despite the observation that administration of the “new” glucagon formulation resulted in

slightly higher mean plasma glucagon concentrations, no remarkable differences between the two formulations were noted. None of these findings were considered adverse and the NOAEL for Xeris glucagon was 2 mg/kg (19-fold safety margin² based on BSA).

12 Appendix/Attachments

References

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² NOAEL for 14-day repeat dose rat study = 2 mg/kg = 12 mg/m². MRHD = 1 mg or 0.017 mg/kg for a 60 kg individual = 0.629 mg/m². 12 mg/m² / 0.629 mg/m² = 19

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/s/

ELENA K BRAITHWAITE
05/02/2019 04:15:16 PM

FEDERICA BASSO
05/02/2019 04:32:33 PM
On behalf of Calvin (Lee) Elmore

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR
DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: 115091
Supporting document/s: IND-115091; ORIG-1; SD-4; Vols.1, 2
Sponsor's letter date: August 23, 2013
CDER stamp date: August 26, 2013
Product: G-Pen™ (Glucagon for Injection)
Indication: Treatment of Severe Hypoglycemia
Sponsor: Xeris Pharmaceuticals Inc.
Review Division: DMEP
Reviewer: Robert W. Maher Ph.D., DABT
Supervisor/Team Leader: Karen Davis-Bruno Ph.D.
Acting Division Director: Jean Marc Guettier M.D.
Project Manager: Elisabeth Hanan M.S.

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1 Executive Summary

1.1 Introduction

Xeris was notified by teleconference (17 January 2013) that the proposed Phase 2 study (Protocol No. XSGP-201) submitted in the Initial IND (S-0000, Volume 1, Page 42) is on full clinical hold and may not be initiated.

The following specific deficiencies (*italics*) were summarized in the 24 January 2013 FULL CLINICAL HOLD letter:

21 CFR 312.42(b)(1)(iv): Insufficient information to assess risks to human subjects

You submitted a 2-dose toxicity study (CB12-5015-R-TX) "A GLP Pharmacokinetics(PK) and 14-day Subcutaneous Toxicity Study with Glucagon in Rats" which is inadequate to assess human risk based on the limited dosing duration, inadequate doses tested and inability to establish comparability of the investigational glucagon to a listed, U.S. approved glucagon product. Your investigational glucagon is a synthetic product with a liquid formulation containing trehalose and DMSO not present in the comparator glucagon, which is a recombinant human, lyophilized product. While the comparative dose tested of the two glucagon products was the same (b) (4) the PK and toxicity profile was different. The low dose tested appeared to be below the pharmacologic dose in rats.

Information needed to resolve deficiencies:

- Submit data that supports comparability of your glucagon product to a U.S. listed drug in an adequate 2-week toxicity study in a single species with daily dosing at multiple dose levels of the innovator (to establish a dose response) that demonstrates, at a minimum, systemic exposures at your proposed clinical dose to support safety of your proposed clinical trial.*

Please submit the final study reports for any draft reports within 120-days of the initial IND submission (e.g. CB12-5015-R-TX).

1.2 Brief Discussion of Nonclinical Findings

Sponsor provided a second study (XSGPE-TX02/ (b) (4) Study Number 20041521); a 14-day repeat dose study in rats with both G-Pen™ (Glucagon Injection) and Lilly Glucagon for Injection and compared the toxicology profiles, toxicokinetics, and glucose responses of the two drugs at equivalent doses (0.24, 1 and 2 mg/kg/day). The highest dose (2 mg/kg) provides a 20-fold exposure margin over the highest recommended human dose (1 mg) on an HED basis. (It should be noted that a previous report of Lilly's rDNA Glucagon (NDA 20-928) stated that the NOAEL in rat following 14 days of subcutaneous dosing was 4000 µg/kg [4 mg/kg]).

In this second study, all male and female rats survived until scheduled euthanasia.

For some of the male rats at 2 mg/kg/day and all the female in the Xeris Glucagon dose groups, scabs and/or red, white and/or brown areas were exhibited at the injection site(s). The gross findings of 'scab' were correlated to areas of epidermal necrosis and serocellular crust formation in those animals with full thickness necrosis at injection sites. Any test article-related lesions were confined to injection sites and no systemic effects related to compound administration were noted.

There were no adverse observations at the injection site(s) apparent in male rats at any Lilly Glucagon dose level during the dose or at the recovery period or in female Lilly Glucagon rats at the recovery period.

There were between one and three female rats at all dose groups administered the Lilly Glucagon vehicle and the Lilly Glucagon test article observed with either scabs at the injection site(s) or a red area at the injection site(s) during the dose period.

Except for the site administration gross and histopathology findings and pharmacological effects of glucagon, the following parameters and end points evaluated in this study were unremarkable: clinical observations, body weights, body weight changes, food consumption, clinical pathology parameters, urinalysis, organ weights, gross necropsy findings and histopathology evaluation.

Following administration of Xeris Glucagon or Lilly Glucagon, no gender differences in systemic exposure were observed. No accumulation of glucagon was observed following repeated administration of Xeris Glucagon or Lilly Glucagon except for males administered the 0.24 mg/kg/day dose of Xeris Glucagon with an accumulation ratio of 2.04. Xeris Glucagon to Lilly Glucagon $AUC_{(0-t)}$ ratios ranged from 1.13 to 1.78 on DS 1 and from 1.49 to 3.08 on DS 14, indicating that plasma levels of glucagon tended to be higher following repeated administration of Xeris Glucagon compared to Lilly Glucagon. The slight increase in the plasma levels of glucagon after repeated doses of the Xeris Glucagon did not appear to increase toxicity in the dose groups.

Glucose levels appeared generally comparable between the Xeris and the Lilly compounds both on DS 1 and DS14. The time of the peak glucose level generally occurred between 60 and 120 minutes among the dose groups for both the Xeris and the Lilly Glucagon test articles on DSs 1 and 14. On DS 14, there did not appear to be an increase in the predose glucose levels in comparison with the DS 1 values and the time of peak glucose levels did not appear to vary after repeated doses.

Based on the results of this 14-day study with a 14-day recovery period, the no-observed-adverse-effect level (NOAEL) for the Xeris and Lilly Glucagon dose groups are considered to be comparable at 2 mg/kg/day despite there being scabs and/or red, white and/or brown areas apparent at the injection site(s) in the female rats during the dose and recovery periods. The histopathology confirmed that the injection site lesions were apparent in the Xeris vehicle control dose group as well as the groups administered the test article, which could potentially indicate a vehicle effect rather than a test article-related effect.

The Sponsor intends to submit this second study as a final report (XSGPE-TX02) within 120 days of this submission.

Also provided in this Submission, the Sponsor submitted the first study final report and a final pharmacokinetics analysis report (Statistical Analysis Report of Non-clinical GLP Pharmacology Study Number CB12-5015-R-TX of Xeris Non-aqueous Glucagon for Injection in Rats).

1.3 Recommendations

Sponsor has adequately addressed the clinical hold issues related to nonclinical safety evaluation of Xeris glucagon and its comparability to Lilly glucagon. The Sponsor can initiate clinical evaluation of Xeris glucagon.

1.3.1 Clinical Study to Proceed: Yes

The following comment is recommended to be sent to the Sponsor to be included in the initiation of the clinical protocol, XSGP-201:

The 14-day rat subcutaneous toxicity study (CB12-5015-R-TX) has shown some significant injection site reactions with the innovator product that contains (b)(4)% DMSO compared to the referenced glucagon product. Monitor frequency and severity of injection site reactions in study XSGP-201, "Randomized, Phase 2, Double-blind, 3 way Crossover Study with G-Pen to Evaluate Safety, Tolerability and Comparative PK and PD to Lilly Glucagon in Healthy Volunteers."

2 Drug Information

2.1 Drug

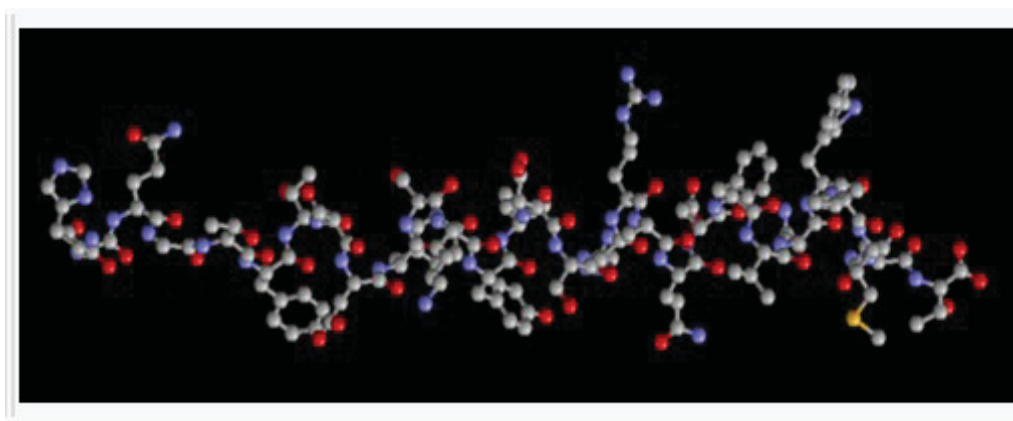
CAS Registry Number 9007-92-5

Generic Name Glucagon

Code Name Glucagonoid; Glukagon; HG-Factor; Hyperglycemic-glycogenolytic Factor; Chemical Name Glucagon

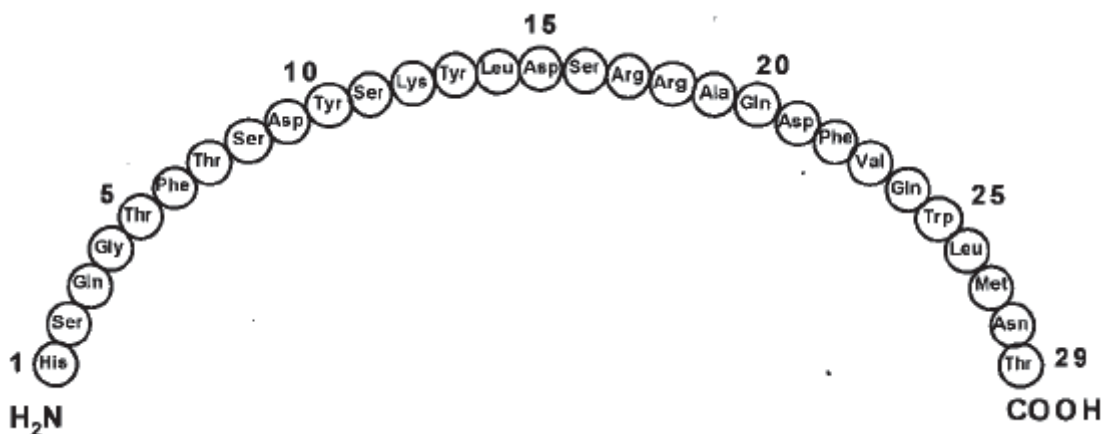
Molecular Formula/Molecular Weight $C_{153}H_{225}N_{43}O_{49}S/3482.75$

Structure or Biochemical Description



Glucagon

NH₂-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gin-Trp-Leu-Met-Asn-Thr-COOH



Pharmacologic Class

Hypoglycemia Antidotes, Diagnostics, Gastrointestinal, Glucose-Elevating Agents, Glycogenolytic Hormone

Mechanism of Action

Glucagon binds to the glucagon receptor, a G protein-coupled receptor, located in the plasma membrane. The conformation change in the receptor activates G proteins, a heterotrimeric protein with α , β , and γ subunits. When the G protein interacts with the receptor, it undergoes a conformational change that results in the replacement of the GDP molecule that was bound to the α subunit with a GTP molecule. This substitution results in the releasing of the α subunit from the β and γ subunits. The alpha subunit specifically activates the next enzyme in the cascade, adenylate cyclase.

Adenylate cyclase manufactures cyclic adenosine monophosphate (cyclic AMP or cAMP), which activates protein kinase A (cAMP-dependent protein kinase). This enzyme, in turn, activates phosphorylase kinase, which, in turn, phosphorylates glycogen phosphorylase, converting into the active form called phosphorylase A. Phosphorylase A is the enzyme responsible for the release of glucose-1-phosphate from glycogen polymers.

2.2 Relevant INDs, NDAs, BLAs and DMFs

Glucagon is currently marketed by Eli Lilly & Co. as Glucagon™ (glucagon for injection [rDNA origin]), and Novo Nordisk as GlucaGen® HypoKit®, both RLDs for treatment of severe hypoglycemia. The Agency first approved purified porcine glucagon HCl, marketed by Lilly, for use in humans in 1960. Quad Pharmaceuticals was later approved to manufacture generic versions of glucagon HCl (ANDA 71-022, 71-023). However all animal- purified glucagon formulations were discontinued as rDNA-derived glucagon was approved for use in 1998. Both Lilly and Novo recombinant glucagon products were approved in 1998 and is currently the subject of two approved NDAs ([NDA 20-928] and [NDA 20-918]).

2.3 Drug Formulation

Glucagon for Injection (rDNA origin) is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Glucagon is synthesized in a special non-pathogenic laboratory strain of Escherichia coli bacteria that has been genetically altered by the addition of the gene for glucagon. Xeris' drug product is produced by solid-phase peptide synthesis (SPPS) which also conserves the glucagon peptide sequence.

G-Pen™ (Glucagon for Injection) 1 mg is a sterile subcutaneous injectable non- aqueous formulation supplied in 1.0 mL long (b) (4) pre-filled (b) (4) (b) (4) syringe with (b) (4) plunger, under investigation for treatment of severe hypoglycemia in type 1 or insulin-dependent type 2 diabetic patients. The composition per 1 mg dose of G-Pen™ (glucagon for injection) is as follows.

G-Pen™ Dose Composition

Component	Dose Amount (mg/unit)
Glucagon	1.00
(b) (4)	
Trehalose (α,α -dihydrate)	11.1 (b) (4)
Dimethyl Sulfoxide (DMSO)	(b) (4)
(b) (4)	(b) (4)

2.4 Comments on Novel Excipients

Excipients in Xeris Glucagon formulation novel to the Lilly Glucagon product:

(b) (4)

Trehalose (α, α -dehydrate) (CAS 6138-23-4), also known as mycose or tremalose is not listed in the USFDA IISADP.

DMSO (CAS 67685) for sc implant has a maximum potency* of (b) (4) mg which is less than the (b) (4) mg contained in Xeris Glucagon.

*maximum potency specifies the maximum amount of inactive ingredient for each route/dosage form containing that ingredient. When there is no calculable potency measurement for the inactive ingredient, the "maximum potency" field will be blank.

2.5 Comments on Impurities/Degradants of Concern

To use the injectable form of glucagon, it must be reconstituted prior to use, a step that requires a sterile diluent to be injected into a vial containing powdered glucagon, because the hormone is highly unstable when dissolved in solution. When dissolved in a fluid state, glucagon can form amyloid fibrils, or tightly woven chains of proteins made up of the individual glucagon peptides, and once glucagon begins to fibrillize, it becomes useless when injected, as the glucagon cannot be absorbed and used by the body.

The Xeris Glucagon product will be in a sterile subcutaneous injectable non-aqueous formulation which will reduce the possibility of glucagon forming amyloid fibrils.

2.6 Proposed Clinical Protocol

Title: A Randomized, Phase 2, Double-blind, 3-way Crossover Study with G-Pen™ (Glucagon for Injection) to Evaluate safety, Tolerability and Comparative Pharmacodynamics to Lilly Glucagon™ (Glucagon for Injection [rDNA Origin]) in Healthy Volunteers (XSGP-201).

The proposed IND study is a Phase 2 study with three objectives:

- (1) to evaluate the safety and tolerability of G-Pen™ (glucagon for injection) 1mg
- (2) to compare the pharmacokinetics of G-Pen™ (glucagon for injection) 1mg [test] administered as 0.5 mg and 1 mg injections, versus Lilly Glucagon™ (glucagon for injection [rDNA origin]) 1 mg (reference), and
- (3) to evaluate the glucodynamics (efficacy) of G-Pen™ (glucagon for injection) 1 mg.

2.7 Previous Clinical Experience

None with the proposed Xeris Glucagon Product.

2.8 Regulatory Background

The safety, tolerability, and pharmacokinetics of rDNA glucagon in humans has been previously characterized. Glucagon has a long history of medical use in the US, and is currently marketed by Eli Lilly & Co. -as Glucagon™ (glucagon for injection [rDNA origin]), and Novo Nordisk as GlucaGen® HypoKit®, both Reference Listed Drugs for treatment of severe hypoglycemia.

3 Studies Submitted

3.1 Studies Reviewed

CB12-5015-R-TX. A GLP Pharmacokinetics and Fourteen-Day Subcutaneous Toxicity Study with Glucagon in Rats. (Draft with PK Report in Preparation) (Unsigned QA Statement/Final Report)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

IND 115091; FDA response; Request Review-Proposed 14-Day Rat GLP Tox Study, Dated, February 12, 2013.

