U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 212097
Supplement #:	
Drug Name:	G-Pen (glucagon for injection)
Indication(s):	Treatment of severe hypoglycemia
Applicant:	Xeris Pharmaceuticals Inc.
Date(s):	Review due date: May 2, 2019
	PDUFA date: Jun 10, 2019
Review Priority:	Standard
Biometrics Division:	II
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Keywords:
Link to keywords: non-inferiority, crossover design

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1 EXECUTIVE SUMMARY

Xeris Pharmaceuticals submitted a new NDA application for G-Pen for the proposed indication of treatment of severe hypoglycemia. The goal of this review is to examine the ability of G-Pen to provide rescue from the state of hypoglycemia in subjects with Type I diabetes (T1D) and determine whether non-inferiority of G-Pen to previously approved rescue medication, Lilly glucagon, could be established.

The applicant claims the advantage of G-Pen when compared to the currently approved rescue medication is in the ease of its administration, thus implying an increase in the likelihood of administration when hypoglycemia rescue is needed.

The submission is comprised of three Phase 3 trials (two adult trials (trials 301 and 303) and one pediatric trial (trial 302)).

The efficacy and safety of G-Pen was compared to Lilly glucagon in adult subjects only. Both adult studies had a crossover design and included a hypoglycemia induction prior to the administration of rescue. The pre-specified primary outcome was based on the treatment success score where the treatment success was defined as an increase in blood glucose (BG) concentration from below 50 mg/dL to greater than 70 mg/dL within 30 minutes after receiving glucagon.

In contrast, the pediatric study was descriptive, did not provide any comparators (besides a descriptive comparison of two strains of G-Pen in the subgroup of eleven subjects), and did not involve hypoglycemia induction.

Since the main goal of this submission was to examine whether G-Pen is non-inferior to Lilly glucagon, my review is focused on the outcomes in the adult population.

Statistical Issues and Findings

1. **Definition of the primary endpoint.** The score-based definition of success (achieving BG>70 mg/dL within 30 minutes from administration of treatment) utilized in the primary endpoint is problematic because the outcome depends on the baseline BG level, i.e. prior to the administration of rescue treatment. Subjects with higher baseline BG level will achieve success earlier than subjects with lower baseline BG level. My suggestion is to examine the rate of increase in BG from baseline, which is not directly dependent on the baseline BG level at the time of administration of rescue treatment.

2. **Inconsistent definition of the formula used to determine non-inferiority**. The sponsor selected the formula for determining noninferiority of G-Pen to Glucagon based on simulation. The formula was not previously validated and was inconsistently used across two studies 301 and 303.

3. **The noninferiority in the pre-specified primary endpoint for the trial 301 was not achieved**. The upper limit using the sponsor prespecified formula (Equation 1) for difference in success/failure score between treatments was (b) (4), which is larger than the pre-specified non-inferiority margin of (b) (4)%

4. **Overall recovery with G-pen was slower.** The applicant claimed advantage of G-Pen when compared to Lilly glucagon is in the ease of administration. Although the preparation and administration time for G-Pen was 1 minute shorter than for Lilly glucagon, it did not completely compensate for the longer time taken for recovery (in study 301, G-pen was approximately 4 minutes slower than Lilly glucagon in achieving recovery and 3 minutes slower in study 303). Of note, the time to prepare and administer rescue was examined only among medical professionals and not among novices who are going to be administrating the hypoglycemia rescue in the real-world situation.

5. **Higher rates of adverse events due to G-Pen treatment.** The number of G-Pen-related adverse events (AEs) was larger than the number of AEs attributed to Lilly glucagon**.**

6. **Issues with data quality and study conduct.** During my review I encountered multiple data management issues such as missing treatment label at nadir observation for 7 subjects from trial 301. Also, some of the score-based variables were coded incorrectly in study 303. I was able to mitigate these issues through careful examination of individual treatment history of each subject with a data issue. On February 10, 2019, the FDA inspectors notified the review team about an undeclared interim analysis (we are still waiting for the final inspection results) and an issue of subjects participating in both adult trials. The analysis that excluded data from subjects who participated in both studies did not change the conclusions.

Conclusions and Recommendations:

The data submitted in this NDA suggests that a trained medical professional required about 1 minute less time to prepare and administer G-Pen than the Lilly glucagon. However, a shorter preparation time for G-pen may not compensate for its slower action on BG recovery in severe hypoglycemia. Therefore, there is no sufficient evidence to support the benefit of G-Pen compared to Lilly glucagon in treatment of severe hypoglycemia by medical professionals. Although, in practice, the rescue will very likely be prepared and administered by untrained personnel and for this category of users, convenience of administration might outweigh the issues of efficacy profile of G-Pen, therefore, I would defer the final recommendation on approvability of G-Pen to the clinical team.

2 INTRODUCTION

2.1 Overview

A brief description of the drug indication and history of the submission is presented below.

2.1.1 History of Drug Development

The initial proposal for the G-Pen was submitted in December 2012 under the IND 115091. The clinical development program that consisted of one Phase 1, two Phase 2, and three Phase 3 trials evaluating G-Pen was initiated in 2013 and the NDA was submitted in August of 2018.

2.1.2 Specific Studies Reviewed

The submission is comprised of three Phase 3 trials (two adult trials (trials 301 and 303) and one pediatric trial (302)). The adult studies were designed to compare efficacy of G-Pen and Lilly Glucagon. The pediatric study focused on questions of dose-response relationship of G-Pen.

Table 1. List of all studies included in analysis

	Phase and Design	Follow-up Period	# of Subjects per Arm	Study Population
XSGP-301	Phase 3, R, DB, PD, 2XO	90 minutes	$N_{randomized}$=80 $N_{completed}$=78	**Adults with T1D**
XSGP-303	Phase 3 R, SB, 2XO	180 minutes	$N_{randomized}$=81 $N_{completed}$=75	**Adults with T1D**
XSGP-302	Phase 3		$N_{randomized}$=31 $N_{2\text{-}6yo}$=7 $N_{6\text{-}12yo}$=13 $N_{12\text{-}18yo}$=11 $N_{completed}$=31	**Pediatrics (2-18 years old) with T1D**

R=Randomized, DB=Double-Blind, SB=Single-blind, 2XO= 2-Way Crossover, PD=Pharmacodynamics

2.2 Data Sources

This submission is in electronic common technical document (eCTD) format. The submission is archived at the following link: \\CDSESUB1\evsprod\NDA212097\212097.enx.

Study datasets were provided as SAS XPORT transport files. The analysis datasets were joinable by unique identifier (USUBJID). My analysis on the primary and secondary efficacy endpoints gives approximately the same results as those reported in the clinical study report (CSR). Also, I explored additional measures of efficacy of glucagon treatment that I see as more statistically and clinically appropriate measures of effectiveness of rescue therapy.

I derived from the submitted datasets all of the results presented in this review. I created all tables and figures in this review unless otherwise noted

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets were in good organization although I encountered multiple data management issues such as missing treatment label at nadir observation for 7 subjects from trial 301. Also, some of the score-based variables were coded incorrectly in study 303. I was able to mitigate these issues through careful examination of individual treatment history of each subject with a data issue. The identification numbers of subjects with data issues are presented in the Appendix A.

On February 10, 2019, the FDA inspectors notified the review team about an issue of subjects participating in both adult trials. I was able to identify 12 subjects who had a matching date of birth, gender, and race in the database.

- One of those subjects (identified as (b) (6) in study 301 and (b) (6) in study 303) was a screen failure in both studies.
- Another subject completed study 301 and was a screen failure in study 303 (subject identified as (b) (6) in study 301 and (b) (6) in study 303).
- A third subject (identified as (b) (6) in study 301 and (b) (6) in study 303), was a screen failure in study 301 and was accepted in study 303 (see tables in Appendix A.).
- Overall, 9 subjects fully participated in both studies

Of note, the subjects who were in the databases of both studies (dual participants) had the same site ID numbers in both studies thus suggesting that study PIs (Principal Investigators) were aware of double participation, enrollment, and screening.

3.2 Evaluation of Efficacy

Since the pediatric study 302 did not involve pre-specified comparisons and induction of hypoglycemia, my efficacy evaluations and review are mostly focused on confirmatory adult studies 301 and 303. The exploratory data and analyses for the pediatric study is presented in Appendix A.

3.2.1 Study Design and Endpoints

Adult studies (301 and 303)

The procedure to evaluate the efficacy of the G-Pen consisted of inducing hypoglycemia by intravenous (IV) administration of insulin diluted in saline. Each participant was to undergo 2 episodes of insulin-induced hypoglycemia in random order, and received G-Pen 1 mg during one episode and Lilly Glucagon 1 mg during the other episode. A combination of 1 or more IV bolus doses of insulin along with an IV infusion of insulin was used to decrease a subject's blood

glucose (BG) to a target value<50 mg/dL. The IV insulin infusion was stopped once the blood glucose was<50 mg/dL. All blood glucose levels were based on an average of 2 readings taken at each time point.
After a confirmatory blood glucose of <50 mg/dL was obtained at least 5 minutes after the initial reading, the subject was treated with either 1 mg Lilly Glucagon or 1 mg G-Pen.
After a wash-out period of 7 to 28 days, subjects returned to the clinic and the procedure was repeated with each subject crossed over to the other treatment.

Blood glucose concentrations were monitored for 90 minutes (Study 301) and for 180 minutes (Study 303) after study drug injection.

