STATISTICAL ANALYSIS PLAN

FOR

G-PEN™ (GLUCAGON INJECTION)
PROTOCOL XSGP-302

A PHASE 3 STUDY TO EVALUATE THE GLUCOSE RESPONSE OF G-PEN™ (GLUCAGON INJECTION) IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES

Version 1.0

DATE: 16 August 2017

Prepared and distributed by:
The Emmes Corporation
Rockville, Maryland USA

SYNOPSIS

Protocol Number Code:	Protocol XSGP-302
Development Phase:	Phase 3
Products:	G-Pen™ (glucagon injection)
Form/Route:	Subcutaneous injection of G-Pen™ glucagon at an age appropriate dose (0.5 mg for 2-<12 years, 0.5 or 1.0 mg for 12-<18 years).
Indication Studied:	*Severe hypoglycemia*
Sponsor:	Xeris Pharmaceuticals, Inc.
Clinical Study Lead (CRO):	Nilay Shah, MD The Emmes Corporation 401 North Washington Street, Suite 700 Rockville, MD 20850
Scientific Lead:	Marty Cummins The Xeris Pharmaceuticals, Inc.
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Clinical Trial Initiation Date:	**27 March 2017**
Clinical Trial Completion Date:	**30 June 2017**
Date of the Analysis Plan:	**09 August 2017**
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

SIGNATURE PAGE

SPONSOR:	Xeris Pharmaceuticals
STUDY TITLE:	A Phase 3 study to evaluate the glucose response of G-Pen™ (glucagon injection) in pediatric patients with type 1 diabetes
PROTOCOL NUMBER:	XSGP-302

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1 STUDY OVERVIEW

1.1 Study Objectives

This is a sequential efficacy and safety study of G-Pen™ (glucagon injection) in pediatric patients with Type 1 diabetes (T1D). In addition, the pharmacokinetics of G-Pen™ will be evaluated.

Subjects 2.0 to <18.0 years old with T1D receiving daily insulin for at least 6 months from the time of diagnosis will be enrolled to the multi-center study across three age groups (2.0-<6.0, 6.0-<12.0, and 12.0-<18.0 years). Subjects using insulin injections will be administered intravenous (IV) insulin and subjects using an insulin pump will have the basal rate increased to induce a low normal glycemic state (plasma glucose of <80 mg/dl). All subjects will then receive an age-appropriate dose of G-Pen™. Subjects aged 2.0-<12.0 will complete a single treatment visit and receive a 0.5 mg dose of G-Pen™. Subjects aged 12.0-<18.0 will receive a 1.0 mg dose of G-Pen™ at an initial treatment visit, and will also be given a 0.5 mg dose at a second treatment visit occurring 7-28 days later. The second visit comprises a secondary analysis. The study protocol consists of:

- Screening visit;
- Treatment 1visit: One daytime clinical research center visit for subjects aged 2.0-<12.0 to receive a 0.5 mg dose of G-Pen™ and for subjects aged 12.0-<18.0 to receive a 1.0 mg dose;
- Treatment 2 visit (7-28 days after the first treatment): Only subjects aged 12.0-<18.0 will return for a second visit to receive a 0.5 mg dose of G-Pen™; and
- Follow-up phone call: The parent or guardian will be contacted by telephone within 3-14 days of completing each dosing visit or premature discontinuation.

Figure 1 further details the flow for study assessments. This document describes the analyses that will be performed to assess efficacy and safety of G-Pen™ for each age group.

1.1.1 Primary Objectives

The primary objective of this study is to assess the increase in plasma glucose of subjects from baseline to 30 minutes after G-Pen™ glucagon injection, without additional interventions. The assessment will be conducted in each of three age groups (2.0-<6.0, 6.0-<12.0, and 12.0-<18.0 years). The mean of the initial plasma glucose measurement <80 mg/dL and a second confirmatory measurement at least 5 minutes later after stopping the insulin infusion comprises the baseline measurement.

1.1.2 Secondary Objectives

The secondary objectives of this study are:

- Evaluate the pharmacodynamics (PD) of G-Pen™. Additionally, in the 12.0-<18.0 year-old age group, to independently assess the plasma glucose change from baseline to 30 minutes after administration of G-Pen™ at a dose of 0.5 mg.
- Determine the safety and tolerability of G-Pen™ for each age group.
- Evaluate the pharmacokinetics (PK) of G-Pen™. The PK analysis will be performed by another organization, IMD (See Appendix II).