IND-115091; ORIG-1; SD-4; Vols.1, 2, Review date, January 16, 2013.

IND 115,091; G-Pen glucagon for injection/Xeris, 30-Day safety memo, Review dated, January 15, 2013.

Follow-up Questions to Pre-IND 115091 Written Response, Dated June 21, 2012.

4 Pharmacology

4.1 Primary Pharmacology

Glucagon is an insulin antagonist, which stimulates cAMP synthesis to accelerate hepatic glycogenolysis and gluconeogenesis.

4.2 Secondary Pharmacology

Glucagon relaxes smooth muscles of the gastrointestinal tract.

4.3 Safety Pharmacology

Glucagon acts very quickly; commonly side-effects include headache and nausea. Generalized allergic reactions, including urticaria, respiratory distress, and hypotension have been reported in the clinical literature.

5 Pharmacokinetics

5.1 PK

CB12-5015-R-TX. A GLP Pharmacokinetics and Fourteen-Day Subcutaneous Toxicity Study with Glucagon in Rats.

Table 8-5. Summary Pharmacokinetic Data, Study CB12-5015-R-TX

Parameter (units)	Group/Glucagon Dose							
	2.5 µg Xeris		5 µg Xeris		50 µg Xeris		5 µg Lilly	
	Male	Female	Male	Female	Male	Female	Male	Female
C_{max} (pg/mL)	7,423	9,782	14,909†	10,043‡	73,716†	83,564†	7,620‡	5,575‡
T_{max} (min)	6.25	3.89	6.00	3.61	7.50	7.50	6.39	4.75
AUC (pg·min/mL)	69,134	94,751	169,569	106,589	1,206,337†	1,446,123†	107,799	66,337
CL (mL/min)	66.6	49.4	58.9	106.4	50.3	38.4	74.9	102.6
$t_{1/2}$ (min)	13.6	9.2	7.9	10.5	8.2	9.4	8.8	11.3
V_{ex} (mL)	1,677	694	816	2,002	899	667	1,227	1,723

*p < 0.0001 comparing all groups

†P < 0.0001 versus each other group

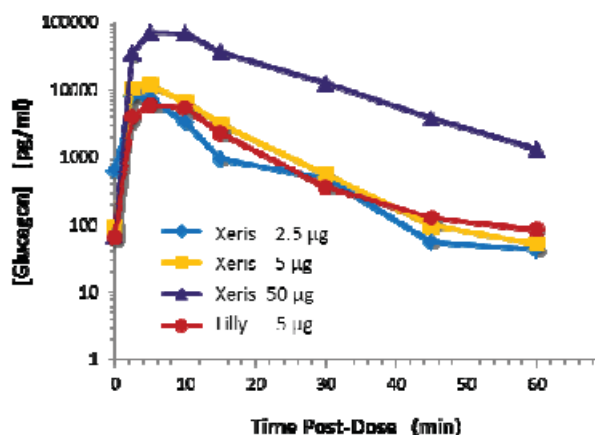
‡p = 0.0424 comparing specific groups

Mean Average Comparison of 5 µg Xeris Group with 5 µg Lilly Group

	<u>5 µg Xeris vs. 5 µg Lilly</u>	
	Male Rats	Female Rats
$C_{\max}$ (pg/mL)	↑51%	↓32%
$T_{\max}$ (min)	↓7%	↓24%
AUC (pg.min/mL)	↑57%	↑61%
CL (mL/min)	↓22%	↑4%
$t_{1/2}$ (min)	↓10%	↓7%
V_{ex} (mL)	↓33%	↑16%

The pharmacokinetics and pharmacodynamics phase of Study CB12-5015-R-TX consisted of 4 groups of jugular vein-cannulated (JVC) outbred SD-HLAR(SD)CVFR male (n=10) and female (n=10) rats. Prior to study start, the animals were examined, weighed, and assigned randomly to any one of 4 study treatment groups. Animals were fasted overnight before dosing. The rats were injected SC with 2.5 µg Xeris glucagon, 5 µg Xeris glucagon, 50 µg Xeris glucagon or with 5 µg Lilly glucagon. Blood was collected from each animal pre-dosing (t=0 min), and 2.5., 5, 10, 15, 30, 45 and 60 min post-dose for determination of blood glucose and plasma glucagon concentrations.

Plasma Glucagon Concentrations of Xeris Glucagon and Lilly Glucagon Post-Dose



Dosing of rats with 2.5 mg Xeris glucagon, 5 mg Xeris glucagon, 50 mg Xeris glucagon or with 5 mg Lilly glucagon resulted in a rapid rise (2.5 min to 5 min post-dose) in plasma glucagon concentrations in all treatment groups from the t=0 min pretreatment levels (see Figure above).

6 General Toxicology

6.1 Fourteen Day Repeat Dose Rat Toxicity Study

Study title: A 14-Day Subcutaneous Study of Xeris' Concentrated, Non-Aqueous Solution of Glucagon in Rats with a 2-Week Recovery Period and Satellite Toxicokinetic Evaluation

Study no.: XSGPE-TX02

Study report location:

(b) (4)

Conducting laboratory and location:

(b) (4)

Date of study initiation: 30 April 2013

GLP compliance: Audited Draft Report with intended GLP compliance.

QA statement: Unsigned

Drug, lot #, and % purity: FFM-12-019, Glucagon Related Substances by RP-HPLC, 98% purity; by SE-HPLC, 99% purity.

Key Study Findings

- Males in the 2 mg/kg Xeris group had an increased incidence and severity of necrosis, as well as an increased severity of inflammation at injection sites when compared to Lilly males at the same dosage.
- Full thickness necrosis was present in 14 animals (seven from the 2 mg/kg group and seven from the control Xeris group) and was not present in any of the Lilly control or 2 mg/kg animals.

Experimental Design - Main Study

Group No.	Test Material	Target Dose Level (mg/kg/day) ^a	Dose Volume (mL)	No. of Animals					
				Main Study		Recovery Study		Toxicokinetic Animals	
				M	F	M	F	M	F
1	Xeris Vehicle	0	80	10	10	5	5	NA	NA
2	Xeris Glucagon	0.24	10	10	10	5	5	10	10
3	Xeris Glucagon	1	40	10	10	5	5	10	10
4	Xeris Glucagon	2	80	10	10	5	5	10	10
5	Lilly Vehicle	0	400	10	10	5	5	NA	NA
6	Lilly Glucagon	0.24	48	10	10	5	5	10	10
7	Lilly Glucagon	1	200	10	10	5	5	10	10
8	Lilly Glucagon	2	400	10	10	5	5	10	10

M = Male; F = Female

NA = Not Applicable

^a Initial target doses were established based on a 5 mg/mL dose concentration for the Xeris test article and a 1 mg/mL for the Lilly test article and a 200 g rat. A constant dose volume was used throughout the study to imitate what will occur in the clinic.

Experimental Design - Glucose Extension Study

Group No.	Test Material	Target Dose Level (mg/kg) ^a	Dose Volume (mL)	No. of Animals	
				Glucose Extension Study	
				M	F
2	Xeris Glucagon	0.24	10	5	5
3	Xeris Glucagon	1	40	5	5
4	Xeris Glucagon	2	80	5	5
6	Lilly Glucagon	0.24	48	5	5
7	Lilly Glucagon	1	200	5	5
8	Lilly Glucagon	2	400	5	5

M = Male; F = Female

^a Initial target doses were established based on a 5 mg/mL dose concentration for the Xeris test article and a 1 mg/mL for the Lilly test article and a 200 g rat. A constant dose volume was used throughout the study to imitate what will occur in the clinic.

Frequency of dosing	Daily for 14 days
Route of administration	Subcutaneous injection into the scapular and mid-dorsal areas
Formulation/Vehicle	115091 Xeris Glucagon, a concentrated, non-aqueous proprietary formulation of the peptide hormone (also known as G-Pen™ [glucagon for injection] and Xerisol Glucagon).
Species/Strain	(b) (4):CD(SD) Sprague Dawley rats
Number/Sex/Group	Refer to Tables above
Age	Approximately 50 days of age upon arrival at the Testing Facility.
Weight	At study assignment, the males weighed 206 g to 262 g and the females weighed 179 g to 213 g.

Satellite groups	Refer to Tables above
Unique study design	Yes, with addition of Glucose satellite group
Deviation from study protocol	Deviations occurred but were not considered by the Study Director to have affected the interpretation of the study.

Observations and Results

Mortality All rats survived until scheduled sacrifice.

Clinical Signs

No clinical observations in the Xeris Glucagon and Lilly Glucagon dose groups during the dose and recovery periods were considered related to the test article, except for the following:

Males

There was an increase or statistically significant increase ($p \leq 0.01$) in the number of male rats in the 2 mg/kg/day Xeris Glucagon dose group observed with white and/or red areas at the injection site(s) and/or scabs at the injection site(s) during the dose period. There was also a statistically significant increase ($p \leq 0.01$) in the number of male rats in the 2 mg/kg/day Xeris Glucagon dose group observed with scabs at the injection site(s) during the recovery period.

There were no adverse observations at the injection site(s) apparent in the male rats at any Lilly dose level during the dose period or recovery period.

Females

In the female rats, there were scabs and/or red, white and/or brown areas apparent at the injection site(s) in the Xeris vehicle group and all Xeris Glucagon dose groups. There was a statistically significant decrease ($p \leq 0.01$) in the incidence of female rats in the 0.24 mg/kg/day Xeris Glucagon dose group observed with scabs at the injection site(s) during the dose period. There was also a statistically significant increase ($p \leq 0.01$) in the number of female rats at 2 mg/kg/day observed with red, white and/or brown areas at the injection sites during the dose period. Although not statistically significant, there was an increase in the number of female rats in the Xeris vehicle group and all Xeris Glucagon dose groups observed with scabs at the injection site(s) during the recovery period.

There were between one and three female rats at all dose groups administered the Lilly vehicle and the Lilly Glucagon test article observed with either scabs at the injection site(s) or a red area at the injection site(s) during the dose period. There were no adverse observations at the injection site(s) apparent in the female rats at any Lilly Glucagon dose level during the recovery period.

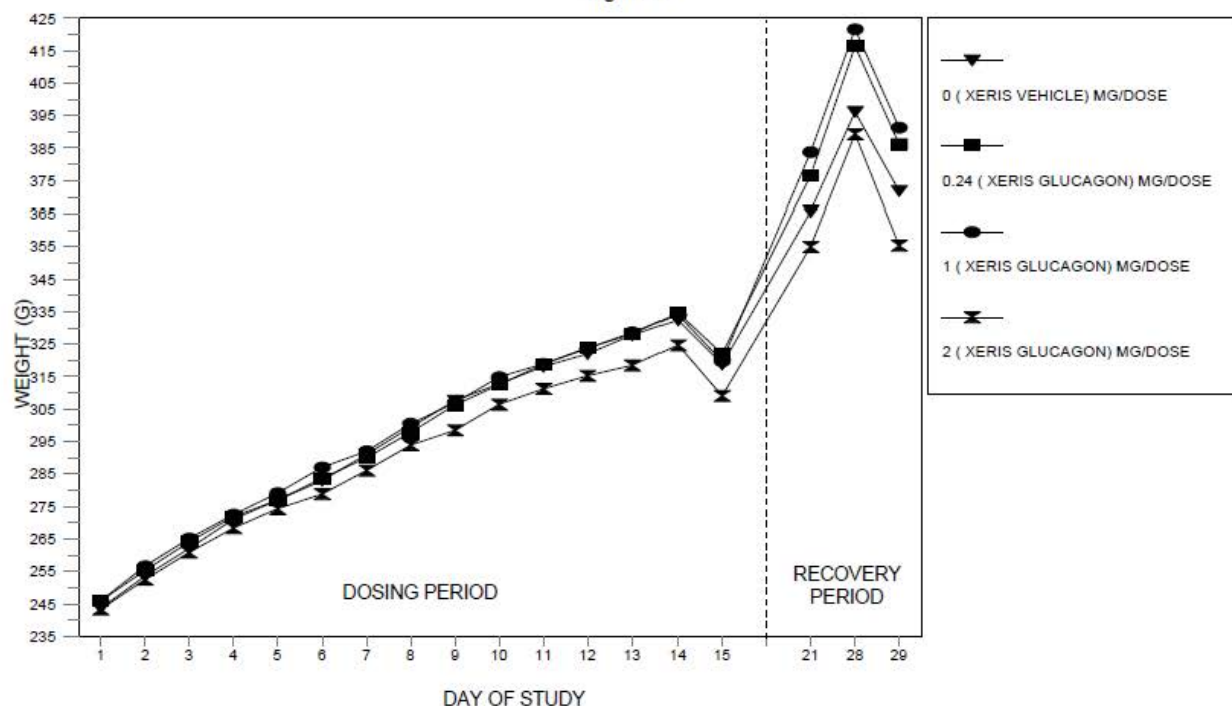
Body Weights

There were no meaningful test article-related effects on body weight or body weight gain observed in the male and female rats in the Xeris and Lilly Glucagon dose groups during the dose period (DSs 1 to 14) or during the recovery period (DSs 14 to 28).

PROTOCOL 20041521: A 14-DAY SUBCUTANEOUS STUDY OF XERIS' CONCENTRATED, NON-AQUEOUS SOLUTION OF GLUCAGON IN RATS WITH A 2-WEEK RECOVERY PERIOD AND SATELLITE TOXICOKINETIC EVALUATION (SPONSOR'S REFERENCE NUMBER: XSGPE-TX02)

BODY WEIGHTS - MALE RATS - GROUPS 1 THROUGH 4

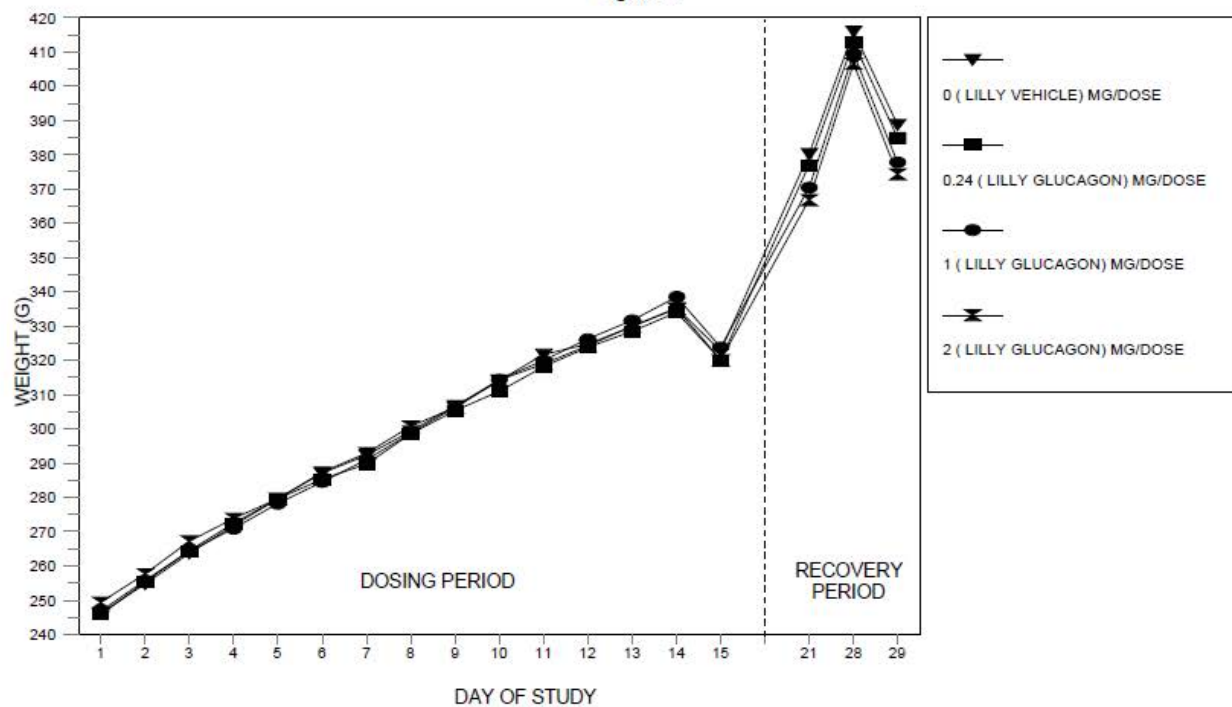
Figure 1



PROTOCOL 20041521: A 14-DAY SUBCUTANEOUS STUDY OF XERIS' CONCENTRATED, NON-AQUEOUS SOLUTION OF GLUCAGON IN RATS WITH A 2-WEEK RECOVERY PERIOD AND SATELLITE TOXICOKINETIC EVALUATION (SPONSOR'S REFERENCE NUMBER: XSGPE-TX02)