Blinding procedures

The blinding procedures were different between studies 301 and 303. Study 301 was double-blind. Study 303 was single-blinded and open label to the investigator.

On February 10, 2019, the FDA inspectors notified the review team about an undeclared interim analysis. In the response from 2/19/2019, the applicant stated the following: "There was no interim analysis conducted for study XSGP-301." We are still waiting for the complete documentation from the inspection.

Primary endpoint

Treatment success was defined as an increase in blood glucose concentration from below 50 mg/dL to greater than 70 mg/dL within 30 minutes after receiving study treatment.

Primary endpoint (non-inferiority) was based on treatment success/failure scores. If treatment success was achieved, the score was set to 0; if not, the score was set to 1. If a treatment success cannot be determined due to missing values, the score was set to 0.2 in G-pen group and 0.1 in the Lilly glucagon group.

The primary endpoint, the non-inferiority criterion, was defined as

$$\mathbf{Dht + coefficient^{*}\ SE \leq 0.1} \quad \textbf{(Equation 1)}$$

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

Since the applicant was unable to demonstrate non-inferiority in the pre-specified primary endpoint in study 301, the applicant proposed a post-hoc alternate definition for treatment success: glucose > 70 mg/dL or increased > 20 mg/dL within 30 minutes of study treatment administration.

Reviewer's comment: The applicant selected the formula for determining noninferiority of G-Pen to Lilly glucagon based on simulation. I think that the proposed formula is acceptable because the result from the formula using a coefficient of 2.6 is approximately equal to upper 99% confidence limit for mean difference. Although it was not validated and was not used consistently across two studies 301 and 303.

Secondary endpoints

The secondary endpoints were PK/PD parameters and are not covered by this review document.

3.2.2 Statistical Methodologies

Applicant's approach:

For each drug administration (G-Pen and Lilly glucagon), the applicant calculated the success/failure scores and included those results in the calculation designed to examine non-inferiority (as defined by Dht + coefficient* SE ≤ 0.1 (Equation 1) in the section above). The applicant performed these calculations using all randomized subjects (the intent to treat (ITT) population). The calculations were repeated using only subjects who completed both of their treatments (the per protocol population).

Since the major advantage of G-Pen over Lilly glucagon is supposed to be the ease of administration (no need to premix the solution prior to the injection), the applicant examined the time between decision to dose and actual dosing time for a subset of subjects in study 303.

Reviewer's comment: The current definition of the primary outcome has two major issues:

1. The recovery is dependent on the lowest BG value (baseline), i.e. the BG value right before study treatment administration which cannot be easily controlled in a real-world situation. Subjects with higher baseline BG level will be faster and more likely to achieve success than subjects with lower baseline BG level.

2. The pre-specified primary endpoint only addresses recovery within 30 minutes after hypoglycemia state was achieved and does not provide the qualitative patterns, such as amount of physical discomfort during recovery that could be important to the patient.

FDA approach:

In my view, the best way to mitigate both of these issues is to examine the rate and magnitude of change in blood glucose after the rescue drug was administered. In addition to examination of recovery status at 30 minutes from administration of rescue, I examined the rates of blood glucose change (blood glucose velocity) as well as the change in blood glucose from baseline. Specifically, I compared those parameters using two separate clinical definitions of BG recovery:

1. first BG increase of 20mg/dL or more
2. BG increase above 70mg/dL.

The rates of BG recovery were based on the assumption of linear raise in BG. Since the clinical team was mostly interested in the two specific BG thresholds (BG increase of 20 mg/dL and BG of >70mg/dL) and not all of the subjects could have been measured at those specific cut offs (the measurements were made based on time from baseline and not BG levels), I estimated the time to recovery (as defined above) using the collected BG values and the BG velocity. My review also includes graphical visualization of treatment-specific changes in BG and BG-based recovery rates.

Reviewer's comment: In light of the FDA inspection results, I identified the subjects who participated in both adult studies (dual participants) by matching them by date of birth, gender, and race. The primary concern of dual participation is a possibility of overstated treatment efficacy in study 303 due to inclusion of more responsive subjects into study 303, since all dual participants that were included in study 303 (conducted after study 301 was completed) were successfully rescued (BG>70 at 30 minutes from nadir) during trial 301. In order to evaluate the impact of potential non-random patient selection, I examined all major outcomes after dual participants were removed from the analyses.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Demographics and baseline characteristics for adult study participants from studies 301 and 303 are presented in Table 2 and Table 3.

Adult studies
The overall age range of subjects in both studies was similar (between 18 to 74 years in study 301 and between 18 and 72 years in study 303). Subjects in in study 301 were slightly older (mean age was 43.5 in study 301 and 38.6 in study 303) than subjects in study 303. Subjects in study 301 were slightly heavier than subjects in study 303 (mean weight 83kg vs 78.3kg).

Table 2. Baseline demographic characteristics

Study 301	N	Median	Minimum	Maximum	Mean	Std Dev
Age	79	45.00	18.00	74.00	43.54	15.33
Baseline Weight (kg)	79	82.20	47.70	161.60	83.01	20.15
Baseline Height (cm)	79	171.00	147.00	194.00	171.84	10.82
Baseline BMI (kg/m2)	79	26.97	19.28	60.24	28.03	6.24
Baseline Systolic Blood Pressure (mmHg)	79	120.00	96.00	165.00	125.25	15.88
Baseline Diastolic Blood Pressure (mmHg)	79	72.00	55.00	88.00	72.97	7.23
Study 303	**N**	**Median**	**Minimum**	**Maximum**	**Mean**	**Std Dev**
Age	78	33.00	18.00	72.00	38.58	14.47
Baseline Weight (kg)	78	80.50	47.40	106.40	78.31	13.93
Baseline Height (cm)	78	174.50	150.00	194.00	172.54	9.63
Baseline BMI (kg/m2)	78	25.92	18.84	36.88	26.22	3.83
Baseline Systolic Blood Pressure (mmHg)	78	124.00	91.00	158.00	123.67	14.94
Baseline Diastolic Blood Pressure (mmHg)	78	69.00	46.00	90.00	69.92	9.12

Both study cohorts consisted of mostly white subjects (91.1% participants in study 301 and 87.2% of study 303 participants).

Table 3. Demographic Table

RACE	Study 301		Study 303	
	treated	randomized	treated	randomized
Race				
Asian	1 (1.27%)	1(1.25%)	6 (7.69%)	6(7.41%)
Black or African American	4 (5.06%)	4(5%)		
Multiple	2 (2.53%)	2(2.5%)	3 (3.85%)	3(3.7%)
White	72 (91.14%)	73(91.25%)	68 (87.18%)	71(87.65%)
Other			1 (1.28%)	1(1.23%)
Sex				
Female	36 (45.57%)	36(45%)	34 (43.59%)	37 (45.68%)
Male	43 (54.43%)	44(55%)	44 (56.41%)	44 (54.32%)
Age				
>=18 to <65	70 (88.61%)	71(88.75%)	72 (92.31%)	75(92.59%)
>=65	9 (11.39%)	9(11.25%)	6 (7.69%)	6(7.41%)

Gender was roughly equally distributed in both studies (54.4% of subjects in study 301 and 56.4% of subjects from study 303 were male). Only a few subjects were 65 years of age or older (9 subjects in study 301 and 6 subjects in study 303). All subjects in both studies were from the USA.

Missing data

Missing data in trials 301 and 303 was not large. Since both study 301 and study 303 had a crossover design, in order to have no missing data, each subject had to have data for both drugs. The patterns of missing data for both studies are presented in Table 4. Of note, study 301 had multiple study violations and one of the subjects in that study did not have any observations on both drugs.

Table 4. Missing data

study	randomized	Treated (ITT)		Medication Errors	Trial issues	
	# of subjects	G-Pen	Lilly glucagon		# of subjects with missing data	
301	80	78 (97.5%)	79 (98.75%)	1 subject received glucagon twice 1 subject received treatment in incorrect order 1 subject withdrew from study	G-Pen Lilly glucagon	2 1
303	81	76 (93.83%)	78 (96.3%)	5 subjects did not receive G-pen 3 subjects did not receive glucagon	G-Pen Lilly glucagon	5 3

3.2.4 Results and Conclusions

Primary outcomes

Based on the inspection's findings, I identified 9 subjects who participated in both studies. I evaluated the pre-specified primary endpoint for each study separately and examined the results that excluded dual participants. The outcomes of my analyses are presented in Table 5. In both scenarios (with and without dual participants), the Study 301 did not demonstrate non-inferiority of G-pen compared to Lilly glucagon in treatment of severe hypoglycemia, regardless of the coefficient being used in the non-inferiority formula. Study 303 demonstrated non-inferiority of G-pen compared to Lilly glucagon in treatment of severe hypoglycemia regardless of duplicate participation and use of different coefficients.

Table 5. Primary outcomes – success/failure score

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

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

Blood glucose kinetics and recovery

Among subjects who participated in study 301, while using G-Pen, four of them did not achieve, success defined as achieving the threshold of BG > 70 mg/dL within the first 30 minutes from nadir (Table 6). The applicant claims that subjects who failed to meet the target BG threshold on G-pen did so because their nadir value was too low. Of note, not all subjects in study 303 achieved the pre-specified BG nadir<50 mg/dL, i.e. they had their nadir BG values above 50 mg/dL (Table 19. Measurements at 70mg/dL, part B, Appendix B.2.).
All subjects in study 303 achieved success defined as reaching the threshold of BG > 70 mg/dL or increase in BG ≥ 20 mg/dL within the first 30 minutes from nadir (Table 6).