1.2 Endpoints

1.2.1 Primary Endpoints

The primary endpoint for this study is an evaluation of the change in plasma glucose following treatment with G-Pen™ (glucagon injection), particularly to quantify the increase from baseline to 30 minutes post-dosing, in each of three age groups.

1.2.2 Secondary Endpoints

The secondary endpoints for this study are as follows:

- PK parameters, including: descriptive analysis of serum glucagon $AUC_{0\text{-}180m}$, C_{max} and T_{max} of the different age group and overall population. These analyses will be conducted by IMD (See Appendix II).
- PD characteristics, including: descriptive analysis of plasma glucose $AUC_{0\text{-}90m}$, C_{max}, T_{max} and time to achieve an increase in plasma glucose of at least 25 mg/dL for each age group. In addition, in the 12.0-<18.0 year-old age group, plasma glucose change from baseline to 30 minutes after administration of G-Pen™ at a dose of 0.5 mg will be evaluated.
- Safety-related endpoints including:
  - Vital signs, including blood pressure (BP) and heart rate.
  - Incidence of adverse events (AEs) and serious adverse events (SAEs).
  - Subjective injection site discomfort assessed using the Faces Pain Scale (FPS-R).
  - Subjects with sufficient comprehension will further describe the nature and duration of any injection site discomfort using a second questionnaire.
  - Erythema and/or edema formation at site of injection assessed by an investigator using the modified Draize Scale.

1.3 Sample Size

In the Phase 2 study XSGP-201, healthy normal adults were treated using the G-Pen™ after subject completed an overnight fast and presented with baseline plasma glucose values similar to the target levels (< 80 mg/dL) planned for this study. The mean increase in glucose at 30 minutes post-dosing was approximately 25 mg/dL (standard deviation = 18). Based on these assumptions, a sample size of 6 subjects per age group is required to provide 90% power to detect at least this change in the primary endpoint, i.e., an increase of plasma glucose from baseline to 30 minutes after treatment, assuming a type 1 error rate of 5%.

Therefore, approximately forty-eight subjects are anticipated to be screened for this study, and 36 (up to 12 per age group) will be enrolled and receive study treatment to achieve the goal of 18 evaluable subjects equally distributed (n=6 per age group) across the three age groups: 2.0-<6.0, 6.0-<12.0, and 12.0-<18.0 years old. Each age group is an independent clinical experiment with its own α-level of 0.05.

2 ANALYSIS PLAN

All endpoints will be analyzed descriptively within each of the three age groups. N (non-missing sample size), mean, standard deviation, median, minimum, and maximum will be presented for continuous variables. Count and percentage (based on the non-missing sample size) will be presented for discrete variables.

2.1 Analysis Population and Protocol Compliance

The study flow chart displays the enrollment process from screened subjects to the analysis population (Figure 1). Reasons for screening failures will be summarized (Table 1). Subject disposition will be summarized by age group (Table 2). Reasons for discontinued treatment and early termination (Table 3), as well as completion rate for the post-dosing phone call follow-up (Table 4), will be additionally summarized by age group. Protocol deviations will be summarized by age group (Table 5), and a full listing of all deviations will be summarized by site (Listing 1).

2.2 Demographic and Baseline Clinical Characteristics

Summaries of age, gender, ethnicity, race, clinical sites, and baseline clinical characteristics will be presented by age group (Table 6). Ethnicity is categorized as Hispanic or Latino, or not Hispanic or Latino.

2.3 Efficacy Analysis

2.3.1 Efficacy Primary Endpoint

The primary endpoint is the change in plasma glucose at 30 minutes post-dosing from baseline, which is defined as the average of the two plasma glucose measurements (i.e., -5 and 0 minutes) completed immediately prior to dosing. In additional to the descriptive summary, a simple *t*-test will be used to test whether there is a significant change in glucose from baseline to 30 minutes within each of the three age groups (Table 7). All three tests are 2-sided with α-level of 0.05.

2.4 Pharmacokinetic and Pharmacodynamic Analyses

The PK endpoints will be derived from the individual serum glucagon profiles. The PD endpoints will be derived from the individual glucose profiles.

2.4.1 Pharmacokinetic Endpoints

The data for each age group and the overall population will be analyzed descriptively, including serum glucagon $AUC_{0\text{-}180m}$, C_{max} and T_{max}. The analysis will be conducted by IMD (See Appendix II).