BODY WEIGHTS - MALE RATS - GROUPS 5 THROUGH 8

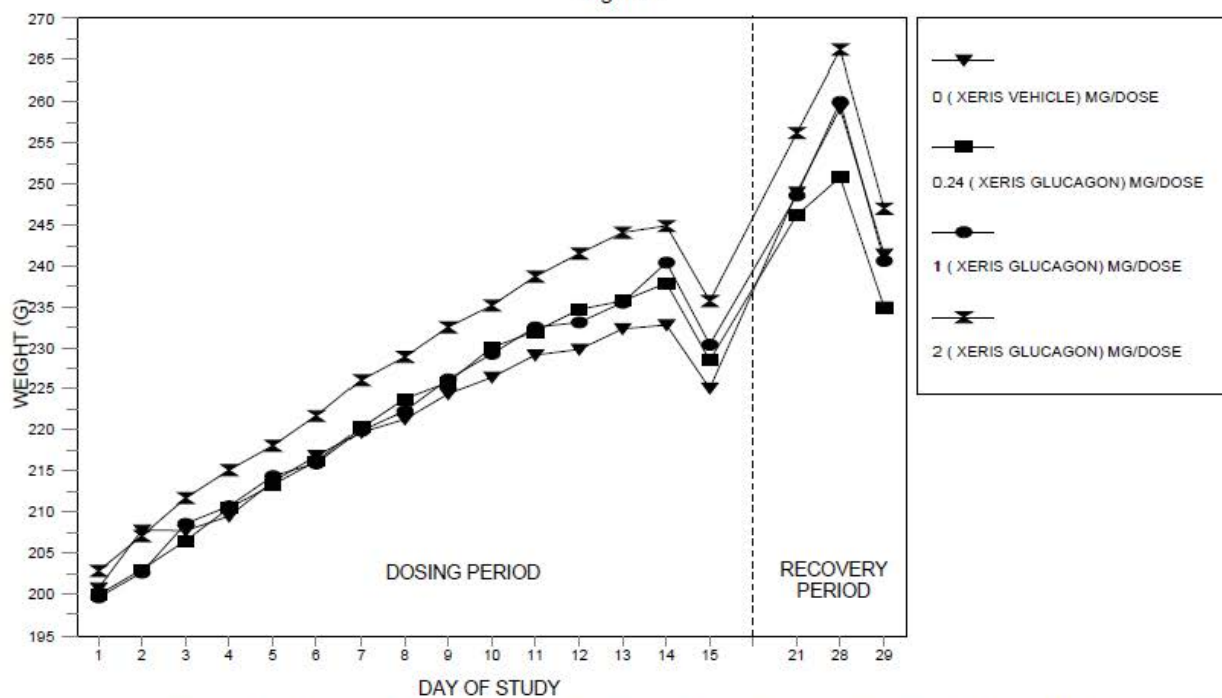
Figure 2



PROTOCOL 20041521: A 14-DAY SUBCUTANEOUS STUDY OF XERIS' CONCENTRATED, NON-AQUEOUS SOLUTION OF GLUCAGON IN RATS WITH A 2-WEEK RECOVERY PERIOD AND SATELLITE TOXICOKINETIC EVALUATION (SPONSOR'S REFERENCE NUMBER: XSGPE-TX02)

BODY WEIGHTS - FEMALE RATS - GROUPS 1 THROUGH 4

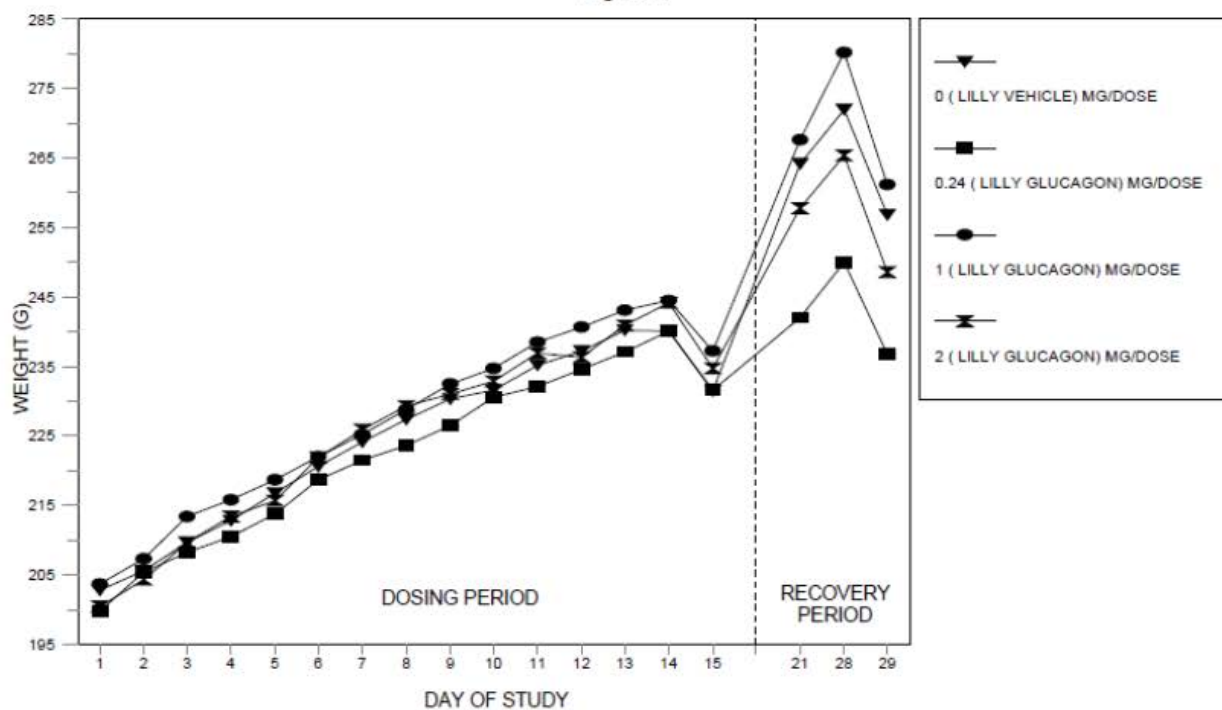
Figure 3



PROTOCOL 20041521: A 14-DAY SUBCUTANEOUS STUDY OF XERIS' CONCENTRATED, NON-AQUEOUS SOLUTION OF GLUCAGON IN RATS WITH A 2-WEEK RECOVERY PERIOD AND SATELLITE TOXICOKINETIC EVALUATION (SPONSOR'S REFERENCE NUMBER: XSGPE-TX02)

BODY WEIGHTS - FEMALE RATS - GROUPS 5 THROUGH 8

Figure 4



Feed Consumption

There were no test article-related effects on absolute (g/day) and relative (g/kg/day) food consumption values in the male and female rats in the Xeris and Lilly Glucagon dose groups during the dose period (DSs 1 to 14) or the recovery period (DSs 14 to 28).

Hematology

There were no adverse changes in hematology response variables present in male or female rats at the end of the dose period (DS 15) or at the end of the recovery period (PND 29).

At the end of the dose period, the following changes in hematology were present in the Xeris and Lilly Glucagon test article groups and they included:

- a decrease or statistically significant decrease ($p \leq 0.05$) in fibrinogen in the male rats at 1 and 2 mg/kg/day in both the Xeris and the Lilly Glucagon test articles; and
- a statistically significant decrease ($p \leq 0.05$) in the mean corpuscular hemoglobin concentration in the female rats at 2 mg/kg/day in both the Xeris and the Lilly Glucagon test articles.

Based on the fact that these observations were apparent at comparable doses in both test articles, these changes were presumed to be the result of a pharmacologic effect caused by the test articles, rather than a specific test article-related effect caused by the Xeris Glucagon test article.

Clinical Chemistry

There were no adverse changes in serum chemistry variables present in male or female rats at the end of the dose period (DS 15) or at the end of the recovery period (PND 29).

At the end of the dose period, changes in serum chemistry that were present in the Xeris and Lilly Glucagon test articles included:

- a decrease or statistically significant decrease ($p \leq 0.05$) in cholesterol at all doses of the Xeris Glucagon test article in the male and female rats and at the 1 and 2 mg/kg/day doses of the Lilly Glucagon test article in the male and female rats;
- an increase or statistically significant increase ($p \leq 0.05$) in the albumin and the albumin/globulin ratio in the male and female rats at all doses in both the Xeris and Lilly Glucagon test articles (including the Lilly vehicle);
- a decrease or statistically significant decrease ($p \leq 0.05$) in the globulin values in the male rats in all Xeris Glucagon dose groups and in the male rats in the 1 and 2 mg/kg/day Lilly Glucagon dose groups.

Urinalysis**Males**

At the end of the dose period (DS 15), there were a number of similarities observed between the male rats administered the Xeris and the Lilly Glucagon test articles with regards to the urinalysis parameters. In the 1 and/or 2 mg/kg/day Xeris and Lilly Glucagon dose groups, there was also an increase or statistically significant increase ($p \leq 0.01$) in the number of male rats observed with a small, moderate or large amount of blood in the urine. This resulted in a statistically significant decrease ($p \leq 0.01$) in the amount of male rats observed with blood absent from the urine in the 1 and 2 mg/kg/day Lilly Glucagon dose group.

At the end of the dose period (DS 15), there was a statistically significant increase ($p \leq 0.01$) in the number of male rats observed with opaque dark brown urine in the 2 mg/kg/day Xeris and Lilly Glucagon dose groups. There was a statistically significant decrease ($p \leq 0.01$) in the number of male rats in the 1 and 2 mg/kg/day Xeris Glucagon dose groups observed with clear yellow urine at the end of the dose period.

Females

At the end of the dose period (DS 15), there was a decrease or statistically significant decrease ($p \leq 0.05$ or $p \leq 0.01$) in the pH of the urine that occurred in the 1 and 2 mg/kg/day Xeris Glucagon dose groups and the 2 mg/kg/day Lilly Glucagon dose group.

Gross Pathology**NECROPSY OBSERVATIONS - SUMMARY - MALE RATS**

GROUP		1	2	3	4
TEST MATERIAL		XERIS VEHICLE	XERIS GLUCAGON	XERIS GLUCAGON	XERIS GLUCAGON
TARGET DOSE LEVEL (MG/DOSE) ^a		0	0.24	1	2
MORTALITY	N	0	0	0	0
DOSE PERIOD (EUTHANIZED ON DAY 15 OF STUDY):					
RATS EXAMINED	N	15	15	15	15
APPEARED NORMAL	N	14	14	14	13
KIDNEY:					
RIGHT, PELVIS, SLIGHT DILATION	N	0	0	0	1
RIGHT, CLEAR, FLUID-FILLED CYST	N	0	0	0	1
SPLEEN:					
WHITE AREA	N	1	0	1	1
TESTES:					
BILATERAL, SMALL	N	0	1	0	0
EPIDIDYMIDES:					
BILATERAL, SMALL	N	0	1	0	0

a. Dose administration occurred on Days 1 through 14 of study.

GROUP		1	2	3	4
TEST MATERIAL		XERIS VEHICLE	XERIS GLUCAGON	XERIS GLUCAGON	XERIS GLUCAGON
TARGET DOSE LEVEL (MG/DOSE) ^a		0	0.24	1	2
MORTALITY	N	0	0	0	0
RECOVERY PERIOD (EUTHANIZED ON DAY 29 OF STUDY):					
RATS EXAMINED	N	5	5	5	5
APPEARED NORMAL	N	4	4	5	3
THYROID:					
LEFT LOBE, SMALL	N	0	0	0	1
THYMUS:					
RED AREA	N	1	0	0	0
SPLEEN:					
WHITE AREA	N	0	0	0	1
KIDNEYS:					
RIGHT, PELVIS, SLIGHT DILATION	N	0	1	0	0

a. Dose administration occurred on Days 1 through 14 of study.

GROUP		5	6	7	8
TEST MATERIAL		LILLY VEHICLE	LILLY GLUCAGON	LILLY GLUCAGON	LILLY GLUCAGON
TARGET DOSE LEVEL (MG/DOSE) ^a		0	0.24	1	2
MORTALITY	N	0	0	0	0
DOSE PERIOD (EUTHANIZED DAY 15 OF STUDY):					
RATS EXAMINED	N	15	15	15	15
APPEARED NORMAL	N	15	14	15	15
KIDNEY:					
RIGHT, PELVIS, SLIGHT DILATION	N	0	1	0	0
RECOVERY PERIOD (EUTHANIZED DAY 29 OF STUDY):					
RATS EXAMINED	N	5	5	5	5
APPEARED NORMAL	N	5	5	4	3
LUNGS:					
RIGHT APICAL LOBE, RED	N	0	0	0	1
TESTES:					
BILATERAL, SMALL	N	0	0	1	0
EPIDIDYIMIDES:					
BILATERAL, SMALL	N	0	0	1	0
RIGHT CAUDA, TAN FIRM MASS	N	0	0	0	1

a. Dose administration occurred on Days 1 through 14 of study.

NECROPSY OBSERVATIONS - SUMMARY - FEMALE RATS

GROUP		1	2	3	4
TEST MATERIAL		XERIS VEHICLE	XERIS GLUCAGON	XERIS GLUCAGON	XERIS GLUCAGON
TARGET DOSE LEVEL (MG/DOSE) ^a		0	0.24	1	2
MORTALITY	N	0	0	0	0
DOSE PERIOD (EUTHANIZED ON DAY 15 OF STUDY):					
RATS EXAMINED	N	15	15	15	15
APPEARED NORMAL	N	13	12	15	15
LIVER:					
CAUDATE LOBE ADHERED TO RIGHT KIDNEY	N	1	1	0	0
CAUDATE LOBE AND PAPILLARY PROCESS ADHERED	N	1	0	0	0
KIDNEYS: CLEAR, BILATERAL FLUID-FILLED CYST	N	0	1	0	0
RIGHT, MISSHAPEN	N	0	1	0	0
LACRIMAL GLAND:					
LEFT, RED AREA	N	0	1	0	0
RECOVERY PERIOD (EUTHANIZED ON DAY 29 OF STUDY):					
RATS EXAMINED	N	5	5	5	5
APPEARED NORMAL	N	5	5	5	5

a. Dose administration occurred on Days 1 through 14 of study.

GROUP		5	6	7	8
TEST MATERIAL		LILLY VEHICLE	LILLY GLUCAGON	LILLY GLUCAGON	LILLY GLUCAGON
TARGET DOSE LEVEL (MG/DOSE) a		0	0.24	1	2
MORTALITY	N	0	0	0	0
DOSE PERIOD (EUTHANIZED DAY 15 OF STUDY):					
RATS EXAMINED	N	15	15	15	15
APPEARED NORMAL	N	14	15	15	15
SPLEEN: CLEAR FLUID FILLED CYSTS	N	1	0	0	0
RECOVERY PERIOD (EUTHANIZED DAY 29 OF STUDY):					
RATS EXAMINED	N	5	5	5	5
APPEARED NORMAL	N	5	5	4	5
SPLEEN: RED AND FIRM MASS	N	0	0	1	0
a. Dose administration occurred on Days 1 through 14 of study.					

Increased liver weights were noted in Xeris and Lilly Glucagon 2 mg/kg males and females, as well as Lilly Glucagon males in the 1 mg/kg dose group.
Decreases in adrenal gland weights may be treatment related, but no microscopic correlate was present. Decreases in thymic weight may be due to normal involution or stress.

Summary of Organ Weight Data – Terminal Euthanasia (Day 15)

	Males			
Group	3	4	7	8
Dose (mg/kg/day)	1	2	1	2
No. Animals per Group	10	10	10	10
Liver (No. Weighed) ^a	-	10	10	10
Absolute value	-	10.01 ± 1.35	10.16 ± 0.73	10.50 ± 1.59
% of body weight	-	3.343 ± 0.296**	3.230 ± 0.199*	3.375 ± 0.312**
% of brain weight	-	492.0 ± 55.7	497.2 ± 27.5	514.5 ± 70.6
Thymus (No. Weighed)	-	10	-	-
Absolute value	-	0.49 ± 0.11*	-	-
% of body weight	-	0.165 ± 0.034*	-	-
% of brain weight	-	24.2 ± 4.9*	-	-
Adrenal gland (No. Weighed)	-	10	-	-
Absolute value	-	0.042 ± 0.005**	-	-
% of body weight	-	0.012 ± 0.004**	-	-
% of brain weight	-	2.1 ± 0.2**	-	-

^a All values expressed as means ± SD from each group.

Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – P ≤ 0.05* or P ≤ 0.01**; refer to data tables for actual significance levels and tests used.