Table 6. Difference in proportion of success

Study 301	G-pen (N=78)	Lilly Glucagon (N=79)
# of successes n (%)	74 (94.9%)	79 (100%)
Difference in Proportion of success (95% C.I.)	-5.1% (-10.5%, 0.3%)	
Study 303	**G-pen (N=76)**	**Lilly Glucagon (N=78)**
# of successes n (%)	76 (100%)	78 (100%)
Difference in Proportion of success (95% C.I.)	0 (-2.5%, 2.5%)	

*obtained using Wald + 2 method proposed by Agresti and Min (2005)

Time to recovery (BG>70 mg/dL or increase in BG > 20mg/dL from nadir) was summarized in Table 7. G-pen was approximately 4 minutes slower than Lilly glucagon in achieving recovery in study 301 and 3 minutes slower in study 303.

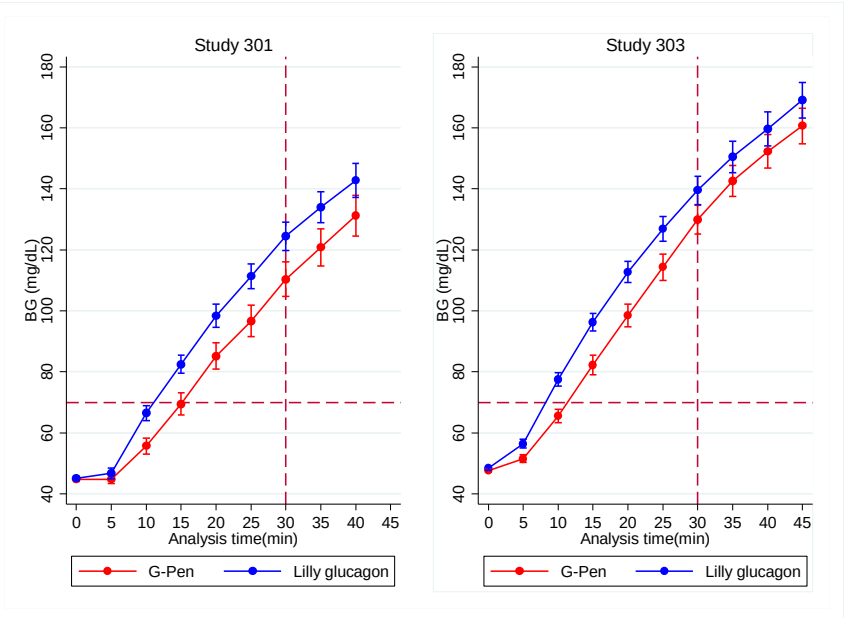
Table 7. Time to recovery from baseline

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

In order to understand the dynamics of recovery, I decided to examine the longitudinal changes of BG and BG kinetics (magnitude of change and rate of change) from BG nadir. The nadir and BG kinetics data stratified by dual participation is presented in Appendix E.

The longitudinal patterns of BG from nadir are presented in Figure 1. The patterns seem to be similar in both studies (301 and 303). On both graphs, the blue lines (Lilly glucagon) come across the 70mg/dL earlier than the red lines (G-Pen), suggesting a faster recovery for patients on Lilly glucagon. Of note, the 95% confidence intervals for the mean BG values for subjects on both drugs begin to overlap only around the benchmark of 30 minutes. The estimates and their confidence intervals based on values achieved with Lilly glucagon are consistently higher during the first 30 minutes.

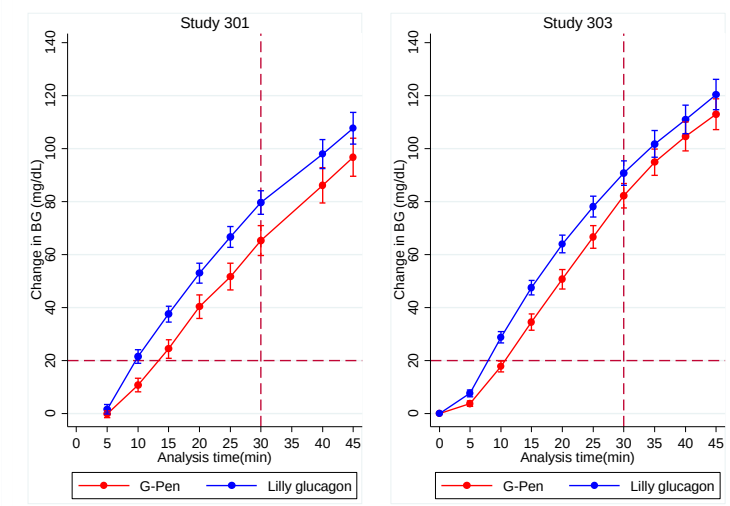
Figure 1. Mean BG trajectories from nadir



Legend: The graph shows the longitudinal means and their 95% Confidence Intevals for each of the rescue drugs. The horizontal red dashed line indicates the BG cut off of 70 mg/dL and the vertical red dashed line identifies the 30-minute time inteval from the observed BG nadir (baseline).

Since the applicant claimed that low nadir values were the reason of G-pen being slower in reaching the benchmark of 70mg/dL, I examined the change in BG towards reaching an increase of 20mg/dL from nadir. Similar to the BG levels, the rise rates that the subjects achieved using Lilly glucagon were higher. Of note, in this scenario, the raise in BG did not depend on the subjects' nadir BG values (Figure 2).

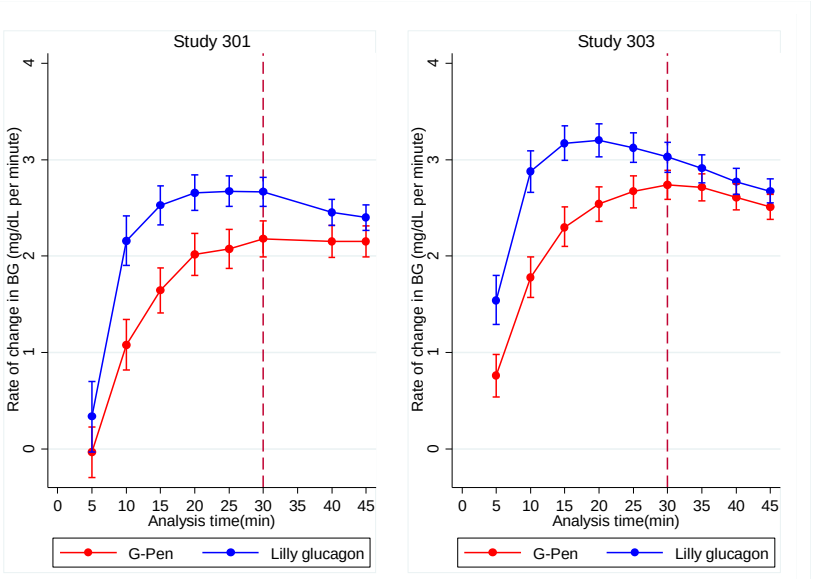
Figure 2. BG changes from nadir



Legend: The graph shows the longitudinal means and their 95% Confidence Intevals for each of the rescue drugs. The horizontal red dashed line indicates the first 20 mg/dL raise in BG and the vertical red dashed line identifies the 30-minute time inteval from the observed BG nadir.

Finally, the rates of change in BG (or BG velocity, calculated as difference in BG measurements divided by time between observations) clearly show that the BG values of subjects on Lilly glucagon begin to accelerate earlier than subjects on G-Pen
Figure 3).

Figure 3. Rates of change in BG from nadir (BG velocity)



The numeric data at the threshold of 70 mg/dL or 20 mg/dL are presented in Table 19, sections A and B, Table 20, section C and D (Appendix B.2.) The visit (time point) corresponds to the time of the first observation measured with BG above the threshold of 70 mg/dL. The estimated time to the threshold corresponds to the calculated value that approximates the time the subjects crossed the threshold.
The estimated time to BG above 70mg/dL or increase ≥ 20mg/dL was shorter for subjects on Lilly glucagon vs. those on G-Pen.

Recovery rates

A brief examination of recovery rates (based on 20mg/dL increase) revealed that the majority of subjects on Lilly glucagon (75.94% in study 301 and 94.87% in study 303) achieved recovery at 10 minutes. Among subjects on G-Pen, only 44.3% of them in study 301 and 65.31% in study 303 recovered within first 10 minutes. The data are illustrated in
Figure 4 and Figure 5. The detailed numeric information on recovery is presented in Appendix D.