2.4.2 Pharmacodynamic Endpoints

In the 12.0-<18.0 year-old age group, the plasma glucose change from baseline to 30 minutes after administration of G-Pen™ at a dose of 0.5 mg will be evaluated using the same approach described in Section 2.3.1 (Table 8).

Time for plasma glucose to increase by ≥25 mg/dL from baseline, maximum glucose concentration (C_{max}) between 0 and 90 min, the time to maximum concentration (T_{max}) will be directly obtained from the observed glucose concentration-time profile. If two identical values are recorded for C_{max}, the first one will be used for T_{max}. The area under the curve from 0 to 90 min ($AUC_{0\text{-}90m}$) of glucose will be calculated as the sum of areas of trapezoids, which are composed of adjacent glucose values. The following rules will be considered:

1. If there are missing data points before the last observed value, they will not be imputed.
2. If there are missing data points after the last observed value, they will be extrapolated using the last two data points.

Baseline-adjusted $AUC_{0\text{-}90m}$ with negative values set at 0 will also be calculated. All PD endpoints will be analyzed descriptively for each age group (Table 9) and by treatment dose for subjects aged 12.0-<18.0 (Table 10). Actual time instead of protocol time will be used for calculating the time for plasma glucose to increase by ≥25 mg/dL from baseline, T_{max}, $AUC_{0\text{-}90m}$, and baseline-adjusted $AUC_{0\text{-}90m}$. In addition, plasma glucose concentration-time profile by age group (Figure 2 and Table 11) and by treatment dose for subjects aged 12.0-<18.0 (Figure 3 and Table 11) will be presented.

2.5 Safety Analysis

The following variables will be evaluated for safety purposes:

- AEs and SAEs.
- Vital signs, including BP and heart rate.
- Local tolerability, including:
  - Subjective injection site discomfort as reported by subjects using age-appropriate discomfort scales.
  - Erythema and/or edema formation at site of injection assessed using the Draize scale.

2.5.1 Adverse events

All AEs will be coded by the Data Coordinating Center (The Emmes Corporation) using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class and preferred term, as well as by treatment dose. Number and percentage of subjects experiencing at least one AE after the G-Pen™ was administrated will be presented (Table 12). In addition, the severity of AEs post-dosing and their relatedness to study drug, device, and procedure will be assessed (Tables 13). Treatment emergent adverse event (TEAE), defined by AE occurring after administration of G-Pen™, and non-TEAE, defined by any AE that occurred after signing informed consent, will be presented in Tables 12 and 13.

2.5.2 Physical examination

Subjects with any abnormal physical examination findings at screening will be listed (Listing 2). Changes in physical examination findings from screening to end of trial will be recorded as AEs if they are untoward or the investigator judges them to be clinically significant changes.

2.5.3 Vital signs

BP and heart rate immediately before and after administration of G-Pen™ in each age group and by treatment dose for subjects aged 12.0-<18.0 will be summarized by descriptive statistics (Table 14 and Figure 4).

2.5.4 Local Tolerability

The incidence of any injection site discomfort (i.e., FPS-R score >0 on the ordinal rating scale) by age group and by treatment dose for subjects aged 12.0-<18.0 will be analyzed descriptively (Table 15 and Figure 5). The incidences of erythema (Table 16 and Figure 5) and edema (Table 17, and Figure 5) will be analyzed in a similar manner. Descriptive statistics will be provided for time of onset, duration (of discomfort), and discomfort description (i.e., pain, irritation, itching, etc.) by age group and by treatment dose for subjects aged 12.0-<18.0 (Table 18).

2.5.5 Pregnancies

The active pharmaceutical product in Xeris Pharmaceuticals' G-Pen™ is Glucagon, which is in Pregnancy Category B. Any subject found to be pregnant at any time during the study will be withdrawn from the study immediately. If a pregnancy is reported or initiated within 7 days following administration of the study medication, the pregnancy will be followed until resolution (i.e., birth or voluntary or spontaneous termination of the pregnancy) and reported using the pregnancy Case Report Form. Any pregnancy outcome that meets the criteria for an SAE will be reported both as a SAE and on the pregnancy Case Report Form.

A listing of pregnancies and outcomes will be presented (Listing 3).