Summary of Organ Weight Data – Terminal Euthanasia (Day 15)

	Females			
Group	3	4	7	8
Dose (mg/kg/day)	1	2	1	2
No. Animals per Group	10	10	10	10
Liver (No. Weighed) ^a	-	10	-	10
Absolute value	-	8.68 ± 1.07**	-	7.78 ± 0.55
% of body weight	-	3.794 ± 0.369**	-	3.420 ± 0.172**
% of brain weight	-	440.2 ± 63.3**	-	384.8 ± 27.4

^a All values expressed as means ± SD from each group.

Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – P ≤ 0.05* or P ≤ 0.01**; refer to data tables for actual significance levels and tests used.

No microscopic correlate was present for the increased ovarian weight in Xeris Glucagon treated females at 2 mg/kg. The increase in this group may be treatment related, but the increase in ovarian weights noted in the 1 mg/kg Lilly Glucagon females is more equivocal as the 2 mg/kg Lilly Glucagon females were unaffected. Lilly Glucagon dosed females at 1 mg/kg were not evaluated in this review. There were no other organ weight changes notes that were statistically different from their respective controls.

Summary of Organ Weight Data – Terminal Euthanasia (Day 29)

	Females			
Group	3	4	7	8
Dose (mg/kg/day)	1	2	1	2
No. Animals per Group	10	10	10	10
Ovary (No. Weighed) ^a	10	10	10	10
Absolute value	-	0.131 ± 0.010**	0.137 ± 0.028*	-
% of body weight	-	0.055 ± 0.006	0.052 ± 0.008*	-
% of brain weight	-	6.7 ± 0.7**	6.7 ± 1.4*	-

^a All values expressed as means ± SD from each group.

Histopathology

All test article-related microscopic findings were noted in injection sites. The microscopic findings observed consisted primarily of acute changes such as inflammation and necrosis affecting variable layers of the skin including epidermis, dermis, pannicular muscle, and panniculus. Additional acute findings were present such as hemorrhage, muscle degeneration, and epidermal lesions such as serocellular crust formation and ulceration; however, these were considered secondary to the main lesions of inflammation and necrosis. Other lesions were considered more chronic in nature and were thought to represent various phases of healing. Of these, fibrosis was considered the most important indicator of chronicity. Additional indicators of healing was present including atrophy of the panniculus muscle and telogen follicles. Inflammation, necrosis and fibrosis were deemed to be the primary lesions as they occurred in most animals across all dose groups in at least one injection site. Some degree of inflammation, necrosis and fibrosis is expected with repeated subcutaneous injection; therefore, the severity and extent of the lesions was used to determine significance.

Treated males in the 2 mg/kg Xeris group had an increased incidence and severity of necrosis, as well as an increased severity of inflammation at injection sites when compared to Lilly males at the same dosage. Additionally, Xeris injected males at 2 mg/kg had an increased incidence of hemorrhage, degeneration of the panniculus muscle and an increased severity of atrophy in the pannicular muscle. Xeris injected male rats in the 2 mg/kg group also had a low incidence of epidermal squamous hyperplasia, serocellular crust formation, thrombosis of blood vessels, and epidermal ulceration, while Lilly males at the same dose displayed none of these findings. In females, a high incidence of inflammation, necrosis, and fibrosis were considered equivocal across all groups of animals, both control and treated.

The inflammation present in injection sites was characterized as primarily mixed in most levels of the skin except in areas of epidermal ulceration where it was more suppurative in nature. Necrosis was most often associated with the formation of injection pockets noted deep within the panniculus that were lined by a thin eosinophilic necrotic lining. Typically the interior of the pocket was devoid of contents, but occasionally contained a small amount of eosinophilic granular material, possibly injection material or cellular breakdown products. Pannicular vasculature was often necrotic surrounding these injection pockets as well and thromboses were occasionally present.

Lesions of epithelial hyperplasia, serocellular crust, thrombosis, and ulceration, in addition to pannicular muscle necrosis, dermal necrosis and epidermal necrosis were often seen together in a single injection site and represent full thickness necrosis of injection sites (necrosis extending from the panniculus to the epidermis). Full thickness necrosis was present in 14 animals (seven from the 2 mg/kg group and seven from the control Xeris group) and was not present in any of the Lilly control or 2 mg/kg animals. The presence of full thickness necrosis in the Xeris control group may indicate sensitivity to the vehicle used. The necrosis present in the 2 mg/kg Xeris male 8747 affected all layers of the skin (full thickness) at site 1; however, sloughing of the epidermis over the affected area occurred in site 3. Epidermal necrosis is therefore absent from the individual findings for site 3 in animal number 8747. Five additional animals displayed extensive necrosis that reached the dermis but did not affect the epidermis (males' 8546 site 3, 8550 site 3, 9200 site 4, and females' 8706 site 4 and 8758 site 3).

Animals with Full Thickness Necrosis

Xeris - 0 mg/kg Animal Number/Admin. Site	Xeris- 2 mg/kg Animal Number/Admin. Site	Sex
	8547/2	M
	8551/2 & 3	M
	8558/3	M
	8747/1 & 3	F
	8750/1	F
	8751/2 & 3	F
	8752/1	F
8701/2		F
8702/3		F
8706/1		F
8710/2 & 3		F
8711/1		F
8713/1		F
8714/1 & 2		F

The tables presented below represent a compilation of data to highlight comparisons between groups. The data were obtained by averaging lesions of the same type from all anatomic locations and all injection sites per animal while accepting the highest severity grade of any affected site. For example, if 'dermis – necrosis, minimal, site 1' and 'panniculus – necrosis, moderate, site 3' were present in the same animal, the moderate severity seen in the panniculus of site 3 was retained and the minimal severity noted in the dermis of site 1 was disregarded. The lesions were considered without regard to location or administration site and thus in the previous example, only 'necrosis, moderate' was recorded. Each individual animal's score for a particular lesion was then combined with all other animals of that dose group and an average severity was calculated by totaling the severity scores for that group and dividing by the number of animals affected. Lesion significance was designated when the incidence was increased by greater than five animals or when the severity was increased one full grade. Note, severity grades are minimal=1, mild=2, moderate=3, marked=4, severe=5.

Injection Site Findings in Terminal Sacrifice Males
(Combined Site Results with Highest Severity)

	Xeris 0 mg/kg	Xeris 2 mg/kg	Lilly 0 mg/kg	Lilly 2 mg/kg
Inflammation	9 (1.9)*	10 (3.2)	9 (2.4)	6 (1.8)
Necrosis	9 (1.2)	10 (3.1)	8 (2.8)	4 (2.0)
Fibrosis	6 (3.0)	8 (3.0)	9 (2.3)	6 (2.3)
Hemorrhage	5 (1.2)	9 (1.3)	7 (1.6)	3 (1.7)
Panniculus Muscle Degeneration	7 (1.4)	9 (2.3)	6 (1.2)	4 (1.5)
Panniculus Muscle Atrophy	7 (2.3)	5 (3.0)	6 (1.7)	6 (1.3)
Panniculus Muscle Regeneration	1 (1.0)	5 (1.0)	2 (1.0)	1 (1.0)
Epidermis Squamous Hyperplasia	2 (1.5)	3 (1.7)	1 (2)	0
Serocellular Crust	1 (2.0)	3 (1.7)	0	0
Thrombosis	0	3 (1.7)	1 (1.0)	0

Ulcer	0	2 (1.0)	0	0
Telogen	0	2 (3.5)	2 (1.5)	2 (2.5)

*Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe

**Injection Site Findings in Terminal Sacrifice Females
(Combined Site Results with Highest Severity)**

	Xeris 0 mg/kg	Xeris 2 mg/kg	Lilly 0 mg/kg	Lilly 2 mg/kg
Inflammation	10 (2.9)*	10 (2.9)	8 (2.2)	10 (3.4)
Necrosis	9 (3.0)	10 (2.6)	7 (2.3)	10 (2.7)
Fibrosis	10 (2.8)	9 (3.0)	8 (2.0)	10 (2.9)
Hemorrhage	7 (1.7)	9 (1.6)	4 (1.5)	7 (2.0)
Panniculus Muscle Degeneration	8 (2.5)	8 (2.5)	5 (2.0)	5 (2.0)
Panniculus Muscle Atrophy	3 (2.0)	8 (2.8)	6 (1.5)	9 (1.8)
Panniculus Muscle Regeneration	2 (1.5)	4 (1.0)	2 (1.0)	3 (1.0)
Epidermis Squamous Hyperplasia	7 (2.3)	6 (2.8)	0	0
Serocellular Crust	8 (3.1)	5 (3.0)	0	0
Thrombosis	5 (1.8)	4 (1.3)	0	1 (1.0)
Ulcer	4 (2.3)	2 (3.0)	0	0
Telogen	1 (2.0)	0	1 (1.0)	0

*Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe

Some of the same microscopic findings noted at the terminal euthanasia were observed at the end of the recovery period (Day 29) though of lesser incidence and severity than the main study

In recovery animals, low incidences of necrosis, inflammation or fibrosis remained in all groups of animals, except the 2 mg/kg Lilly group. Muscular changes such as pannicular degeneration, regeneration, and atrophy, as well as epithelial hyperplasia persisted in 2 mg/kg Xeris males and females and were completely absent from Lilly treated animals of both sexes.

Nearly every animal in the recovery phase displayed hair follicles in late catagen to telogen phase, simply recorded as 'telogen'. These lesions appeared as shortened hair follicles present only along the superficial dermis with the deep dermis completely devoid of follicles. The severity of follicular telogen was determined by the percentage of skin affected in the submitted injection site. Telogen may be related to repeated injection and similar incidence across groups indicates that is unlikely related to the tested compounds.

Injection Site Findings in Recovery Sacrifice Males
(Combined Site Results with Highest Severity)

	Xeris 0 mg/kg	Xeris 2 mg/kg	Lilly 0 mg/kg	Lilly 2 mg/kg
Inflammation	1 (1.0)*	4 (1.5)	2 (1.0)	0
Necrosis	0	0	1 (1.0)	0
Fibrosis	0	4 (1.8)	1 (1.0)	0
Panniculus Muscle Degeneration	0	3 (2.0)	0	0
Panniculus Muscle Regeneration	0	1 (1.0)	0	0
Epidermis Squamous Hyperplasia	0	2 (2.0)	0	0
Telogen	5 (5.0)	5 (4.8)	5 (5.0)	5 (4.8)

*Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe

Injection Site Findings in Recovery Sacrifice Females
(Combined Site Results with Highest Severity)

	Xeris 0 mg/kg	Xeris 2 mg/kg	Lilly 0 mg/kg	Lilly 2 mg/kg
Inflammation	1 (1.0)*	1 (1.0)	0	0
Necrosis	0	0	0	0
Fibrosis	0	3 (1.7)	0	0
Panniculus Muscle Degeneration	0	2 (2.0)	0	0
Panniculus Muscle Atrophy	0	3 (2.0)	0	0
Epidermis Squamous Hyperplasia	0	3 (1.7)	0	0
Telogen	4 (5.0)	5 (5.0)	5 (5.0)	5 (5.0)

*Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked, 5 = severe

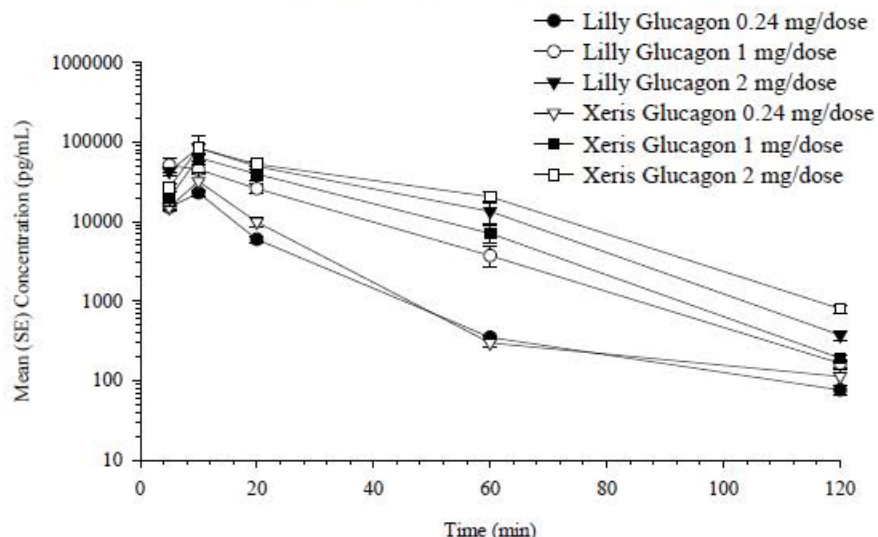
Battery Considered Adequate? Yes

Peer Review Performed? No. Audited second draft report ("not for Regulatory Submission") was submitted.

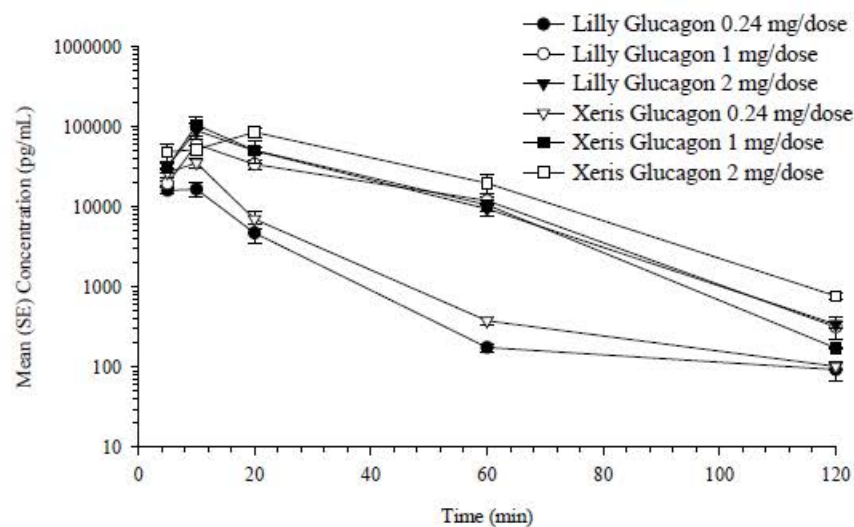
Special Evaluation – Glucose Extension Study

Maximum blood glucose levels were observed between 10 and 120 minutes after injection of Xeris Glucagon or Lilly Glucagon and did not appear to increase with increasing dose. No apparent differences in maximum blood glucose concentration between males and females and between Days 1 and 14 were observed following subcutaneous injection of Xeris Glucagon or Lilly Glucagon.