Figure 4. Recovery rates (study 301)

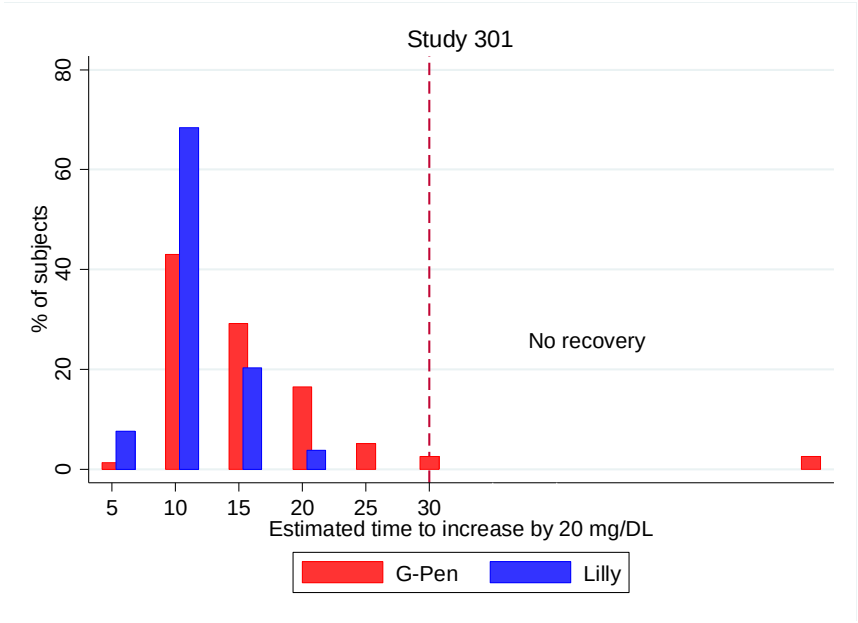
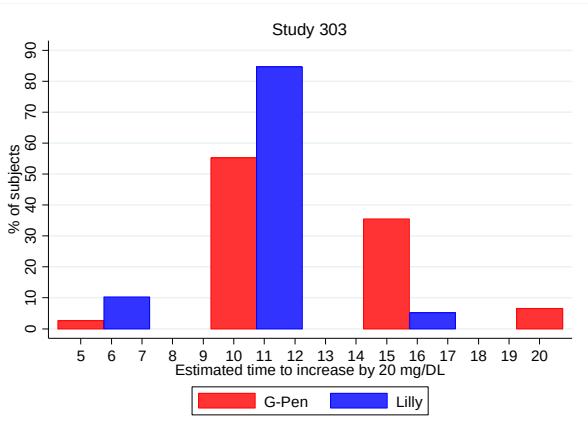


Figure 5. Recovery rates (study 303)



Time from decision to dose to drug administration

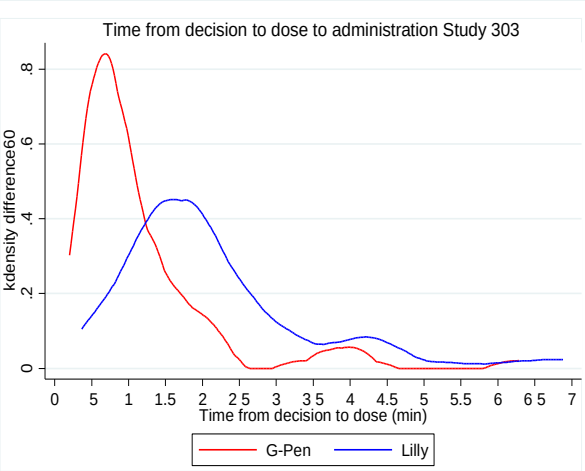
To evaluate ease of administration, the applicant collected the time points of decision to dose and actual dosing thus measuring the time to get the medication ready. The data were only collected in study 303 and all rescue was administered by medical professionals. No testing was performed by untrained administrators. The numerical distribution parameters of time to administration in each arm are presented in Table 8. Overall, the time to prepare G-Pen took about one minute shorter than the time to prepare Lilly glucagon.

Table 8. Time from decision to dose to drug administration (study 303)

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

The distributions for preparatory times are visualized by kernel densities presented in Figure 6.

Figure 6. Time from decision to dose



3.3 Evaluation of Safety

The adverse events (AEs) reported in studies 301 and 303 were not considered to be serious. Most frequently reported types of AEs were the gastrointestinal (GI) disorders. In study 301, 25.6% of subjects on G-Pen experienced GI disorders and only 17.7% of subjects experienced those AEs (Table 9). Similarly, in study 303, 55.3% of subjects on G-pen experienced GI AEs and 42.3% of study participants experienced it while using Lilly glucagon. Overall, 32.1% of subjects on G-Pen and 24.1% of subjects on Lilly glucagon experienced an AE in study 301. The directionality of the AEs was similar in study 303, more subjects on G-Pen than on Lilly glucagon experienced at least one AE. A more detailed description of AEs based on severity is presented in Appendix C.

Table 9. Adverse events by body system or organ class (studies 301 and 303)

Study 301		
Body System or Organ Class	**G-Pen N=78 n (%)**	**Lilly Glucagon N=79 n (%)**
Cardiac disorders	1(1.3)	0
Endocrine disorders	0	2 (2.5)
Gastrointestinal disorders	20 (25.6)	14(17.7)
Immune system disorders	1(1.3)	0
Infections and infestations	1(1.3)	0
Musculoskeletal and connective tissue disorders	1(1.3)	1(1.3)
Nervous system disorders	2(2.6)	3(3.8)
Respiratory, thoracic and mediastinal disorders	1(1.3)	1(1.3)
Skin and subcutaneous tissue disorders	1(n1)	0
Surgical and medical procedures	1(n=1)	0
Total	25(32.1)	19(24.1)

Study 303		
Body System or Organ Class	**G-Pen N=76 n (%)**	**Lilly Glucagon N=78 n (%)**
Cardiac disorders	1(1.3)	0
Endocrine disorders	1(1.3)	0
Gastrointestinal disorders	42(55.3)	33(42.3)
General disorders and administration site conditions	4(5.3)	4(5.1)
Infections and infestations	4(5.3)	0
Metabolism and nutrition disorders	1(1.3)	1(1.3)
Nervous system disorders	9(11.8)	5(6.4)
Renal and urinary disorders	0	1(1.3)
Skin and subcutaneous tissue disorders	1(1.3)	0
Total	63(82.9)	44 (56.4)

Based on the information provided by the applicant in the CSR documentation for both studies, the treatment-emergent AEs were more frequently reported by subjects while on G-Pen (Table 10).

Table 10. Incidence of Treatment-Emergent AEs Related to Study Drug by Treatment and Preferred Term (data based on applicant's tables and CSR)

AE	Study 301 $n_{subjects}$ (%)		Study 303 $n_{subjects}$ (%)	
	G-Pen N=78	Glucagon N=79	G-Pen N=76	Glucagon N=78
TEAEs*	20(25.6)	15(19)	46 (60.5)	34 (43.6)
Nausea	16(21.8%)	10(12.7)	28(38.2)	26(33.3)
Vomiting	4(5.1)	4(5.1)	20(26.3)	11(14.1)
Discomfort after administration	No information in CSR	No information in CSR	60(78.9)	27(34.6)

* treatment-emergent adverse event
Source: Table 21, p.66 of CSR, study 301 and Table 12.2.1, p. 87 of CSR, study 303

For additional information on safety events readers are referred to Dr. Suchitra Balakrishnan's review.

3.4 Benefit-Risk Assessment

According to the applicant, the current treatments of hypoglycemia are underutilized due to complexity of preparation (Lilly glucagon requires mixing and G-pen does not require mixing prior to injection of the drug). The applicant claims that "…the emergency glucagon therapy is under-appreciated, under-evaluated, and under-taught ..." (Clinical Overview, Section 6, p.29). At the same time, the applicant states that the overall incidence of adverse events associated with glucagon is low, claiming that in 2017, there were 37 reports received by the FDA. Thus, suggesting that the convenience of the new device and drug will improve the administration.

Based on the data and information provided in this submission, the G-Pen treatment does result in an increase in blood glucose, but recovery from hypoglycemia is slower when compared with Lilly glucagon. The slower recovery could lead to more incidents of irreparable damage to patients reaching extremely low BG levels who are treated with G-Pen instead of Lilly glucagon. Although, generally serious AEs for glucagon treatments are not frequently reported to FDA, the G-Pen treatment caused more AEs than the drug that is already on the market.

Since both efficacy and safety profiles do not favor G-Pen, the ease of administration becomes the key point in improvement of hypoglycemia rescue. Therefore, the following three questions need to be answered:

1. Who is going to be administering the rescue, i.e. who is the target (intended use) population (trained professionals, untrained users, or both)?
2. How likely is an untrained person to be able to appropriately administer G-Pen?
3. How long will it take for an untrained person to administer G-Pen?

The data submitted as a part of this NDA suggests that a trained professional requires about 1 minute longer to prepare the Lilly glucagon than G-Pen, thus not completely overcoming the issue of slow BG response, especially in subjects with low BG levels. Therefore, administration of G-Pen in an emergency by medical professionals might not be recommended. An additional study that examines ease and likelihood of use by untrained subjects may provide a more appropriate benefit-risk assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 11 summarizes success rates by subgroup for Study 301. Since all subjects in study 303 achieved success (BG>70mg/dL within 30 minutes and BG>20mg/dL), success by subgroup was not presented for Study 303.

Table 11. Success rates by subgroup – Study 301

Study 301	G-pen n/N (%)	Lilly Glucagon n/N (%)
Sex		
Males	41/44 (93.2%)	43/43 (100%)
Females	33/34 (97.1%)	36/36 (100%)
Race		
White	68/71 (95.8%)	72/72 (100%)
Non-White	6/7 (85.7%)	7/7 (100%)
Age		
≥ 18 to <65	66/69 (95.7%)	70/70 (100%)
≥ 65	8/9 (88.9%)	9/9 (100%)

Time to the blood glucose benchmark

The results of the subgroup analyses for the time to the estimated BG benchmarks (BG >= 20mg/dL and BG > 70 mg/dL) are presented in Appendix B.2. Similar to the overall cohort, the results in the subgroups had the same directionality: G-Pen rescue was slower than rescue using Lilly glucagon in all subgroups.