3 STATISTICAL CONSIDERATIONS

3.1 Timing of Analyses

No interim analysis is planned for this study. The final analysis will be performed after the final database lock. There will be a single database lock after all data capture and cleaning is completed.

3.2 Analysis Cohort

The efficacy and PD analyses will include all participants who completed the dosing visit with the following exceptions:

- Dosing visits during which a glucose-elevating intervention is given after administration of G-Pen™ will be included in the analysis, but the glucose values after the additional intervention post-dosing will be censored.
- For the efficacy analysis, if the additional intervention is given before 30 minutes post-dosing, then the 30-minute post-dosing measurement will be replaced with the last glucose measurement prior to the intervention.
- For the PD analysis., if the additional intervention is given shortly after administration of G-Pen™ (i.e., more than half of the glucose values is censored), the subject will be excluded from the analysis.

3.3 Missing Data

For the efficacy analyses, last observation carried forward (LOCF) will be applied for subjects who drop out before 30 minutes post-dosing or who otherwise have missing primary endpoint data (e.g. missed blood draws). Baseline glucose is calculated as the mean of the initial glucose measurement <80 mg/dL and a second confirmatory measurement prior to dosing. If either one measurement is missing, then the available one will be used as the baseline glucose value. If both measurements are missing, the patient will not be included in the efficacy analyses, given there is no confirmation measurements the subject reached a blood glucose value of <80 mg/dL prior to receiving the glucagon injection. The proportion of non-analyzable subjects is expected to be low and will be monitored by the Clinical Research Associate (CRA) (or designee) throughout the trial.

3.4 Interim Analyses and Data Monitoring

As detailed in Section 15.3 of the protocol, the CRA (or designee) will review and evaluate each related AE in addition to accumulated trial data for participant safety, trial conduct and trial progress after trial initiation. Since this is a single-arm trial, safety results will be listed in an unblinded fashion and reviewed by the Sponsor regularly. There will be no interim analysis of the efficacy endpoint planned for this study.

3.5 Multicenter Studies

Data will be pooled within each age group across all clinical sites. Center effects are not anticipated because the sites are using standardized procedures for treatment with G-Pen™ and assessment of solicited and unsolicited adverse events.

3.6 Multiple Comparisons/Multiplicity

There is only one primary endpoint. Each age group is individually powered. No adjustments for multiple testing are planned.

3.7 Covariates and Subgroups

Neither covariate adjustments nor additional subgroup analyses are planned for this study.

4 REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; *P*-values less than 0.001 will be reported as "<0.001"; *P*-values greater than 0.999 will be reported as ">0.999". The mean, standard deviation (SD), and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

5 TECHNICAL DETAILS

SAS version 9.4 will be used to generate all tables, figures and listings and perform statistical analyses, and Phoenix WinNonLin version 6.4 will be used to perform the PD analysis.

APPENDICES

Appendix I: TABLE/FIGURE/LISTING MOCK-UPS

Appendix II: PHARMACOKINETIC ANALYSIS (CONDUCTED BY INTEGRATED MEDICAL DEVELOPMENT, NEW JERSEY USA)