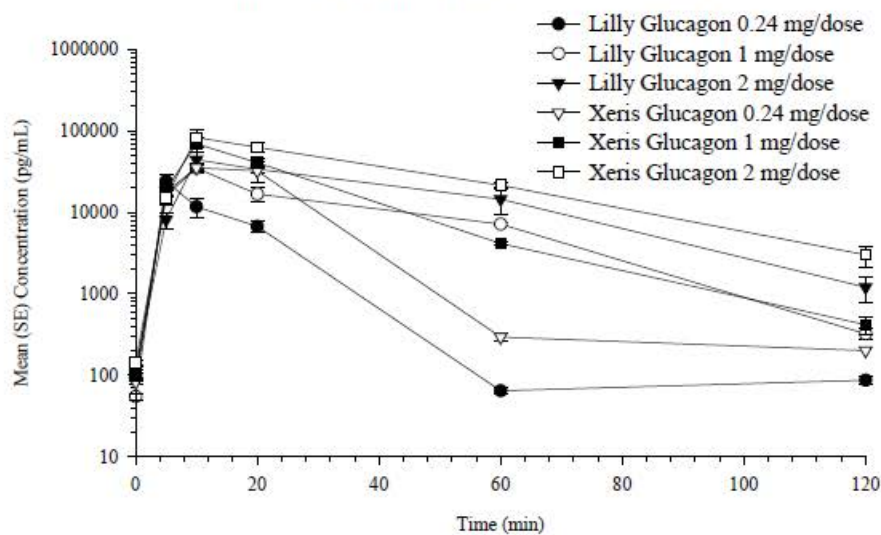
Summary Male Sprague-Dawley Rat Plasma Glucagon Concentrations
Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous
Injection of Lilly Glucagon and Xeris Glucagon on Day 1



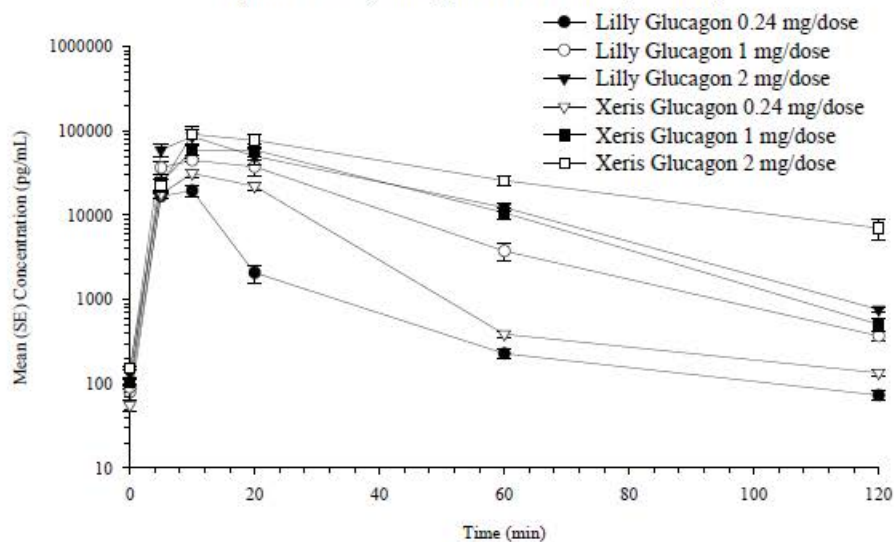
Summary Female Sprague-Dawley Rat Plasma Glucagon Concentrations
Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous
Injection of Lilly Glucagon and Xeris Glucagon on Day 1



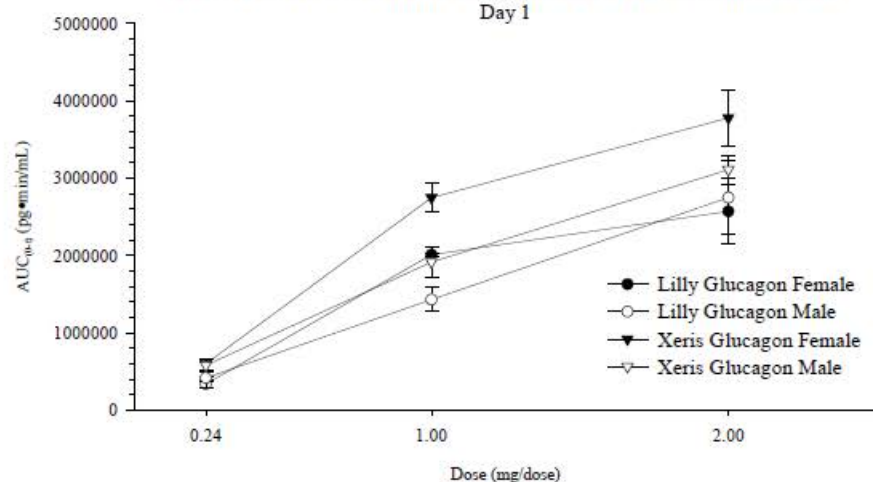
Summary Male Sprague-Dawley Rat Plasma Glucagon Concentrations
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Injection of Lilly Glucagon and Xeris Glucagon on Day 14



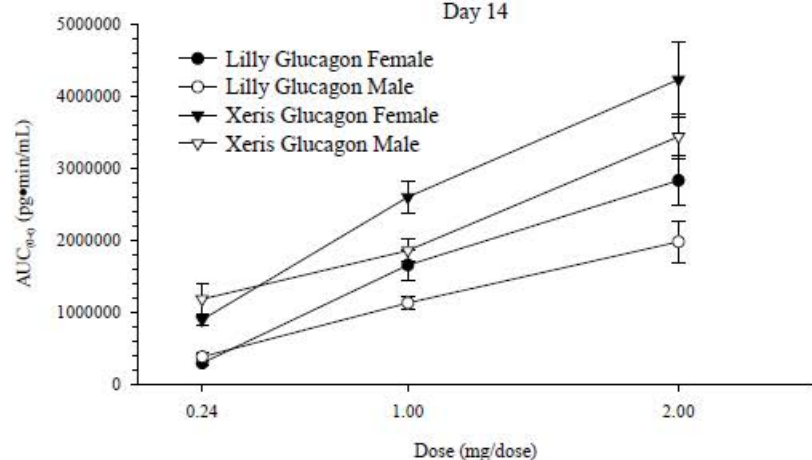
Summary Female Sprague-Dawley Rat Plasma Glucagon Concentrations
Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous
Injection of Lilly Glucagon and Xeris Glucagon on Day 14



Summary (Mean $\pm$ SE) Glucagon AUC_(0-t) vs. Dose in Female and Male Sprague-Dawley Rat Plasma Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Lilly Glucagon and Xeris Glucagon on Day 1



Summary (Mean $\pm$ SE) Glucagon AUC_(0-t) vs. Dose in Female and Male Sprague-Dawley Rat Plasma Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Lilly Glucagon and Xeris Glucagon on Day 14



Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Xeris Glucagon on Day 1

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC _(0-t) (pg•min/mL)	AUC _(0-t) /D (pg•min/mL/mg/dose)	T _{1/2} (min)
0.24	Female	10.0	35,400 $\pm$ 5220	147,000	596,000 $\pm$ 72,700	2,490,000	13.8
	Male	10.0	31,900 $\pm$ 8670	133,000	578,000 $\pm$ 76,000	2,410,000	13.7
1	Female	10.0	105,000 $\pm$ 27,900	105,000	2,750,000 $\pm$ 184,000	2,750,000	12.2
	Male	10.0	63,100 $\pm$ 5150	63,100	1,910,000 $\pm$ 201,000	1,910,000	13.2
2	Female	20.0	85,500 $\pm$ 11,700	42,700	3,780,000 $\pm$ 365,000	1,890,000	14.6
	Male	10.0	83,200 $\pm$ 9980	41,600	3,110,000 $\pm$ 185,000	1,550,000	16.8

Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Xeris Glucagon on Day 14

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC _(0-t) (pg•min/mL)	AUC _(0-t) /D (pg•min/mL/mg/dose)	T _{1/2} (min)	R _{AUC} ^a
0.24	Female	10.0	31,200 $\pm$ 2840	130,000	898,000 $\pm$ 77,500	3,740,000	13.3	1.51
	Male	10.0	35,100 $\pm$ 3240	146,000	1,180,000 $\pm$ 223,000	4,920,000	13.6	2.04
1	Female	20.0	59,300 $\pm$ 9010	59,300	2,600,000 $\pm$ 220,000	2,600,000	14.5	0.945
	Male	10.0	69,300 $\pm$ 13,400	69,300	1,860,000 $\pm$ 153,000	1,860,000	14.8	0.970
2	Female	10.0	90,700 $\pm$ 21,900	45,400	4,220,000 $\pm$ 512,000	2,110,000	29.3	1.12
	Male	10.0	83,000 $\pm$ 19,900	41,500	3,430,000 $\pm$ 313,000	1,720,000	23.0	1.10

^aR_{AUC} = Day 14 AUC_(0-t) / Day 1 AUC_(0-t)

Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma
Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Lilly Glucagon on Day 1

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC ₍₀₋₄₎ (pg•min/mL)	AUC ₍₀₋₄₎ /D (pg•min/mL/mg/dose)	T _{1/2} (min)	AUC ₍₀₋₄₎ Ratio Xeris/Lilly
0.24	Female	10.0	16,600 $\pm$ 3160	69,100	334,000 $\pm$ 44,300	1,390,000	15.1	1.78
	Male	10.0	22,800 $\pm$ 1950	95,100	415,000 $\pm$ 27,300	1,730,000	13.9	1.39
1	Female	10.0	60,400 $\pm$ 14,300	60,400	2,010,000 $\pm$ 180,000	2,010,000	14.9	1.37
	Male	5.00	50,800 $\pm$ 10,300	50,800	1,430,000 $\pm$ 156,000	1,430,000	13.7	1.34
2	Female	10.0	89,700 $\pm$ 19,400	44,800	2,570,000 $\pm$ 424,000	1,280,000	13.8	1.47
	Male	10.0	84,000 $\pm$ 32,300	42,000	2,750,000 $\pm$ 474,000	1,370,000	14.3	1.13

Summary Mean ($\pm$ SE) Glucagon Toxicokinetic Parameters in Female and Male Sprague-Dawley Rat Plasma Following 0.24 mg/dose, 1 mg/dose, and 2 mg/dose Subcutaneous Injection of Lilly Glucagon on Day 14

Dose (mg/dose)	Sex	T _{max} (min)	C _{max} (pg/mL)	C _{max} /D (pg•dose/mL/mg)	AUC ₍₀₋₄₎ (pg•min/mL)	AUC ₍₀₋₄₎ /D (pg•min/mL/mg/dose)	T _{1/2} (min)	R _{AUC} ^a	AUC ₍₀₋₄₎ Ratio Xeris/Lilly
0.24	Female	10.0	19,600 $\pm$ 3050	81,500	296,000 $\pm$ 29,500	1,230,000	21.5	0.885	3.03
	Male	5.00	24,100 $\pm$ 5080	100,000	383,000 $\pm$ 49,200	1,600,000	NC	0.924	3.08
1	Female	10.0	44,900 $\pm$ 2230	44,900	1,650,000 $\pm$ 217,000	1,650,000	15.4	0.823	1.58
	Male	10.0	34,900 $\pm$ 4580	34,900	1,130,000 $\pm$ 94,000	1,130,000	17.0	0.792	1.65
2	Female	10.0	85,500 $\pm$ 17,700	42,700	2,830,000 $\pm$ 343,000	1,410,000	16.4	1.10	1.49
	Male	10.0	44,300 $\pm$ 10,500	22,100	1,980,000 $\pm$ 286,000	988,000	21.3	0.719	1.73

^aR_{AUC} = Day 14 AUC₍₀₋₄₎ / Day 1 AUC₍₀₋₄₎.

Toxicokinetics

In-life and necropsy data for TK animals are presented in Appendix 13 and Appendix 14. Following administration of Xeris Glucagon, the C_{max} of glucagon was generally observed at 10 minutes postdose. The T_{1/2} ranged from 12.2 to 16.8 minutes on Day 1 and from 13.3 to 29.3 minutes on Day 14. The increase in exposure was generally less than dose proportional on DSs 1 and 14 except between 1 and 2 mg/kg/day dose on DS 14 where the increase in exposure was roughly dose proportional.

Following administration of Lilly Glucagon, the C_{max} of glucagon was generally observed at 10 minutes postdose. When estimable, the T_{1/2} ranged from 13.7 to 15.1 minutes on DS 1 and from 15.4 to 21.5 minutes on DS 14. On DS 1, the increase in exposure was generally less than dose proportional within the dose range tested except for males between 1 and 2 mg/kg/day where the increase in exposure was approximately dose proportional. On DS 14, the increase in exposure was generally less than dose proportional within the dose range tested except between 1 and 2 mg/kg/day where the increase in exposure was roughly dose proportional.

Following administration of Xeris Glucagon or Lilly Glucagon, no gender differences in systemic exposure was observed. No accumulation of glucagon was observed following repeated administration of Xeris Glucagon or Lilly Glucagon except for males administered the 0.24 mg/kg/day dose of Xeris Glucagon with an accumulation ratio of 2.04. Xeris Glucagon to Lilly Glucagon AUC_(0-t) ratios ranged from 1.13 to 1.78 on DS 1 and from 1.49 to 3.08 on DS 14, indicating that plasma levels of glucagon tended to be higher following repeated administration of Xeris Glucagon compared to Lilly Glucagon. The slight increase in the plasma levels of glucagon after repeated doses of the Xeris Glucagon did not appear to increase toxicity in the dose groups.

Dosing Formulation Analysis

Finished formulations were analyzed prior to start of study and Statements of Testing indicate that the labeled concentrations of Xeris Glucagon met adequate acceptance criteria. The Xeris Glucagon vehicle also met adequate acceptance criteria of absent API.

Toxicology Data on Glucagon from the published literature and approved labeling

6.2 Repeat-Dose Toxicity

Under NDA No. 20-928, a fourteen-day toxicity study was conducted with Lilly Glucagon. Ten Fischer 344 rats/sex/group were administered daily subcutaneous doses of 0, 0.24, 1, or 4 mg rGlucagon/kg for 2 weeks. All rats survived the 2-week treatment period. There were no treatment-related clinical observations, changes in body weight or food consumption, or ocular effects.

Plasma concentrations of rGlucagon increased linearly with dose and reached peak concentrations at approximately 10 to 20 minutes after treatment. Females had higher apparent clearances, generally producing lower maximum plasma concentration (C_{max}) and AUC values compared to males. On Day 14, C_{max} and AUC values for both sexes and for each dose group were nearly double those reported on Day 0. The difference between Days 0 and 14 was interpreted as being due to a change in bioavailability. Treatment-related hematological changes included slight increases in thrombocyte and neutrophil counts in females given 4 mg/kg, increases in glucose, albumin, total protein, and slight decreases in cholesterol and blood urea nitrogen. These hematological changes and clinical chemistry effects might not appear to be toxicologically significant due to the magnitude and direction of the changes. There were slight, dose-related increases in absolute and relative liver weights (8% in the 0.25 mg group and 35% in the 4 mg group) which were not accompanied by distinctive histopathologic correlates or clinical chemistry evidence of liver toxicity.

The subcutaneous NOAEL for this fourteen day study was reported to be 4 mg/kg/day (4000 μ g/kg) for the rat.

Rat Safety Margin for Lilly Glucagon

Toxicity	Species	NOAEL (mg/kg) M/F	Safety Margin Based on Highest Clinical Dose*
14 Day Repeat Dose Study	Rat	4000 µg/kg	240X
		24,000 µg/M ²	38.8X

**Approved human dose for Lilly Glucagon is 1000 µg SC injection.
(1000 ug/60 kg = 16.7 ug/kg; 16.7 x 37 = 618 ug/M²).

In two-week studies with three beagle dogs per sex per group under NDA No. 20-928, IV glucagon injection (up to 0.2 mg/kg daily) did not result in mortality, although increased heart rate was observed 30 minutes following IV administration of 0.2 mg/kg/day. There were no treatment-related increases in body weight gain and food consumption. No treatment-related ocular and hematological changes were noted. The mean, absolute, and relative kidney and liver weights of all the treated groups were higher than those of the controls. There was no gross or histopathological evidence of toxicity in any of the organs and tissues examined. The intravenous NOAEL for this two-week study was observed to be 0.2 mg/kg/day for the beagle dog.

10 Integrated Summary and Safety Evaluation

Subcutaneous administration of Xeris Glucagon once a day to Sprague-Dawley rats from Days 1 to 14 at doses of 0, 0.24, 1, or 2 mg/kg resulted in no early deaths. Increased liver weights were noted in males and females in both the Xeris and Lilly Glucagon 2 mg/kg dose groups. The increased liver weight is likely a treatment related effect, though no histologic correlate was present. Decreased adrenal gland weights were also noted in the 2 mg/kg Xeris Glucagon males and may be treatment related; however, no histologic correlate was present. At the end of the treatment period gross findings of 'scab' were correlated to areas of epidermal necrosis and serocellular crust formation in those animals with full thickness necrosis at injection sites. Any test article related lesions were confined to injection sites and no systemic effects related to compound administration were noted. Injection site lesions in Xeris treated (2 mg/kg) animals at Day 15 were considered to be more severe overall, as full thickness necrosis occurred only in Xeris 0 mg/kg and 2 mg/kg animals, possibly indicating a vehicle effect. The 2 mg/kg Xeris males demonstrated increased incidence and severity of most injection site lesions when compared with 2 mg/kg Lilly males; however, females of all dose groups responded similarly, possibly indicating a sex-specific difference in response to injected material. In the recovery phase, low incidences of necrosis, inflammation and fibrosis remained in all groups of animals, except the 2 mg/kg Lilly group. The deeper changes of pannicular muscle degeneration, regeneration, and atrophy, as well as epithelial hyperplasia, persisted in the 2 mg/kg Xeris males at Day 29. None of these lesions were present in 2 mg/kg Lilly males or females. Telogen was present in nearly every animal across all groups and is likely the result of repeated injections and unrelated to test article administration.

Subcutaneous administration of Xeris Glucagon once a day to Sprague-Dawley rats from Days 1 to 14 at doses of 0, 0.24, 1, or 2 mg/kg resulted in no early deaths. Increased liver weights were noted in males and females in both the Xeris and Lilly Glucagon 2 mg/kg dose groups. The increased liver weight is likely a treatment related effect, though no histologic correlate was present. Decreased adrenal gland weights were also noted in the 2 mg/kg Xeris Glucagon males and may be treatment related; however, no histologic correlate was present. At the end of the treatment period gross findings of 'scab' were correlated to areas of epidermal necrosis and serocellular crust formation in those animals with full thickness necrosis at injection sites. Any test article related lesions were confined to injection sites and no systemic effects related to compound administration were noted. Injection site lesions in Xeris treated (2 mg/kg) animals at Day 15 were considered to be more severe overall, as full thickness necrosis occurred only in Xeris 0 mg/kg and 2 mg/kg animals, possibly indicating a vehicle effect. The 2 mg/kg Xeris males demonstrated increased incidence and severity of most injection site lesions when compared with 2 mg/kg Lilly males; however, females of all dose groups responded similarly, possibly indicating a sex-specific difference in response to injected material. In the recovery phase, low incidences of necrosis, inflammation and fibrosis remained in all groups of animals, except the 2 mg/kg Lilly group. The deeper changes of pannicular muscle degeneration, regeneration, and atrophy, as well as epithelial hyperplasia,

persisted in the 2 mg/kg Xeris males at Day 29. None of these lesions were present in 2 mg/kg Lilly males or females. Telogen was present in nearly every animal across all groups and is likely the result of repeated injections and unrelated to test article administration.