The relationships between the subgroups and recovery rates in settings where recovery approach mediates the issue of the nadir BG value being too low (using the first increase of 20 mg/dL from baseline/nadir as definition of recovery) are illustrated in Appendix D. These graphs show that consistently, subjects on Lilly glucagon (depicted by blue bars) mostly recovered within the first 10 minutes following the nadir value. The tables with specific numbers addressing recovery rates over time are also presented in Appendix D.

4.2 Other Special/Subgroup Populations

The exploratory analyses and BG kinetics in pediatric patients are presented in Appendix B.1.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

1. **Definition of the primary endpoint (success score).** The definition of the success score utilized in the primary endpoint (achieving BG>70 mg/dL within 30 minutes from baseline) is problematic because the outcome is strongly dependent on the BG level at baseline/nadir, i.e. subjects with higher nadir will recover faster than subjects with low nadir (those that will most likely be needing the rescue in real life). Since there is no possibility to precisely prespecify the nadir in the trial, and in real live situation patient's BG could have a very low nadir, success should be independent of BG nadir levels. I recommend examining the rate of success in BG from nadir (achieving BG>70 mg/dL or increase in BG $\geq$ 20 mg/dL within 30 minutes from baseline) and time to success to evaluate the efficacy of rescue treatment.

2. **The pre-specified primary endpoint (score-based noninferiority) for trial 301 was not met**. In Study 301, the upper limit using the sponsor prespecified equation for difference in success/failure scores between treatments was (b) (4) , which is larger than the pre-specified (b) (4)% non-inferiority margin.

3. **Potential study misconduct.** The Agency conducted an inspection that uncovered an undeclared interim analysis. Because of these findings, trial 301 might have been altered without appropriate blinding procedures. Also 9 subjects participated in study 301 and study 303. Dual participation is not reflecting an appropriate sampling since all subjects who participated in both trials were successful in the first trial (study 301). Of note, subjects who participated in both trials joined the second study at the same study site thus suggesting that the principle (PI) investigator was aware of dual participation.

4. **Not all of the subjects achieved the pre-specified minimal level of hypoglycemia prior to administration of rescue.** Of note, some of the patients in study 303 did not reach BG<50ng/mL and therefore, technically did not meet the requirement for rescue.

5. **Overall recovery with G-Pen was slower and choice of intended use population.** According to the information provided in this submission, the advantage of G-Pen when compared to the currently approved rescue medication is in the ease of administration. The Lilly glucagon requires pre-mixing prior to the injection and G-Pen already contains a pre-mixed solution. Although the preparation and administration time for G-Pen was 1 minute shorter than the average time to prepare and administer Lilly glucagon, it did not completely compensate for the time lost in recovery (in study 301, G-pen was approximately 4 minutes slower than Lilly glucagon in achieving recovery and 3 minutes slower in study 303). Of note, the time to prepare and administer rescue was examined only among medical professionals and not among novices who are going to be the people (intended use population) that will be administering hypoglycemia rescue.

6. **Issue with data quality (mitigated).** During my review I encountered multiple data management issues such as missing treatment label at nadir observation for 7 subjects from trial 301. Also, some of the score-based variables were coded incorrectly in study 303. I was able to mitigate these issues through careful examination of individual treatment history of each subject with a data issue.

5.2 Collective Evidence

Based on the submitted data, G-Pen is able to elevate BG levels. Since this is a rescue medication, the timeliness and safety profile are of great importance to the patient. The data from study 301 and 303 demonstrated that the action of this drug is slower than the action of Lilly glucagon (BG velocity). Also, since difficulty of administration presents a burden in administration of glucagon, the applicant addressed this issue using only trained professionals as their intended use population. The results in testing of professionals produced a difference of approximately 1 minute in administration time. The ease of administration was not tested on untrained subjects who would most likely be administering the rescue mediation. The safety profile of G-Pen was slightly worse than safety profile of Lilly glucagon (more non-sever adverse events were reported on G-Pen).

5.3 Conclusions and Recommendations

Based on the submitted data, a trained medical professional required about 1 minute less time to prepare and administer G-Pen than the Lilly glucagon. However, a shorter preparation time for G-pen may not compensate for its slower action on BG recovery in severe hypoglycemia. Therefore, there is no sufficient evidence to support the benefit of G-Pen compared to Lilly glucagon in treatment of severe hypoglycemia by medical professionals. Although, in practice, the rescue will very likely be prepared and administered by untrained personnel and for this category of users, convenience of administration might outweigh the issues of efficacy profile of G-Pen, therefore, I would defer the final recommendation on approvability of G-Pen to the clinical team.

5.4 Labeling Recommendations (as applicable)

Because of poor choice of primary outcome, my general recommendation is to [redacted] include summary of treatment success/failure and time it took to achieve treatment success in the label, so that a clear comparison between action of G-Pen and Lilly glucagon is presented to the prescribers.

Reference

Agresti, A and Min, Y (2005). Simple improved confidence intervals for comparing matched proportions, Statistics in Medicine, 24:729-740.

APPENDICES

Appendix A.

Data issues

Table 12. Subjects with missing treatment label at nadir

Obs	SUBJID
	(b) (6)
1	
2	
3	
4	
5	
6	
7	

Table 13. Subjects included in databases of studies 301 and 303 (dual participants)

Study 301

Obs	Subjid 301	Subjid 303	AGE	RACE	SEX	WEIGHT	HEIGHT	RFICDTC	EOSDT	ARMCD
1		(b) (6)	52	MULTIPLE	F	47.7	153	2017-04-12	05/16/17	L-G
2			69	WHITE	M	79.5	175	2017-05-17	07/06/17	G-L
3			41	WHITE	M	88.3	181	2017-03-17	05/09/17	L-G
4			30	WHITE	M	.	.	2017-03-17	03/17/17	SCRNFAIL
5			26	WHITE	M	93.1	190	2017-03-22	05/18/17	G-L
6			52	WHITE	M	76.0	171	2017-03-24	06/09/17	G-L
7			36	WHITE	M	94.0	175	2017-04-06	05/05/17	G-L
8			35	WHITE	M	88.3	179	2017-04-12	05/19/17	L-G
9			36	WHITE	M	.	.	2017-05-04	05/18/17	SCRNFAIL
10			63	WHITE	M	94.3	187	2017-03-27	05/01/17	L-G
11			70	WHITE	F	77.0	160	2017-03-28	05/01/17	G-L
12			56	WHITE	F	59.7	168	2017-03-29	05/01/17	L-G

Study 303

Obs	Subjid 301	Subjid 303	AGE	RACE	SEX	WEIGHT	HEIGHT	RFICDTC	EOSDT	ARMCD
1		(b) (6)	53	MULTIPLE	F	47.4	151	2018-01-18	02/09/18	G-L
2			70	WHITE	M	84.7	176	2018-02-15	03/27/18	L-G
3			36	WHITE	M	84.6	180	2018-01-23	02/25/18	G-L
4			27	WHITE	M	92.6	189	2018-01-29	03/03/18	L-G
5			42	WHITE	M	90.3	181	2018-02-20	04/15/18	L-G
6			31	WHITE	M	.	.	2018-03-01	03/01/18	SCRNFAIL
7			37	WHITE	M	91.4	175	2018-03-16	04/13/18	G-L
8			37	WHITE	M	91.4	175	2018-03-16	04/13/18	G-L
9			53	WHITE	M	.	.	2018-04-02	04/02/18	NOTASSGN
10			63	WHITE	M	90.2	188	2018-01-08	02/06/18	G-L
11			70	WHITE	F	79.0	159	2018-01-18	02/14/18	L-G
12			57	WHITE	F	63.2	171	2018-03-15	04/13/18	G-L

Appendix B.1.

Pediatric study 302

Demographic data for subjects from the pediatric study 302 is presented in Table 14. Among pediatric subjects, the youngest group (ages 2 to 6) had the smallest number of participants.

Table 14. Demographic table: Pediatric study

Age group	Pediatric (302)
Age	
[2.0-<6.0)	7 (22.58%)
[6.0-<12.0)	13 (41.94%)
[12.0-<18.0)	11 (35.48%)
Sex	
Female	16 (51.6%)
Male	15 (48.39%)
Race	
Black or African American	3(9.68%)
White	28(90.32%)

Similar to adult studies, the gender was equally distributed in the pediatric study.

Among pediatric subjects, only 3 were Black or African American. All other 28 children and adolescents were white.

Findings (subjects who experienced two G-Pen doses)

Because of ethical reasons, pediatric subjects were not brought into the state of deep hypoglycemia. Among pediatric subjects, nobody had a BG measurement below 50 at nadir. All subject received 0.5mg dose of G-Pen. Only subjects in the 12-18 age group had a second test when the 1 mg G-Pen dose was administered.
A graphical illustration of BG trajectories for subjects in the 12-18 age group is presented below.