Appendix I: TABLE/FIGURE/LISTING MOCK-UPS

Demographic Data

Figure 1: Study flow chart

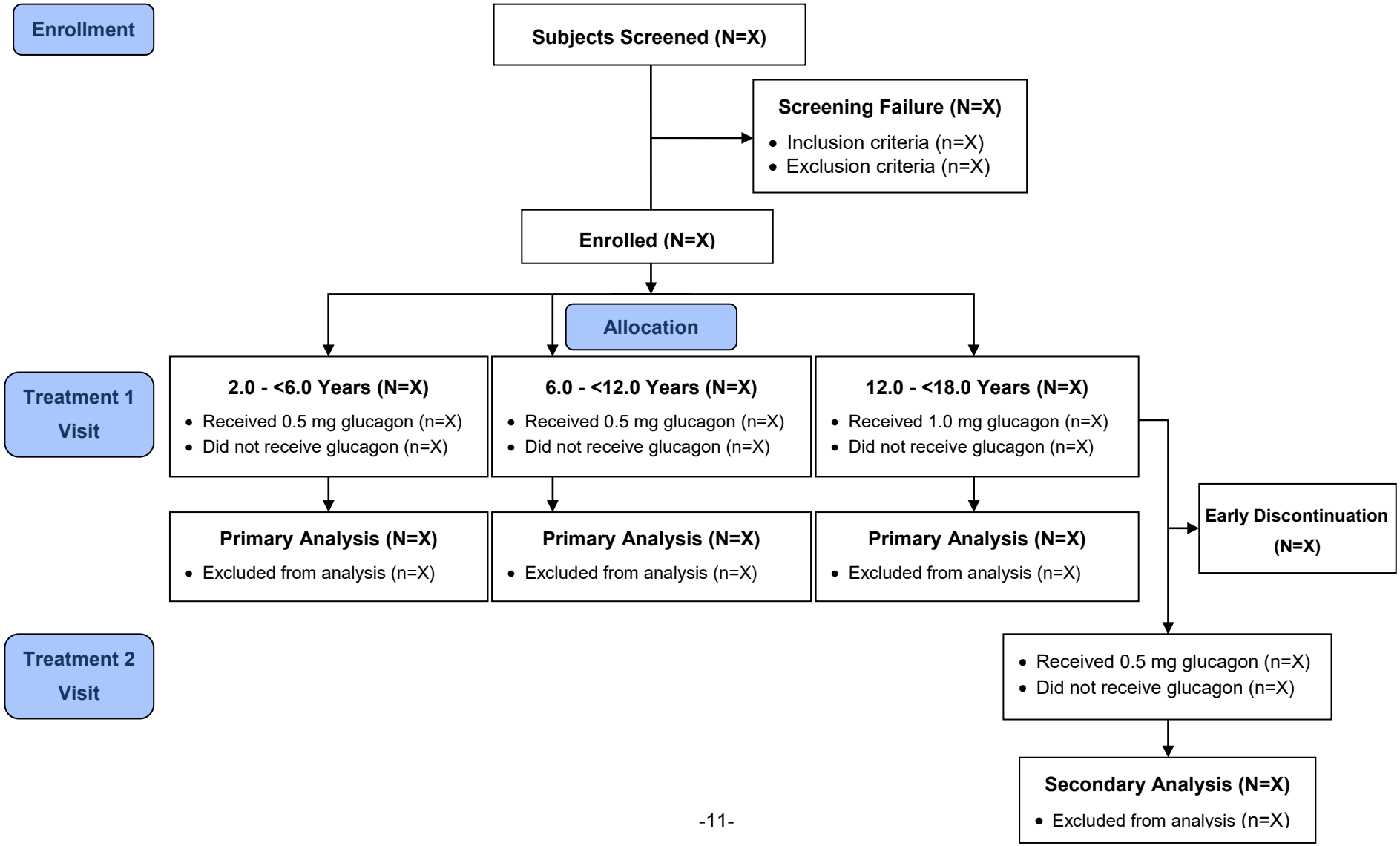


Table 1: Ineligibility summary of screen failures		
Inclusion/Exclusion Category	**Inclusion/Exclusion Criterion**	**Number of Subjects who did not meet the criteria[a]**
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x
Inclusion	Any inclusion criterion	x
	1.Subject is a male or female diagnosed with T1D for at least 6 months at Screening	x
	2.Subject is currently using daily insulin treatment	x
	3.Subject is at least 2.0 and less than 18.0 years of age, and will be <18.0 for the duration of the study	x
	4.Subject and adult guardian are willing to follow all study procedures, including attending all clinic visits	x
	5.Parent or guardian has provided written informed consent, and assent has been obtained from subjects if appropriate for age according to IRB requirements	x
Exclusion	Any exclusion criterion	x
	1.Subject is pregnant and/or nursing	x
	2.Subject has renal insufficiency (serum creatinine >1.5 mg/dL in males or >1.4 mg/dL in females)	x
	3.Subject has serum ALT > 3 times the upper limit of normal	x
	4.Subject has serum AST > 3 times the upper limit of normal	x
	5.Subject has hepatic synthetic insufficiency as defined as a serum albumin of <3.0 g/dL	x
	6.Subject has serum bilirubin >2.0 mg/dL	x
	7.Subject has hematocrit of <30%	x
	8.Subject has mean of triplicate blood pressure readings at Screening where systolic blood pressure or diastolic blood pressure was >95% of normal for age and height percentile	x
	9.Subject uses >2.0 U/kg total insulin dose per day	x