Rat Safety Margin for Xeris Glucagon

Toxicity	Species	NOAEL* (mg/kg) M/F	Safety Margin Based on Highest Clinical Dose**
14 Day Dose Study Injection sites Males- ↑necrosis, ↑inflammation Males & Females-full thickness necrosis	Rat	2 mg/kg M/F or	20X

*NOAEL is the highest dose (2 mg/kg) administered (Toxicology Study XSGPE-TX02) which provides a 20-fold exposure margin over the highest recommended human dose (1 mg) on an HED basis.

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/s/

ROBERT W MAHER
09/23/2013

KAREN L DAVIS BRUNO
09/24/2013

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: 115091
Supporting document/s: IND-115091; ORIG-1; SD-4; Vols.1, 2
Sponsor's letter date: December 17, 2012
CDER stamp date: December 21, 2012
Product: G-Pen™ (Glucagon for Injection)
Indication: Treatment of Severe Hypoglycemia
Sponsor: Xeris Pharmaceuticals Inc.
Review Division: DMEP
Reviewer: Robert W. Maher Ph.D., DABT
Supervisor/Team Leader: Karen Davis-Bruno Ph.D.
Division Director: Mary Parks, M.D.
Project Manager: Meghna M. Jairath Pharm. D.

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Sponsor submitted a pre-IND Information Package on April 17, 2012 which included a statement to initiate a single nonclinical two week toxicology subcutaneous rat study that would compare the Xeris' synthesized Glucagon product with Lilly's rDNA Glucagon product. The study would compare the toxicity of the two products along with a kinetics profile. Literature would be provided to describe the safety and efficacy of Xeris' synthesized Glucagon by referencing Lilly's rDNA Glucagon. Literature would also adequately support the use of novel excipients in the Xeris Glucagon formulation.

1.2 Brief Discussion of Nonclinical Findings

Sponsor provided a single 14 Day rat toxicity study in which two daily doses of 5 µg/rat of Xeris Glucagon was administered subcutaneously to compare with the toxicity of 5 µg Lilly Glucagon along with the respective vehicles for each formulation (n = 10 rats/sex/gp). Following a 13 day observation period in which all the animals survived, a complete clinical and histopathology examination was completed on each animal. The findings of toxicity were found to be generally unremarkable due to the low dose exposure of glucagon.

A previous report of Lilly's rDNA Glucagon stated that the NOAEL following 14 days of subcutaneous dosing is 4000 µg/kg in rat. A comparison dose of 5 µg/rat for Xeris Glucagon vs. Lilly Glucagon is inadequate to determine a meaningful safety profile similarity of these two products.

1.3 Recommendations

Partial Clinical Hold

Listed below is a comparison of the differences between the Xeris Glucagon product and the currently approved Lilly Glucagon product:

Comparison of G-Pen™ and Eli Lilly's Glucagon™

	Component	Concentration (% w/w)	To deliver Concentration (mg/unit)	Function
G-Pen™ (glucagon for injection)	Glucagon (synthetic)	(b) (4)	1.00	Drug Substance
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Trehalose	(b) (4)	11.1	(b) (4)
	DMSO	(b) (4)	(b) (4)	(b) (4)
	Totals	(b) (4)	(b) (4)	(b) (4)
Glucagon™ [Glucagon for Injection (rDNA origin)]	Component	Concentration (% w/w)	To deliver Concentration (mg/unit)	Function
	Glucagon (rDNA origin)	(b) (4)	1.0	Drug Substance
	Lactose	(b) (4)	49.0	(b) (4)
	Totals	(b) (4)	(b) (4)	(b) (4)

Each component in the Xeris Glucagon product is different from those present in the Lilly Glucagon product, except for HCl. Xeris Glucagon is a novel product by method of glucagon manufacture and excipients used to formulate.

In this IND application, a single toxicity study was submitted: "A GLP Pharmacokinetics and Fourteen-Day Subcutaneous Toxicity Study with Glucagon in Rats. Study no.: CB12-5015-R-TX.

This comparative study is inadequate in determining the safety profile of Xeris Glucagon compared to Lilly Glucagon. A pharmacological dose of 5 µg/rat of Xeris Glucagon was administered sc on two consecutive days followed by a 13 day observation period. This dose was compared to the same dose of Lilly Glucagon. This study design is not a 14 day repeat dose toxicity study, which would be designed to determine the NOAEL and/or MTD of the novel formulation of Xeris Glucagon following daily repeat dosing for 14 days with a comparison to Lilly Glucagon dosed at a known NOAEL or MTD.

1.3.1 Clinical Study (ies) to Proceed: No, Partial Clinical Hold

1.3.2 If Not Safe to Proceed

Nonclinical deficiencies

Inadequate nonclinical safety evaluation of Xeris Glucagon. Provide a repeat dose toxicity study (minimum 2 week dosing duration) which provides a margin of safety for the product for comparison to the proposed clinical dose. The 14 day Xeris Glucagon rat study (two daily doses) was dosed sc with (b) (4)/rat or (b) (4). The proposed human clinical sc dose for Glucagon is 1 mg/patient or (b) (4).

(b) (4) The 14-day rat toxicity study submitted is inadequate with regard to the dose and duration tested.

Nonclinical information needed to resolve deficiencies

Provide a 14 day daily repeat dose rat toxicity study utilizing three dose levels of Xeris Glucagon, a Xeris Glucagon Vehicle Control, and for a safety comparison, the reported 14 day repeat dose rat NOAEL (4 mg/kg/day) or MTD dose of Lilly Glucagon. The proposed study protocol design should be submitted for review prior to initiation.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional) 9007-92-5

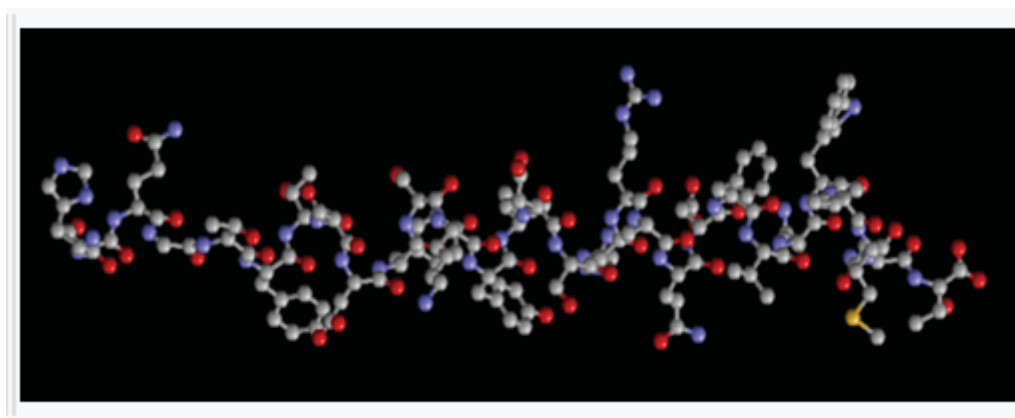
Generic Name Glucagon

Code Name Glucagonoid; Glukagon; HG-Factor; Hyperglycemic-glycogenolytic Factor;

Chemical Name Glucagon

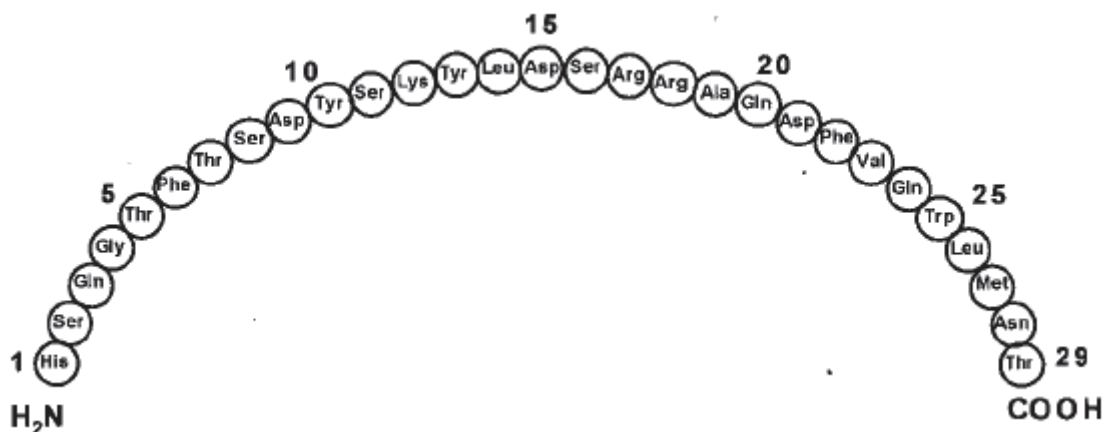
Molecular Formula/Molecular Weight $C_{153}H_{225}N_{43}O_{49}S/3482.75$

Structure or Biochemical Description



Glucagon

NH₂-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu- Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gin-Trp-Leu-Met-Asn-Thr-COOH



Pharmacologic Class

Hypoglycemia Antidotes, Diagnostics, Gastrointestinal, Glucose-Elevating Agents, Glycogenolytic Hormone

Mechanism of Action

Glucagon binds to the glucagon receptor, a G protein-coupled receptor, located in the plasma membrane. The conformation change in the receptor activates G proteins, a heterotrimeric protein with α , β , and γ subunits. When the G protein interacts with the receptor, it undergoes a conformational change that results in the replacement of the GDP molecule that was bound to the α subunit with a GTP molecule. This substitution results in the releasing of the α subunit from the β and γ subunits. The alpha subunit specifically activates the next enzyme in the cascade, adenylate cyclase.

Adenylate cyclase manufactures cyclic adenosine monophosphate (cyclic AMP or cAMP), which activates protein kinase A (cAMP-dependent protein kinase). This enzyme, in turn, activates phosphorylase kinase, which, in turn, phosphorylates glycogen phosphorylase, converting into the active form called phosphorylase A. Phosphorylase A is the enzyme responsible for the release of glucose-1-phosphate from glycogen polymers.

2.2 Relevant INDs, NDAs, BLAs and DMFs

Glucagon is currently marketed by Eli Lilly & Co. as Glucagon™ (glucagon for injection [rDNA origin]), and Novo Nordisk as GlucaGen® HypoKit®, both RLDs for treatment of severe hypoglycemia. The Agency first approved purified porcine glucagon HCl, marketed by Lilly, for use in humans in 1960. Quad Pharmaceuticals was later approved to manufacture generic versions of glucagon HCl (ANDA 71-022, 71-023). However all animal- purified glucagon formulations were discontinued as rDNA-derived glucagon was approved for use in 1998. Both Lilly and Novo recombinant glucagon products were approved in 1998 and is currently the subject of two approved NDAs ([NDA 20-928] and [NDA 20-918]).

2.3 Drug Formulation

Glucagon for Injection (rDNA origin) is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Glucagon is synthesized in a special non-pathogenic laboratory strain of *Escherichia coli* bacteria that has been genetically altered by the addition of the gene for glucagon. Xeris' drug product is produced by solid-phase peptide synthesis (SPPS) which also conserves the glucagon peptide sequence.

G-Pen™ (Glucagon for Injection) 1 mg is a sterile subcutaneous injectable non- aqueous formulation supplied in 1.0 mL long (b) (4) pre-filled (b) (4) (b) (4) syringe with (b) (4) plunger, under investigation for treatment of severe hypoglycemia in type 1 or insulin-dependent type 2 diabetic patients. The composition per 1 mg dose of G-Pen™ (glucagon for injection) is as follows.

G-Pen™ Dose Composition

Component	Dose Amount (mg/unit)
Glucagon	1.00
(b) (4)	
Trehalose (α,α -dihydrate)	11. (b) (4)
Dimethyl Sulfoxide (DMSO)	(b) (4)
(b) (4)	

2.4 Comments on Novel Excipients

Excipients in Xeris Glucagon formulation novel to the Lilly Glucagon product:

(b) (4)

Trehalose (α,α -dehydrate) (CAS 6138-23-4), also known as mycose or tremalose is not listed in the USFDA IISADP.

DMSO (CAS 67685) for sc implant has a maximum potency* of (b) (4) mg which is less than the (b) (4) mg contained in Xeris Glucagon.

*maximum potency specifies the maximum amount of inactive ingredient for each route/dosage form containing that ingredient. When there is no calculable potency measurement for the inactive ingredient, the "maximum potency" field will be blank.

2.5 Comments on Impurities/Degradants of Concern

To use the injectable form of glucagon, it must be reconstituted prior to use, a step that requires a sterile diluent to be injected into a vial containing powdered glucagon, because the hormone is highly unstable when dissolved in solution. When dissolved in a fluid state, glucagon can form amyloid fibrils, or tightly woven chains of proteins made up of the individual glucagon peptides, and once glucagon begins to fibrillize, it becomes useless when injected, as the glucagon cannot be absorbed and used by the body.

The Xeris Glucagon product will be in a sterile subcutaneous injectable non-aqueous formulation which will reduce the possibility of glucagon forming amyloid fibrils.

2.6 Proposed Clinical Protocol

Title: A Randomized, Phase 2, Double-blind, 3-way Crossover Study with G-Pen™ (Glucagon for Injection) to Evaluate safety, Tolerability and Comparative Pharmacodynamics to Lilly Glucagon™ (Glucagon for Injection [rDNA Origin]) in Healthy Volunteers.

The proposed IND study is a Phase 2 study with three objectives:

- (1) to evaluate the safety and tolerability of G-Pen™ (glucagon for injection) 1mg
- (2) to compare the pharmacokinetics of G-Pen™ (glucagon for injection) 1mg [test] administered as 0.5 mg and 1 mg injections, versus Lilly Glucagon™ (glucagon for injection [rDNA origin]) 1 mg (reference), and
- (3) to evaluate the glucodynamics (efficacy) of G-Pen™ (glucagon for injection) 1mg.

2.7 Previous Clinical Experience

None with the proposed Xeris Glucagon Product.

2.8 Regulatory Background

The safety, tolerability, and pharmacokinetics of rDNA glucagon in humans has been previously characterized. Glucagon has a long history of medical use in the US, and is currently marketed by Eli Lilly & Co. -as Glucagon™ (glucagon for injection [rDNA origin]), and Novo Nordisk as GlucaGen® HypoKit®, both Reference Listed Drugs for treatment of severe hypoglycemia.

3 Studies Submitted

3.1 Studies Reviewed

CB12-5015-R-TX. A GLP Pharmacokinetics and Fourteen-Day Subcutaneous Toxicity Study with Glucagon in Rats. (PK Report in Preparation) (Unsigned QA Statement/Final Report)

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

Follow-up Questions to Pre-IND 115091 Written Response Dated June 21, 2012
Attachment 1

Robert Maher PhD. DABT CDER/ODE2/DMEP

Sponsor: Xeris Pharmaceuticals, Inc.

Product: G-Pen™ (Glucagon for Injection)

Proposed Indication: Treatment of Severe Hypoglycemia

Protocol No.: XSGP-201

Date Received: July 10, 2012

Date Reviewed: July 16, 2012

4 Pharmacology

4.1 Primary Pharmacology

Glucagon is an insulin antagonist, which stimulates cAMP synthesis to accelerate hepatic glycogenolysis and gluconeogenesis.

4.2 Secondary Pharmacology

Glucagon relaxes smooth muscles of the gastrointestinal tract.

4.3 Safety Pharmacology

Glucagon acts very quickly; commonly side-effects include headache and nausea. Generalized allergic reactions, including urticaria, respiratory distress, and hypotension have been reported in the clinical literature.