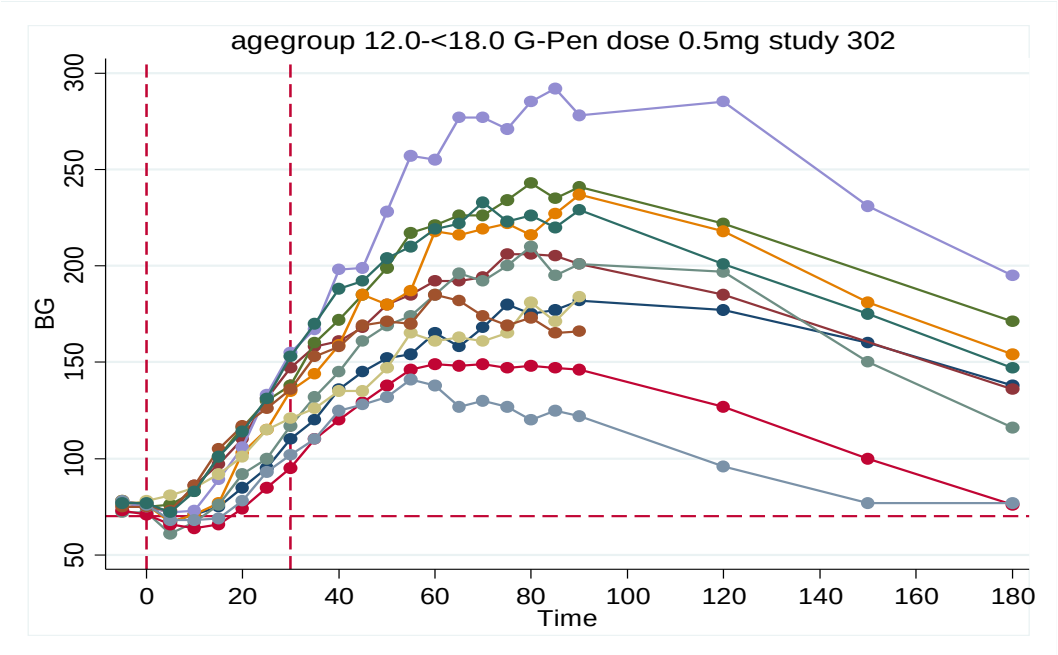
Table 15. Nadir BG for all pediatric subjects

BG at nadir dose 0.5 mg (all subjects)							
N	**Median**	**Minimum**	**Maximum**	**Mean**	**Lower 95% CL for Mean**	**Upper 95% CL for Mean**	**Std Dev**
31	74.00	50.00	79.00	71.23	68.43	74.02	7.62

Table 16. Nadir BG for subjects ages 12-18

BG at nadir dose 1mg (subjects ages 12-18)							
N	**Median**	**Minimum**	**Maximum**	**Mean**	**Lower 95% CL for Mean**	**Upper 95% CL for Mean**	**Std Dev**
11	76.00	61.00	79.00	74.45	71.20	77.71	4.84

Figure 7. Spaghetti plots for subjects between ages 12 and 18 (G-Pen 0.5mg)



Legend: Spaghetti plot of BG values. Each trajectory represents values of an individual subject

Figure 8. Spaghetti plots for subjects between ages 12 and 18 (G-Pen 1 mg)

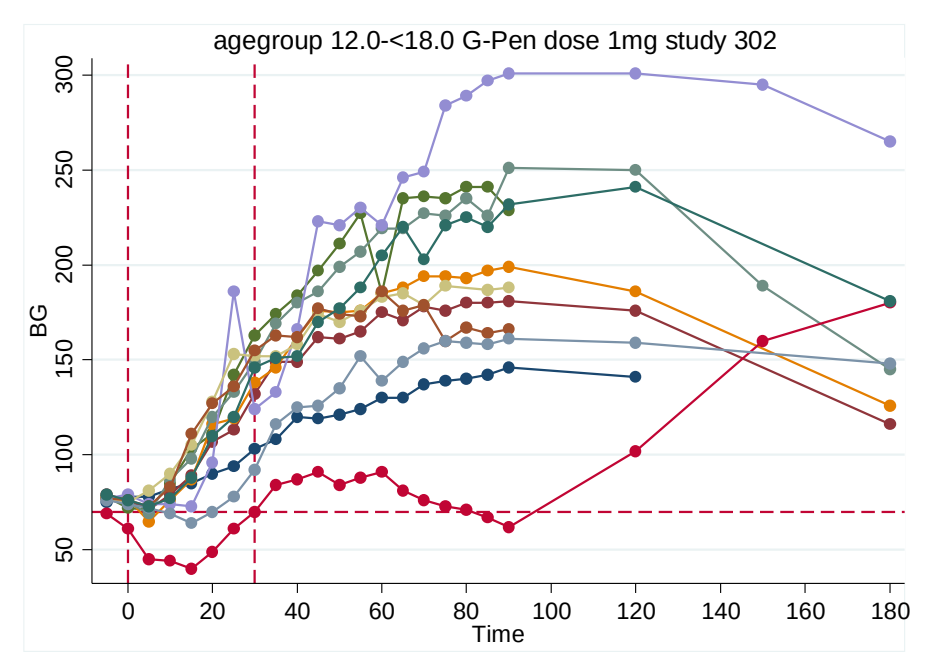


Table 17. Baseline and BG kinetics data for subjects ages 12-18 using 0.5mg dose

G-pen 0.5 mg	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Analysis Value	11	101.00	92.00	110.00	101.18	97.76	104.60	5.10
Change from Baseline	11	24.50	20.00	33.00	25.50	22.82	28.18	3.99
Rate of change in BG	11	1.30	0.77	2.00	1.30	1.05	1.55	0.37
Analysis Timepoint (N)	11	20.00	15.00	30.00	20.91	16.71	25.11	6.25

Table 18. Baseline and BG kinetics data for subjects ages 12-18 using 1mg dose

G-pen 1 mg	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Analysis Value	11	107.00	87.00	186.00	112.91	95.70	130.12	25.61
Change from Baseline	11	29.50	22.00	108.00	37.45	21.21	53.70	24.18
Rate of change in BG	11	1.63	0.55	4.32	1.78	1.12	2.44	0.98
Analysis Timepoint (N)	11	20.00	15.00	40.00	22.73	16.84	28.62	8.76

Appendix B.2.

Table 19. Measurements at 70mg/dL

A Study 301 G-Pen	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline (nadir) BG (mg/dL)	79	44.90	29.70	49.50	44.83	44.10	45.56	3.25
First BG measurement >70 mg/dL	79	78.10	70.10	103.00	79.60	77.96	81.24	7.33
BG kinetics:								
Change in BG(mg/dL)	79	33.70	21.60	56.40	34.77	32.98	36.56	7.99
Rate of change in BG(mg/dL/min)	79	1.97	0.64	5.64	1.97	1.80	2.14	0.76
Time to event BG>70mg/dL								
Visit (time point of first measurement>70 mg/dL)	79	15.00	10.00	65.00	19.81	17.93	21.69	8.38
Estimated time to BG of 70mg/dL (minutes)	79	13.30	4.50	42.35	14.91	13.38	16.44	6.83
Lilly glucagon								
Baseline (nadir) BG (mg/dL)	79	45.80	33.70	50.80	45.20	44.56	45.84	2.88
First BG measurement >70 mg/dL	79	77.50	70.00	101.00	79.00	77.44	80.56	6.97
BG kinetics:								
Change in BG(mg/dL)	79	32.40	21.90	53.10	33.80	32.22	35.38	7.06
Rate of change in BG(mg/dL/min)	79	2.46	1.04	5.31	2.56	2.38	2.75	0.82
Time to event BG>70mg/dL								
Visit (time point of first measurement>70 mg/dL)	79	15.00	5.00	30.00	14.18	13.22	15.13	4.27
Estimated time to BG of 70mg/dL (minutes)	79	9.84	4.16	21.86	10.63	9.85	11.42	3.51

B Study 303 G-Pen	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline (nadir) BG (mg/dL)	76	48.09	40.82	51.86	47.70	47.20	48.19	2.16
First BG measurement >70 mg/dL	76	77.33	70.13	97.10	79.02	77.56	80.49	6.41
BG kinetics:								
Change in BG(mg/dL)	76	30.59	20.72	48.60	31.33	29.71	32.94	7.06
Rate of change in BG(mg/dL/min)	76	2.17	1.13	4.86	2.26	2.10	2.41	0.67
Time to event BG>70mg/dL:								
Visit (time point of first measurement>70 mg/dL)	76	15.00	10.00	25.00	14.67	13.71	15.63	4.19
Estimated time to BG of 70mg/dL (minutes)	76	10.02	4.80	19.15	10.70	9.97	11.43	3.20
Lilly glucagon								
Baseline (nadir) BG (mg/dL)	78	48.89	43.50	57.20	48.74	48.18	49.30	2.48
First BG measurement >70 mg/dL	78	81.00	70.51	96.79	81.09	79.59	82.59	6.64
BG kinetics:								
Change in BG(mg/dL)	78	32.34	21.18	49.03	32.35	30.83	33.87	6.76
Rate of change in BG(mg/dL/min)	78	2.83	1.87	5.60	3.00	2.82	3.18	0.80
Time to event BG>70mg/dL:								
Visit (time point of first measurement>70 mg/dL)	78	10.00	5.00	15.00	11.15	10.61	11.70	2.41
Estimated time to BG of 70mg/dL (minutes)	78	7.79	3.70	13.73	7.55	7.09	8.01	2.05

Table 20. Measurements at the first BG increase by 20 mg/dL

C Study 301 G-Pen	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline (nadir) BG (mg/dL)	79	44.90	29.70	49.50	44.83	44.10	45.56	3.25
First BG measurement after increase in BG>=20 mg/dL	79	71.60	59.20	103.00	73.35	71.51	75.19	8.20
BG kinetics:								
Change in BG(mg/dL)	79	26.30	20.30	54.20	28.52	26.89	30.16	7.30
Rate of change in BG(mg/dL/min)	79	1.76	0.46	4.42	1.83	1.67	1.99	0.71
Time to BG>=20 mg/dL:								
Visit (time point)	79	15.00	5.00	55.00	17.66	16.00	19.32	7.42
First BG measurement after increase in BG>=20 mg/dL (minutes)	79	11.36	4.52	43.48	13.10	11.61	14.59	6.66
Lilly glucagon								
Baseline (nadir) BG (mg/dL)	79	45.80	33.70	50.80	45.20	44.56	45.84	2.88
First BG measurement after increase in BG>=20 mg/dL	79	74.60	61.00	101.00	75.05	73.45	76.65	7.15
BG kinetics:								
Change in BG(mg/dL)	79	29.00	20.40	53.10	29.85	28.36	31.35	6.69
Rate of change in BG(mg/dL/min)	79	2.37	1.04	6.88	2.52	2.31	2.73	0.94
Time to BG>=20 mg/dL:								
Visit (time point)	79	10.00	5.00	30.00	12.85	11.94	13.76	4.06
First BG measurement after increase in BG>=20 mg/dL (minutes)	79	8.44	2.91	19.17	8.90	8.21	9.59	3.08

D Study 303 G-Pen	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline (nadir) BG (mg/dL)	76	48.09	40.82	51.86	47.70	47.20	48.19	2.16
First BG measurement after increase in BG>=20 mg/dL	76	74.69	64.83	95.16	75.63	74.13	77.13	6.57
BG kinetics:								
Change in BG(mg/dL)	76	26.00	20.03	48.60	27.93	26.47	29.39	6.38
Rate of change in BG(mg/dL/min)	76	2.11	1.06	4.86	2.17	2.01	2.32	0.68
Time to BG>=20 mg/dL:								
Visit (time point)	76	15.00	10.00	25.00	13.62	12.77	14.47	3.71
First BG measurement after increase in BG>=20 mg/dL (minutes)	76	9.48	4.12	18.93	10.08	9.38	10.77	3.04
Lilly glucagon								
Baseline (nadir) BG (mg/dL)	78	48.89	43.50	57.20	48.74	48.18	49.30	2.48
First BG measurement after increase in BG>=20 mg/dL	78	78.08	66.83	96.79	78.86	77.24	80.48	7.19
BG kinetics:								
Change in BG(mg/dL)	78	28.91	21.10	46.31	30.12	28.68	31.57	6.40
Rate of change in BG(mg/dL/min)	78	2.65	1.87	5.60	2.94	2.76	3.13	0.81
Time to BG>=20 mg/dL:								
Visit (time point)	78	10.00	5.00	15.00	10.58	10.10	11.06	2.13
First BG measurement after increase in BG>=20 mg/dL (minutes)	78	7.54	3.57	10.68	7.26	6.86	7.66	1.78

Table 21. Subgroup results: Estimated time to achieve BG benchmark (studies 301 and 303)

Attribute	BG Benchmark	Time BG increase (minutes) Mean (95%CI)			
		Study 301		Study 303	
		G-Pen	Lilly glucagon	G-Pen	Lilly glucagon
Race					
White	>=20 mg/dL	13.1(11.6, 14.6)	8.9(8.2,9.6)	10.1(9.4,10.8)	7.3(6.9,7.7)
	>70 mg/dL	14.9(13.4, 16.4)	10.6(9.9, 11.4)	10.77(9.98,11.56)	7.73(7.22,8.24)
Other	>=20 mg/dL	15.78(6.03, 25.53)	10.09(6.05,14.13)	9.45(7.31,11.59)	6.15(5.43,6.88)
	>70 mg/dL	14.71(13.21,16.21)	10.50(9.69,11.30)	10.21(7.79,12.62)	6.34(5.49,7.19)
Sex					
Female	>=20 mg/dL	11.98(9.59, 14.37)	8.75(7.62, 9.88)	9.95(9.05,10.84)	7.07(6.55,7.58)
	>70 mg/dL	13.65(11.33,15.97)	10.07(8.71,11.42)	10.50(9.58,11.43)	7.20(6.64,7.77)
Male	>=20 mg/dL	13.99(12.07,15.92)	9.03(8.14,9.91)	10.17(9.13,11.21)	7.41(6.81,8.01)
	>70 mg/dL	15.91(13.84,17.98)	11.11(10.18, 12.03)	10.85(9.75,11.95)	7.82(7.12,8.52)
Age					
<40	>=20 mg/dL	11.32(9.68, 12.96)	8.31(7.32, 9.30)	9.62(8.88,10.37)	6.70(6.23,7.18)
	>70 mg/dL	13.26(11.55,14.96)	9.69(8.70,10.68)	10.28(9.46,11.10)	6.93(6.42,7.44)
>=40	>=20 mg/dL	14.31(12.09,16.54)	9.33(8.37,10.29)	10.77(9.41,12.13)	8.10(7.48,8.73)
	>70 mg/dL	16.03(13.74,18.33)	11.31(10.17,12.45)	11.35(9.95,12.75)	8.50(7.70,9.29)

Appendix C.

Adverse events

Table 22. AEs (study 301)

Study 301 Mild AEs	G-Pen	Lilly
Bacterial upper respiratory tract infections	0	1
Cardiac signs and symptoms	1	0
Dental and gingival therapeutic procedures	1	0
Dermal and epidermal conditions	1	0
Headaches	2	3
Muscle related signs and symptoms	1	0
Nausea and vomiting symptoms	21	10
Total	27	14

Study 301 Moderate AEs	G-Pen	Lilly
Bacterial upper respiratory tract infections	1	0
Hyperglycaemic conditions	0	1
Joint related signs and symptoms	0	1
Nausea and vomiting symptoms	2	4
Urinary tract infections	1	0
Urticarias	1	0
Total	5	6

Study 301 Severe AEs	G-Pen	Lilly
Hypoglycaemic conditions	0	1
Total	0	1

Table 23. AEs (study 303)

Study 303 Mild AEs	G-Pen	Lilly
Asthenic conditions	0	1
Diarrhoea (excl infective)	2	1
Dyspeptic signs and symptoms	1	1
Eye and eyelid infections	1	0
Feelings and sensations	1	0
Fungal infections	1	0
Gastrointestinal signs and symptoms	1	0
General signs and symptoms	0	1
Headaches	5	3
Hypoglycaemic conditions	1	0
Infusion site reactions	0	1
Injection site reactions	2	1
Nausea and vomiting symptoms	37	29
Neurological signs and symptoms	2	2
Rate and rhythm disorders	1	0
Upper respiratory tract infections	2	0
Total	57	40

Study 303 Mild AEs	G-Pen	Lilly
General signs and symptoms	0	2
Headaches	1	1
Infusion site reactions	1	0
Mass conditions	0	1
Metabolic acidoses (excl diabetic acidoses)	1	1
Nausea and vomiting symptoms	13	9
Neurological signs and symptoms	1	0
Rashes, eruptions and exanthems	1	0
Urinary abnormalities	0	1
Total	18	15

Appendix D.

Recovery rates

Table 24. Recovery rates based on 20mg/dL increase in BG

Study 301	Study 301				Study 303			
	G-Pen		Lilly glucagon		G-Pen		Lilly glucagon	
Recovery time (min)	Number of subjects	%	Number of subjects	%	Number of subjects	%	Number of subjects	%
5	1	1.265822785	6	7.594936709	2	2.631578	8	10.25641
10	34	43.03797468	54	68.35443038	42	62.686557	66	84.61538
15	23	29.11392405	16	20.25316456	27	40.2985	4	5.128205
20	13	16.4556962	3	3.797468354	5	6.578947		
25	4	5.063291139						
30	2	2.53164557						
>30	2	2.53164557						

Table 25. Recovery rates based on 20 mg/dL increase in BG (by sex)

Recovery time (min)	Study 301					Study 303			
		G-Pen		Lilly glucagon		G-Pen		Lilly glucagon	
	Recovery time (min)	Number of subjects	%	Number of subjects	%	Number of subjects	%	Number of subjects	%
Female	5	1	2.857142857	4	11.11111			2	5.882353
	10	19	54.28571429	24	66.66667	19	59.375	32	94.11765
	15	9	25.71428571	6	16.66667	13	40.625		
	20	3	8.571428571	2	5.555556				
	25	2	5.714285714						
	>30	1	2.857142857						
Male	5			2	4.651163	2	4.545455	6	13.63636
	10	15	34.09091	30	69.76744	23	52.27273	34	77.27273
	15	14	31.81818	10	23.25581	14	31.81818	4	9.090909
	20	10	22.72727	1	2.325581	5	11.36364		
	25	2	4.545455						
	30	2	4.545455						
	>30	1	2.272727						

Table 26. Recovery rates based on 20 mg/dL increase in BG (by age group)

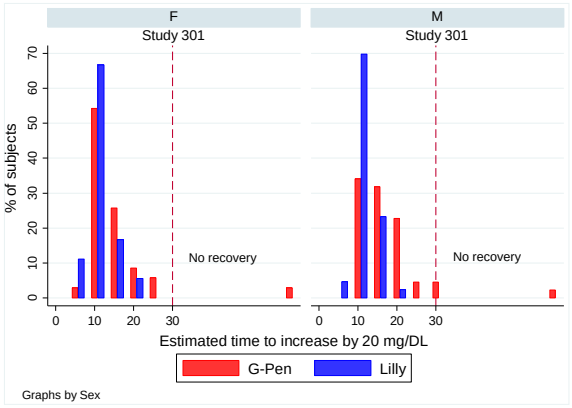
		Study 303				Study 303			
		G-Pen		Lilly glucagon		G-Pen		Lilly glucagon	
	Recovery time (min)	Number of subjects	%	Number of subjects	%	Number of subjects	%	Number of subjects	%
Age >=18 to <65	5	1	1.428571	6	8.571429	2	2.857143	7	9.722222
	10	32	45.71429	48	68.57143	38	54.28571	61	84.72222
	15	19	27.14286	13	18.57143	25	35.71429	4	5.555556
	20	11	15.71429	3	4.285714	5	7.142857		
	25	4	5.714286						
	30	1	1.428571						
	>30	2	2.857143						
Age>=65	5							1	16.66667
	10	2	22.22222	6	66.66667	4	66.66667	5	83.33333
	15	4	44.44444	3	33.33333	2	33.33333		
	20	2	22.22222						
	30	1	11.11111						