5 Pharmacokinetics

5.1 PK

Table 8-5. Summary Pharmacokinetic Data, Study CB12-5015-R-TX

Parameter (units)	Group/Glucagon Dose							
	2.5 µg Xeris		5 µg Xeris		50 µg Xeris		5 µg Lilly	
	Male	Female	Male	Female	Male	Female	Male	Female
C_{max} (pg/mL)	7,423	9,782	14,909†	10,043‡	73,716†	83,564†	7,620‡	5,575‡
T_{max} (min)	6.25	3.89	6.00	3.61	7.50	7.50	6.39	4.75
AUC (pg·min/mL)	69,134	94,751	169,569	106,589	1,206,337†	1,446,123†	107,799	66,337
CL (mL/min)	66.6	49.4	58.9	106.4	50.3	38.4	74.9	102.6
t_{1/2} (min)	13.6	9.2	7.9	10.5	8.2	9.4	8.8	11.3
V_{ex} (mL)	1,677	694	816	2,002	899	667	1,227	1,723

*p < 0.0001 comparing all groups

†P < 0.0001 versus each other group

‡p = 0.0424 comparing specific groups

Mean Average Comparison of 5 µg Xeris Group with 5 µg Lilly Group

	5 µg Xeris vs. 5 µg Lilly	
	Male Rats	Female Rats
C _{max} (pg/mL)	↑51%	↓32%
T _{max} (min)	↓7%	↓24%
AUC (pg·min/mL)	↑57%	↑61%
CL (mL/min)	↓22%	↑4%
t _{1/2} (min)	↓10%	↓7%
V _{ex} (mL)	↓33%	↑16%

Pharmacokinetics report has not been received. The standard deviations are not provided in the pharmacokinetics report summary. The sc injection of 5 µg Xeris Glucagon resulted in a higher mean average (51%) for male rats and a lower mean average (32%) for females compared to 5 µg Lilly Glucagon. In addition, the AUC was 57% higher for males and 61% higher for females in the 5 µg Xeris Glucagon compared to the 5 µg Lilly Glucagon.

6 General Toxicology

6.1 Two-Dose Toxicity Study (one dose daily/2 days, 14 days observation/recovery)

Study title: A GLP Pharmacokinetics and Fourteen-Day Subcutaneous Toxicity Study with Glucagon in Rats.

Study no.: CB12-5015-R-TX.

Study report location: (b) (4)

Conducting laboratory and location: (b) (4)

Date of study initiation: 28 June 2012

GLP compliance: (PK Report in Preparation; Draft Pathology Report, Unsigned QA Statement/Final Report)

QA statement: Unsigned

Drug, lot #, and % purity: Test Article Analyses not provided.

Key Study Findings

Phase 1: This phase consisted of four groups of 20 rats (10 male, 10 female) each. Prior to study start, animals were examined, weighed, and assigned to study groups. Animals were fasted overnight before dosing on Day 0, but not Day 1. On Day 0, overnight-fasted animals of Groups 1 - 4 were injected subcutaneously (SC) with Xeris vehicle (1 microliter), Xeris glucagon, 5 micrograms (5 microliters), Lilly vehicle, 5 microliters or Lilly glucagon, 5 micrograms (5 microliters), (respectively). Dosing was repeated on Day 1 (i.e., a total of 2 doses; no fast before second dose on Day 1). Animals subsequently were assessed by clinical observation (once daily; qd) and body weight (once weekly; q1w). On Day 14, animals were euthanized following terminal bleeds for clinical chemistry and hematology parameters. Carcasses were subjected to gross necropsy, including weighing and collection of the protocol-specified organs and tissues. Specified tissues were fixed and processed for microscopic evaluation by a board-certified veterinary pathologist.

Phase 2: Pharmacokinetics and blood glucose were assessed. Pharmacokinetic report was not provided although Pharmacology/Toxicology Summary includes findings.

There was no mortality in the toxicity study (Phase 1) and the two mortalities seen in the PK study (Phase 2) were associated with cannula problems and trauma induced by

blood collection. The most frequent clinical observation was no significant observation (normal), with only a very few minor observations which were noted across all groups. Body weight gain in males, but not females (Group 4) dosed with Lilly glucagon was significantly decreased ($p < 0.01$) compared with Lilly vehicle treated animals at the two-week time point. In contrast, females dosed with Xeris glucagon, but not males (Group 2) showed a small, but significant ($p < 0.05$) increase in weight gain (for normalized weight only) compared to those receiving the Xeris vehicle (Group 1) at the two-week time point. It is unclear why weight gain effects observed were confined to one sex and why they appear to be in opposite directions for the Xeris and reference (Lilly) glucagon.

There were several significant changes noted in the clinical pathology (hematology, clinical chemistry, and coagulation), but generally only in one sex. Xeris glucagon did not produce some of the changes in clinical pathology parameters that were produced by Lilly glucagon administration: no decrease in reticulocytes (in females); no decrease in coagulation time (in females); and no decrease in alkaline phosphatase (in males). Males dosed with Xeris glucagon did, however, still experienced a significant decrease ($p < 0.05$) in calcium similar to the Lilly glucagon dosed males, while Xeris glucagon dosed females experienced an increase in MCV ($p < 0.01$) and MCH ($p < 0.05$) which was not observed in the Lilly glucagon-dosed animals (male/female).

In terms of organ weight changes, Xeris glucagon induced a significant increase in both the absolute weight as well as body weight and brain weight normalized weight of the kidney in the male ($p < 0.01$, also) and heart in the female ($p < 0.05$, also brain weight normalized) while Lilly glucagon produced a significant decrease in only body weight normalized kidney (in females only) and an increase in body-weight normalized brain (in males only). There was also a significant decrease ($p < 0.05$) in the thyroid weight of Xeris glucagon-treated females, but only in body weight normalized data. It is unlikely that any of the changes described above that were seen in only one sex and not the other had any functional or toxicological significance.

Histopathology:

There were no histopathological findings or changes noted indicative of test article-related toxicity. There were no differences noted in the histology between the Xeris glucagon-treated animals and animals treated with the Xeris vehicle. Similarly, there were no histopathological differences noted between the Lilly glucagon-dosed animals and the animals dosed with the Lilly vehicle. All findings were generally within normal limits for all tissues examined. The only treatment-related finding was a generally trace to mild inflammation of the injection site noted in 9/20 animals treated with Xeris glucagon and only 1/20 animals in each of the other treatment groups. There were a few histopathological findings that were considered incidental or spontaneous findings that occurred at low frequency (typically 1-2 animals) in one or more groups and were not thought to be related to treatment.

These minor findings suggest the Xeris glucagon may have produced a low grade local tissue reaction at the injection site, but there were no findings of toxicological significance.

Phase 2:

Blood Glucose data (BG, from Phase II) was slightly different in males and females for both the Xeris glucagon-treated animals and the Lilly glucagon-treated animals. The peak effect of the Lilly glucagon occurred at approximately 10 minutes in both males and females, but decreased at different rates in males and females. The blood glucose effects of the three doses of Xeris glucagon were generally inversely proportional to the dose in both males and females. The Xeris BG curves had different shapes in males vs. females: in males there was a rapid rise to a peak effect followed by a slow decline (except the high-dose which declined only to approximately 30 minutes and then increased to above previous peak); in females the Xeris glucagon produced a slow rise in BG, generally reaching a peak at 60 minutes (last time point).

Both males and females treated SC on two consecutive days with 5 µg of Xeris glucagon showed no obvious ill effects from the treatment and appeared normal throughout the study. The most frequent clinical observation was no significant observation (normal) small but significant changes in body weight gain were noted, but in opposite directions in males and females: Males administered Lilly glucagon showed a significant decrease ($p < 0.01$) in weight gain (two weeks post dose), while females administered Xeris glucagon showed a small but significant ($p < 0.05$) increase in weight gain (normalized weight only at two weeks post dose). No effects on appetite were noted in any of the groups. Xeris glucagon administration appeared to induce fewer changes in hematology, coagulation and clinical chemistry parameters than Lilly glucagon. Xeris glucagon treatment produced a significant increase in MCV ($p < 0.01$) and MCH ($p < 0.05$) in females and a significant decrease ($p < 0.05$) in calcium in males. Lilly glucagon produced a decrease in alkaline phosphatase and reticulocytes ($p < 0.01$, absolute numbers and %) in males and a decrease in coagulation time in females. Absolute organ weights suggested that in Xeris glucagon-treated animals there was a significant increase ($p < 0.01$) in kidney weight in males and heart weight ($P < 0.05$) in females. The meaning, and importance of the changes seen in only one sex and not the other was unclear, but were not thought to represent toxicologically meaningful changes. Histological examination of H & E stained paraffin-embedded tissue sections by a board-certified veterinary pathologist revealed no macroscopic or microscopic histological changes resulting from administration of Xeris glucagon or the reference compound, Lilly glucagon, when administered under the conditions used in this study and when compared to the respective vehicles used for each of these compounds. Xeris glucagon at 5 µg was well tolerated, showed no treatment-related toxicity and as the only dose given, 5 µg was considered the no observed adverse effect level (NOAEL) dose. This determination is in stark contrast to the Lilly Glucagon reported subcutaneous NOAEL for a fourteen day repeat dose toxicity study, which was observed to be 4 mg/kg/day for the rat. Clearly, the dose utilized in this Xeris Glucagon

safety study was not a toxic dose and was, based on the effects observed on blood glucose, in fact a low pharmacological dose.

Methods

Phase 1 (Toxicology)

Group	Animal No. (male/female)	Dose* (per rat, SC, QD, Days 0 & 1)			Procedures
		Treatment	Dose Size	Dose Volume	
1	101-110/ 151-160	Xeris Vehicle	0 µg	1 µL	• Body weight: pre-dose, q1w, Day 14 • Blood for clinical pathology: Day 14 • Clinical observations: qd, Days 0-14 • Necropsy, organ weights, sample collection, and fixation (Day 14) • Histopathology
2	201-210/ 251-260	Xeris Glucagon	5 µg	1 µL	
3	304-313**/ 351-360	Lilly Vehicle	0 µg	5 µL	
4	401-410/ 451-460	Lilly Glucagon	5 µg	5 µL	

* Injection sites were marked to facilitate collection at necropsy. Animals were fasted overnight prior to Day-0 dosing only.

** See Deviation 1 (Appendix B) regarding Group-3 animal numbers

Phase 2 (Pharmacokinetics)

Group	Animal No. (male/female)	Dose* (per rat, SC)			Bleeds
		Treatment	Dose Size	Dose Volume	
5	501-510/ 551-560	Xeris Glucagon	2.5 µg	0.5 µL	• Collect blood (~0.35 mL/time point) at 0, 2.5, 5, 10, 15, 30, 45, and 60 min • Test 1 drop for blood glucose • Remainder (~0.3 mL) for PK: Add aprotinin, isolate plasma, freeze at -80 °C
6	601-610/ 651-660	Xeris Glucagon	5 µg	1 µL	
7	701-710/ 751-760	Xeris Glucagon	50 µg	10 µL	
8	801-810/ 851-860	Lilly Glucagon	5 µg	5 µL	

* Animals were fasted overnight prior to dosing.

Phase II: After blood collection, animals were euthanized and discarded.

Doses:

Phase 1, Safety: Xeris Glucagon Vehicle, 5 µg Xeris Glucagon, Lilly Glucagon Vehicle, or 5 µg Lilly Glucagon.

Phase 2, Pharmacokinetics: 2.5 µg Xeris Glucagon, 5 µg Xeris Glucagon, 50 µg Xeris Glucagon or with 5 µg Lilly Glucagon.

Frequency of dosing: Daily on Days 0 and 1.

Route of administration Subcutaneous

Dose volume:

Phase 1 Xeris vehicle and Xeris Glucagon - 1 µL; Lilly vehicle and Lilly Glucagon - 5 µL.

Phase 2 Xeris Glucagon 2.5µg, 0.5µL; 5µg, 1µL; 50µg, 10µL; Lilly Glucagon - 5µg, 5µL.

Formulation/Vehicle:

Xeris glucagon, a proprietary non-aqueous formulation of the peptide hormone, was provided by the Sponsor. This test and control articles were manufactured by (b) (4) and was supplied as 14 pre-filled (approximately 200 µL each) syringes, individually packaged in foil pouches and labeled as Lot FFM-12-019, and FFM-12-018, respectively (no expiration dates indicated).

Positive control article was Glucagon for Injection (rDNA Origin) (NDC 0002-8031-01), a product of Eli Lilly (Indianapolis, IN,), Lot A 335580 (exp. Oct 2013). Lilly Vehicle Control was the diluent from the same Lot.

Species/Strain: SD-HLA® (SD)CVF® (Sprague-Dawley equivalent) outbred rats (*Rattus norvegicus*)

Number/Sex/Group: Phase 1 - 5/sex/gp; Phase 2 – 10/sex/gp

Age: Not stated.

Weight: Approximate weight ranges of 200-250 g and 180-200 g each for the males and females (respectively) on arrival

Unique study design: Acute Toxicology study with Single dose/Days 0 and 1, followed by 13 days observation/recovery.

Deviation from study protocol: None that affected the interpretation of the study.

Observations and Results

Mortality Phase 1 (Safety) None; **Phase 2 (Pharmacokinetics)** Two females in the (one in the 2.5 µg group and one in the 5 µg group), within 30 mins, likely due to cannula malfunctions and not considered test article-related.

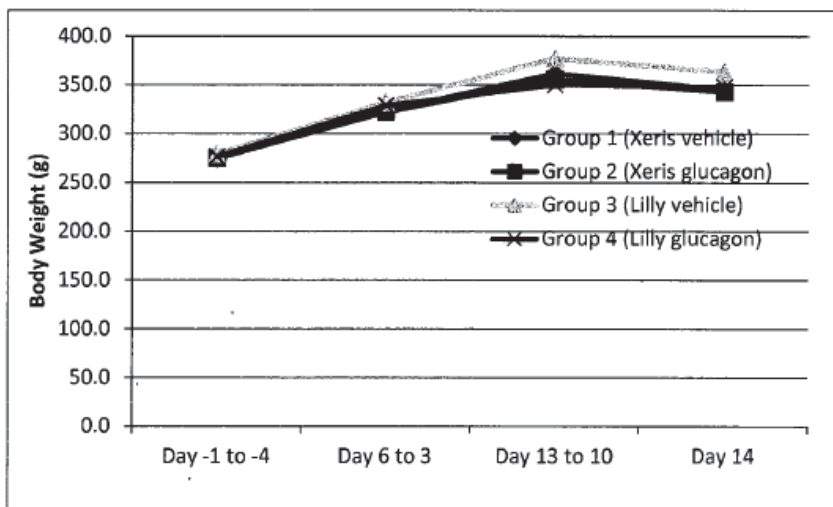
Clinical Signs

Few animals exhibited scabs and/or scrapes on the back, one animal also exhibited swelling of the dorsum for two days. These signs were presumably related to the injection site. A single Group 3 animal had dried blood around the left eye through Day 10. There were no other significant observations.

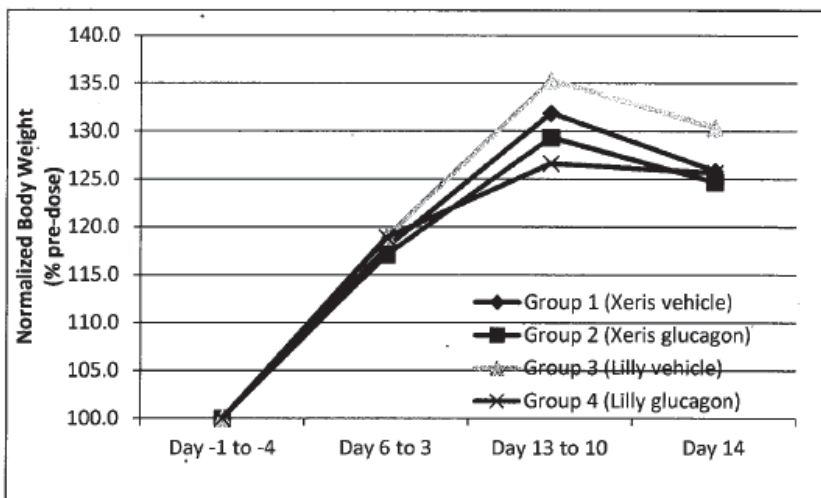
Body Weights

Lilly Glucagon male weight gain was significantly reduced ($p < 0.01$) compared to the vehicle control group, while the female group change was unremarkable. Females in the Xeris Glucagon group exhibited a significant increase ($p < 0.05$) in body weight gain compared to the vehicle control group, while the male group change was unremarkable.