Table 27. Recovery rates based on 20 mg/dL increase in BG (by race)

	Recovery time (min)	Study 301 G-Pen		Lilly glucagon		Study 303 G-Pen		Lilly glucagon	
	Recovery time (min)	Number of subjects	%	Number of subjects	%	Recovery time (min)	Number of subjects	%	Number of subjects
White	5	1	1.388889	6	8.333333	2	2.985075	7	10.29412
	10	32	44.44444	49	68.05556	36	53.73134	57	83.82353
	15	20	27.77778	15	20.83333	25	37.31343	4	5.882353
	20	13	18.05556	2	2.777778	4	5.970149		
	25	3	4.166667						
	30	2	2.777778						
	>30	1	1.388889						
BLACK OR AFRICAN AMERICAN	5								
	10			2	50				
	15	3	75	1	25				
	20			1	25				
	25	1	25						
	30								
	>30								
Asian	5								
	10			1	10	4	66.66667	6	100
	15					1	16.66667		
	20					1	16.66667		

	25								
	30								
	>30	1	100						
Multiple	5							1	33.33333
	10	2	10	2	100	1	50	2	66.66667
	15					1	50		
	20								
	25								
	30								
	>30								
Other	5								
	10					1	100	1	100

Figure 9. Recovery rates by sex subgroup (recovery defined as first BG increase of 20 mg/dL from nadir)



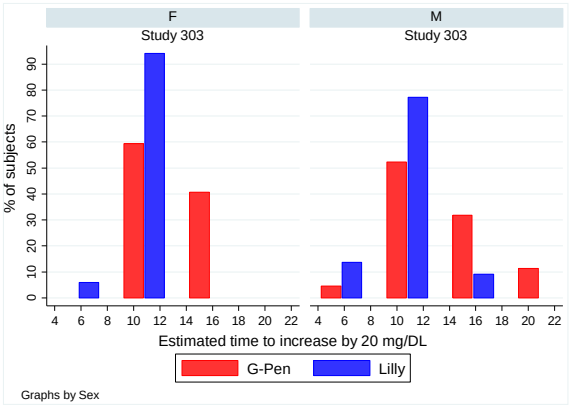
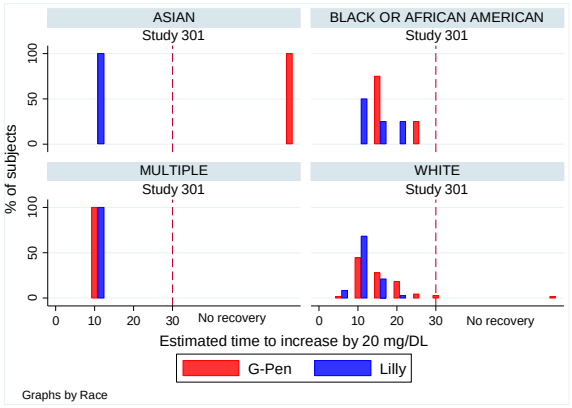


Figure 10. Recovery rates by race subgroup (recovery defined as first BG increase of 20 mg/dL from nadir)



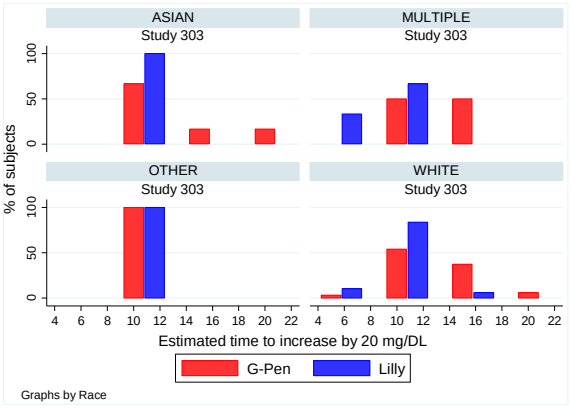
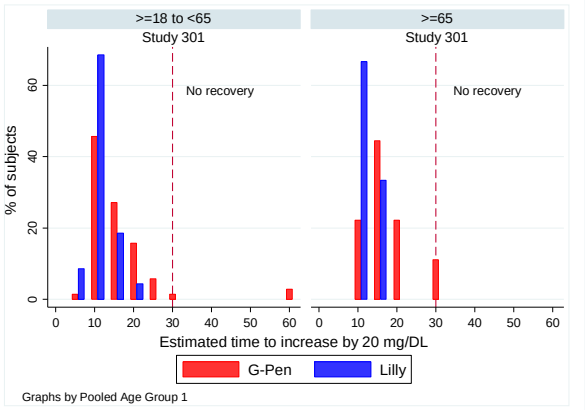
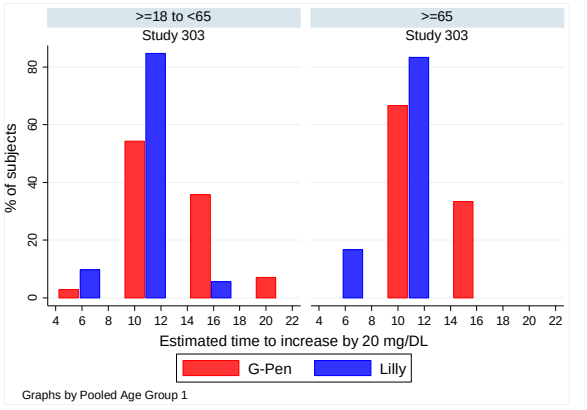


Figure 11. Recovery rates by age subgroup (recovery defined as first BG increase of 20 mg/dL from nadir)





Appendix E.

Data for subjects who participated in both adult studies (dual participants)

Table 28. BG kinetics separate analyses for dual participants (Study 303)

G-Pen dual participants only	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline BG (mg/dL)	9	47.53	43.10	50.70	47.32	45.56	49.07	2.45
First BG measurement after increase in BG>=20 mg/dL	9	72.27	68.77	80.54	72.83	70.22	75.44	3.65
BG kinetics:								
Change in BG(mg/dL)	9	24.86	21.34	32.95	25.51	22.55	28.47	4.14
Rate of change in BG(mg/dL/min)	9	2.17	1.10	2.49	2.05	1.75	2.35	0.41
Time to BG>=20 mg/dL:								
Visit (time point)	9	12.50	10.00	20.00	13.00	10.50	15.50	3.50
First BG measurement after increase in BG>=20 mg/dL (minutes)	9	9.24	8.04	18.20	10.30	8.14	12.45	3.02

G-Pen without dual participants	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline BG (mg/dL)	67	48.08	40.82	51.86	47.71	47.19	48.23	2.13
First BG measurement after increase in BG>=20 mg/dL	67	75.32	64.83	95.16	75.96	74.30	77.62	6.81
BG kinetics:								
Change in BG(mg/dL)	67	26.17	20.03	48.60	28.25	26.65	29.85	6.56
Rate of change in BG(mg/dL/min)	67	2.07	1.06	4.86	2.19	2.02	2.36	0.70
Time to BG>=20 mg/dL:								
Visit (time point)	67	15.00	10.00	25.00	13.66	12.74	14.57	3.75
First BG measurement after increase in BG>=20 mg/dL (minutes)	67	9.65	4.12	18.93	10.01	9.27	10.76	3.05

Lilly glucagon dual participants only	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline BG (mg/dL)	9	47.90	44.30	53.75	48.61	46.68	50.55	2.71
First BG measurement after increase in BG>=20 mg/dL	9	72.32	67.06	86.55	73.61	69.90	77.33	5.19
BG kinetics:								
Change in BG(mg/dL)	9	23.95	21.18	32.80	25.00	22.36	27.65	3.70
Rate of change in BG(mg/dL/min)	9	2.28	1.87	3.28	2.41	2.12	2.69	0.40
Time to BG>=20 mg/dL:								
Visit (time point)	9	10.00	10.00	15.00	10.50	9.37	11.63	1.58
First BG measurement after increase in BG>=20 mg/dL (minutes)	9	8.76	6.10	10.68	8.50	7.57	9.43	1.30

Lilly glucagon without dual participants	N	Median	Minimum	Maximum	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Std Dev
Baseline BG (mg/dL)	67	48.08	40.82	51.86	47.71	47.19	48.23	2.13
First BG measurement after increase in BG>=20 mg/dL	67	75.32	64.83	95.16	75.96	74.30	77.62	6.81
BG kinetics:								
Change in BG(mg/dL)	67	26.17	20.03	48.60	28.25	26.65	29.85	6.56
Rate of change in BG(mg/dL/min)	67	2.07	1.06	4.86	2.19	2.02	2.36	0.70
Time to BG>=20 mg/dL:								
Visit (time point)	67	15.00	10.00	25.00	13.66	12.74	14.57	3.75
First BG measurement after increase in BG>=20 mg/dL (minutes)	67	9.65	4.12	18.93	10.01	9.27	10.76	3.05

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