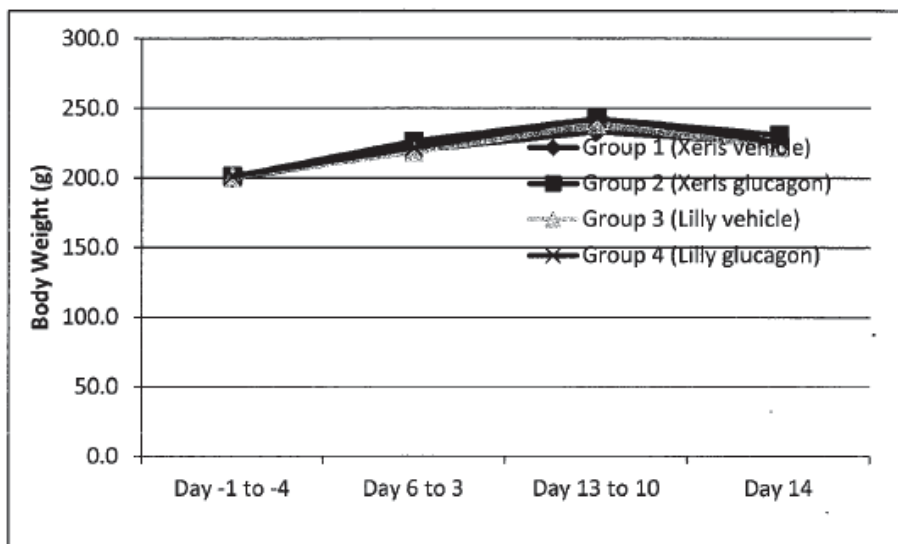
Phase 1 – Body Weight Change, Males



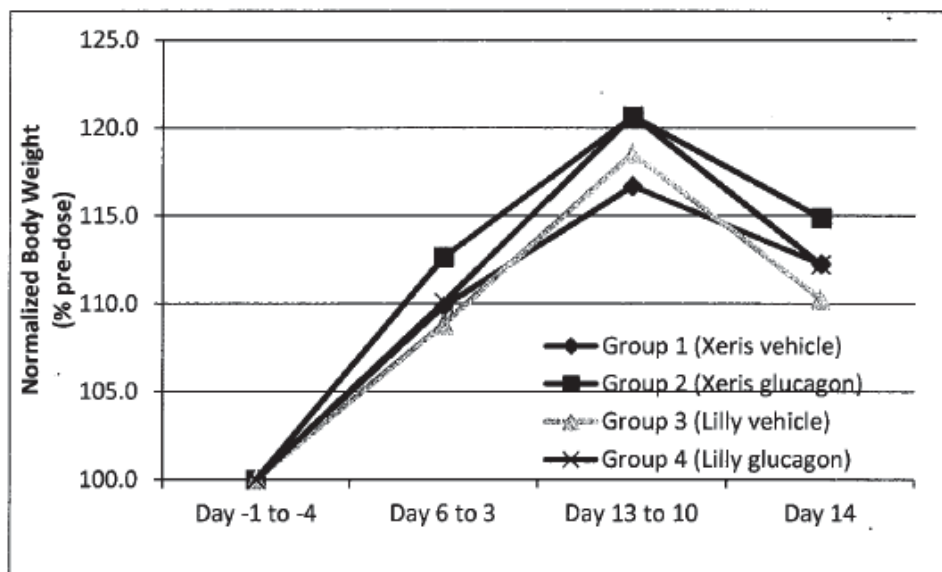
Phase 1 – Normalized Body Weight Change, Males



Phase 1 – Body Weight Change, Females



Phase 1 – Normalized Body Weight Change, Females



Feed Consumption Unremarkable.

Hematology

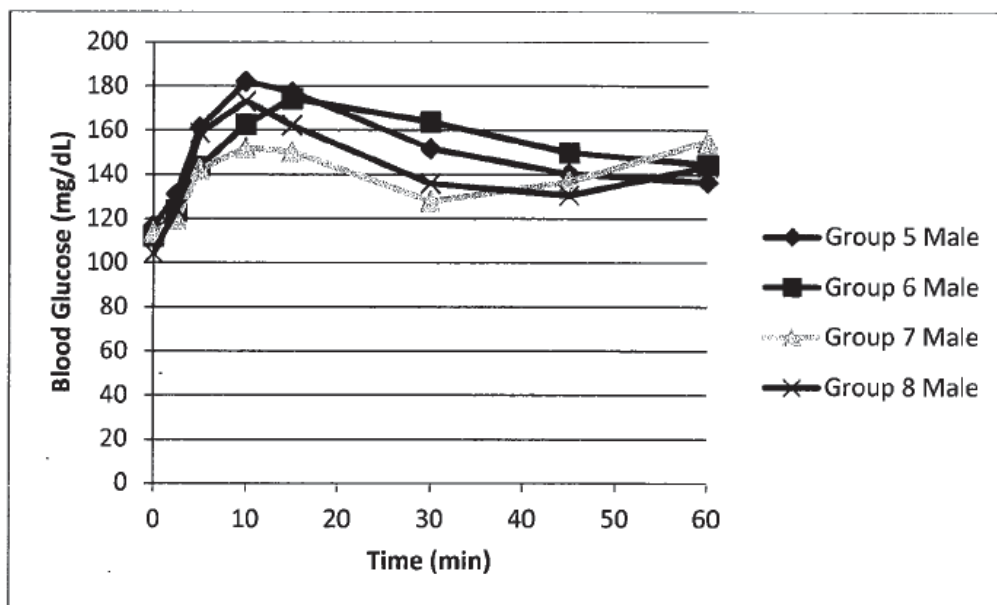
MCV ($p < 0.01$) and MCH ($p < 0.05$) were increased in Xeris Glucagon females, while reticulocytes (absolute and percentages) were reduced in females in Lilly Glucagon females. No other findings were remarkable.

Clinical Chemistry

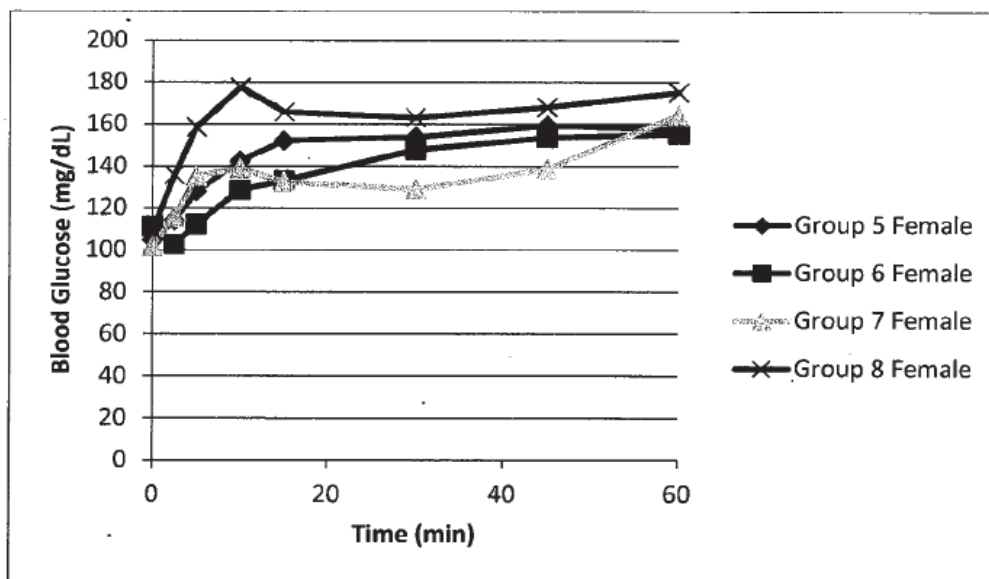
Blood Glucose (Phase 2 Group Only)

Male blood glucose peak occurred approximately 10 min post dose in the Xeris Glucagon low and high dose groups and 15 min post dose in the mid dose group. Female blood glucose peak rise was less than the males and also peaked approximately 10 min postdose. Female blood glucose peaked higher in the Lilly Glucagon approximately 10 min postdose and remained higher over the 60 min period than the Xeris Glucagon female group.

Blood Glucose Time Course - Males



Blood Glucose Time Course - Females



Calcium ($p < 0.05$) was reduced in males in Xeris Glucagon males, while calcium ($p < 0.05$) and ALK ($p < 0.01$) were decreased in males with Lilly Glucagon. No other findings were remarkable.

Gross Pathology

Group 2 (Xeris glucagon-treated group) had 6 males and 3 females with trace to mild subacute multifocal inflammation noted at the injection site, while all other groups had only one male with mild inflammation, except for one Group 3 (Lilly vehicle) animal with moderate inflammation. Although sporadic inflammation at the injection site was seen in all groups, the incidence appeared to be somewhat increased in Group 2 (Xeris glucagon-treated group).

This finding was considered by the pathologist to be treatment-related but was not considered toxicologically meaningful.

Trace to mild to moderate subacute multifocal dermal inflammation was noted at the injection sites in all groups including the vehicle groups. The inflammation was similar in types of cells present, distribution and severity between and among groups and was composed of scattered lymphocytes, monocytes and fewer neutrophils in the dermis.

Organ Weights

Summary of Significant Organ Weight Changes

Vehicle / Glucagon Source	Group	Sex	Effect of Glucagon Dosing on Indicated Organ Weight Parameter (only statistically significant effects are shown)		
			Absolute value	Body weight-normalized	Brain weight-normalized
Xeris	1 vs. 2	Male	↑ kidney**	↑ kidney**	↑ kidney**
		Female	↑ heart*	↓ thyroid*	↑ heart**
Lilly	3 vs. 4	Male		↑ brain**	
		Female		↓ kidney*	

*P <0.05, **P <0.01.

Histopathology

Adequate Battery Yes.

Peer Review No

Histological Findings

Table 3. Summary of Histopathologic Findings

Group	Animal No. (male/female)	Dose* (per rat, SC, QD, Days 0 & 1)			Treatment- Related Histopathologic Findings
		Treatment	Dose	Dose Volume	
1	101-110/ 151-160	Xeris Vehicle	0 µg	1 µL	There were no systemic treatment related histopathologic findings. Mild *inflammation at injectionsite in one male
2	201-210/ 251-260	Xeris Glucagon	5 µg	1 µL	There were no systemic treatment related histopathologic findings. Trace to mild inflammation at injection site was seen in 6/10 males and 3/10 females.
3	304-313/ 351-360	Lilly Vehicle	0 µg	5 µL	There were no systemic treatment related histopathologic findings. Moderate inflammation was seen in 1 male. Ulceration was present in 2 / 10 males. Females were within normal limits.
4	401-410/ 451-460	Lilly Glucagon	5 µg	5 µL	There were no systemic treatment related histopathologic findings. Mild inflammation was present in 1 /10 males and none of the females.

*Multifocal subacute inflammation in the dermis.

There were no treatment-related histopathologic microscopic findings in any of the tissues examined from the four treatment groups, except for a higher incidence (9/20 animals) of trace to mild inflammation at the injection site in the Xeris-treated animals compared to the other vehicle and Lilly Glucagon groups, which each had 1/20 animals with generally trace to mild injection site inflammation.

Histopathologic findings that were considered incidental or spontaneous and not related to treatment-related toxicity included: findings in the adrenal gland (vacuolization, hemorrhage, hyperplasia, congestion); kidney (mineralization); liver (hyperplasia, bile duct, inflammation); lung (congestion, hemorrhage); lymph nodes (lymphoid hyperplasia); spleen (lymphoid hyperplasia); ovary (congestion); prostate (lymphoid infiltration); testes (congestion); thymus (hemorrhage) and uterus dilation. The findings were generally noted in one or two animals per group and were generally mild, thus none were considered by the pathologist to be treatment-related findings with toxicological significance.

Dosing Solution Analysis Not verified. Certificates of Analysis were provided for Xeris Glucagon and Xeris Glucagon Vehicle.

Toxicology Data on Glucagon from the published literature and approved labeling

6.2 Repeat-Dose Toxicity

Under NDA No. 20-928, a fourteen-day toxicity study was conducted with Lilly Glucagon. Ten Fischer 344 rats/sex/group were administered daily subcutaneous doses of 0, 0.24, 1, or 4 mg rGlucagon/kg for 2 weeks. All rats survived the 2-week treatment period. There were no treatment-related clinical observations, changes in body weight or food consumption, or ocular effects.

Plasma concentrations of rGlucagon increased linearly with dose and reached peak concentrations at approximately 10 to 20 minutes after treatment. Females had higher apparent clearances, generally producing lower maximum plasma concentration (C_{max}) and AUC values compared to males. On Day 14, C_{max} and AUC values for both sexes and for each dose group were nearly double those reported on Day 0. The difference between Days 0 and 14 was interpreted as being due to a change in bioavailability. Treatment-related hematological changes included slight increases in thrombocyte and neutrophil counts in females given 4 mg/kg, increases in glucose, albumin, total protein, and slight decreases in cholesterol and blood urea nitrogen. These hematological changes and clinical chemistry effects might not appear to be toxicologically significant due to the magnitude and direction of the changes. There were slight, dose-related increases in absolute and relative liver weights (8% in the 0.25 mg group and 35% in the 4 mg group) which were not accompanied by distinctive histopathologic correlates or clinical chemistry evidence of liver toxicity.

The subcutaneous NOAEL for this fourteen day study was reported to be 4 mg/kg/day (4000 μ g/kg) for the rat.

Rat Safety Margin for Lilly Glucagon

Toxicity	Species	NOAEL (mg/kg) M/F	Safety Margin Based on Highest Clinical Dose*
14 Day Repeat Dose Study	Rat	4000 µg/kg	240X
		24,000 µg/M ²	38.8X

**Approved human dose for Lilly Glucagon is 1000 µg SC injection.
(1000 ug/60 kg = 16.7 ug/kg; 16.7 x 37 = 618 ug/M²).

In two-week studies with three beagle dogs per sex per group under NDA No. 20-928, IV glucagon injection (up to 0.2 mg/kg daily) did not result in mortality, although increased heart rate was observed 30 minutes following IV administration of 0.2 mg/kg/day. There were no treatment-related increases in body weight gain and food consumption. No treatment-related ocular and hematological changes were noted. The mean, absolute, and relative kidney and liver weights of all the treated groups were higher than those of the controls. There was no gross or histopathological evidence of toxicity in any of the organs and tissues examined. The intravenous NOAEL for this two-week study was observed to be 0.2 mg/kg/day for the beagle dog.

7 Genetic Toxicology

Several studies have been conducted to evaluate the mutagenic potential of glucagon. The mutagenic potential tested in the Ames and human lymphocyte assays was borderline positive under certain conditions for both glucagon (pancreatic) and glucagon (rDNA) origin. In vivo, very high doses (100 and 200 mg/kg) of glucagon (both origins) resulted in a slightly higher incidence of micronucleus formation in male mice but there was no effect in female mice.

8 Carcinogenicity

Because glucagon is usually given in a single dose and has a very short half-life, no carcinogenicity studies have been performed.

9 Reproductive and Developmental Toxicology

Glucagon is a Pregnancy Category B drug. Reproductive studies have not been performed with recombinant glucagon. However, studies with animal-sourced

glucagon were performed in rats at doses up to 2 mg/kg glucagon administered two times a day (up to 40 times the human dose based on body surface area, mg/m^2 , and have revealed no evidence of impaired fertility or harm to the fetus due to glucagon. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Reproductive studies have been performed in rats at doses up to 2 mg/kg glucagon administered two times a day (up to 40 times the human dose based on body surface area, mg/m^2 , and have revealed no evidence of impaired fertility. GlucaGen® (rDNA origin) was not tested in animal fertility studies.

10 Integrated Summary and Safety Evaluation

In the fourteen day toxicity study (CB12-5015-R-TX), male and female rats were dosed SC on two consecutive days with 5 μg Xeris Glucagon resulting in no obvious adverse effects from treatment and appeared normal throughout the 14 day observation period. The most frequent clinical finding was small but significant changes in body weight gain with males exhibiting a significant decrease ($p < 0.01$) in body weight gain with Lilly Glucagon, while females exhibited a significant increase ($p < 0.05$) in body weight gain with Xeris Glucagon. No effects on appetite were noted in any of the groups.

Xeris Glucagon and Lilly Glucagon both exhibited small but meaningful changes in hematology and clinical chemistry, specifically, Xeris Glucagon, increased MCV ($p < 0.01$) and MCH ($p < 0.05$) in females and a significant decrease ($p < 0.05$) in Calcium in males.

Absolute organ weight changes occurred with Xeris Glucagon with a significant increase ($p < 0.05$) in kidney weight in males and heart weight ($p < 0.05$) in females. Findings did not occur in males and histological examinations by a board-certified pathologist revealed no adverse macroscopic or microscopic findings.

Under the conditions of the study, the dose of 5 $\mu\text{g}/\text{rat}$ as the only dose of Xeris Glucagon administered daily over a two day period was considered to be the NOAEL.

Rat Safety Margin for Xeris Glucagon

Toxicity	Species	NOAEL* (mg/kg) M/F	Safety Margin Based on Highest Clinical Dose**
2 Day Dose Study	Rat	5 µg/rat M/F or 1.13 µg/kg M, 1.0 µg/kg F	0.06X
		6.4 µg/M ²	0.01X

*NOAEL is based on only dose level administered (5µg/rat in Phase 1, Toxicology Study, CB12-5015-R-TX) with Xeris Glucagon.

**Proposed human doses in Phase 2 Study will be 500 and 1,000 µg SC injections.
Assume 1,000 µg dose, (b) (4)

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/s/

ROBERT W MAHER
01/15/2013

KAREN L DAVIS BRUNO
01/16/2013