Table 1: Ineligibility summary of screen failures		
Inclusion/Exclusion Category	**Inclusion/Exclusion Criterion**	**Number of Subjects who did not meet the criteria[a]**
	10. Subject has inadequate venous access	x
	11. Subject has a current seizure disorder	x
	12. Subject has a history of pheochromocytoma or a disorder with increased risk of pheochromocytoma (e.g. MEN 2, neurofibromatosis, or Von Hippel-Lindau disease)	x
	13. Subject has a history of insulinoma	x
	14. Subject has a history of allergies to glucagon or glucagon-like products, or any history of significant hypersensitivity to glucagon or any related products or to any of the excipients (DMSO and trehalose) in the investigational formulation	x
	15. Subject has a history of glycogen storage disease	x
	16. Subject has any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen	x
	17. Subject is an active user of alcohol or drugs of abuse	x
	18. Subject has had an administration of glucagon within 14 days of the first treatment visit	x
	19. Subject has participated in other studies involving administration of an investigational drug or device within 30 days or 5 half-lives, whichever is longer, before Screening for the current study and during participation in the current study	x
	20. The principal investigator deems this subject exclusionary	x

[a] A subject may fail to meet more than one eligibility criteria.

Table 2: Subject disposition by age group						
Subject Disposition	**Age Group**					
	2.0-<6.0 years (N=X)		**6.0-<12.0 years (N=X)**		**12.0-<18.0 years (N=X)**	
	n	**%**	**n**	**%**	**n**	**%**
Screened	x	x.x	x	x.x	x	x.x
Enrolled	x	x.x	x	x.x	x	x.x
Received All Scheduled Treatments[a]	x	x.x	x	x.x	x	x.x
Completed All Study Follow-ups[b]	x	x.x	x	x.x	x	x.x

[a] Refer to Table 3 for reasons subjects discontinued treatment or terminated early.
[b] Refer to Table 4 for reasons subjects who did not complete the follow-up phone call.

Table 3: Reasons for discontinued treatment or early termination by age group							
		Age Group					
		2.0-<6.0 years (N=X)		6.0-<12.0 years (N=X)		12.0-<18.0 years (N=X)	
Category	Reason	n	%	n	%	n	%
Early Termination Prior to Treatment 1 Visit	Subject did not fast for at least 8 hours	x	x.x	x	x.x	x	x.x
	Subject has severe hypoglycemic event within last 2 weeks	x	x.x	x	x.x	x	x.x
	Ketone results were moderate or greater	x	x.x	x	x.x	x	x.x
	Subject decision	x	x.x	x	x.x	x	x.x
	Investigator/Physician decision	x	x.x	x	x.x	x	x.x
	Sponsor decision	x	x.x	x	x.x	x	x.x
	Other reason	x	x.x	x	x.x	x	x.x
Discontinued After Treatment 1 Visit	Withdrawal early due to adverse event	x	x.x	x	x.x	x	x.x
	Missed visits, lost to follow-up, or lack of cooperation	x	x.x	x	x.x	x	x.x
	Voluntary withdrawal	x	x.x	x	x.x	x	x.x
	Terminated early due to protocol deviation	x	x.x	x	x.x	x	x.x
	Death	x	x.x	x	x.x	x	x.x
Early Termination Prior to	Subject did not fast for at least 8 hours	NA		NA		x	x.x

Table 3: Reasons for discontinued treatment or early termination by age group							
		Age Group					
		2.0-<6.0 years (N=X)		6.0-<12.0 years (N=X)		12.0-<18.0 years (N=X)	
Category	Reason	n	%	n	%	n	%
Treatment 2 Visit (12.0 - <18.0 year-old only)	Subject has severe hypoglycemic event within last 2 weeks	NA		NA		x	x.x
	Ketone results were moderate or greater	NA		NA		x	x.x
	Subject decision	NA		NA		x	x.x
	Investigator/Physician decision	NA		NA		x	x.x
	Sponsor decision	NA		NA		x	x.x
	Other reason	NA		NA		x	x.x

NA=not applicable.

Table 4: Completion rate of follow-up phone call after each treatment visit by age group						
Follow-up Phone Call Assessment	Age Group					
	2.0-<6.0 years (N=X)		6.0-<12.0 years (N=X)		12.0-<18.0 years (N=X)	
	n	%	n	%	n	%
Completed After Treatment Visit 1						
Yes	x	x.x	x	x.x	x	x.x
No	x	x.x	x	x.x	x	x.x
Reason 1	x	x.x	x	x.x	x	x.x
Reason 2	x	x.x	x	x.x	x	x.x
Completed After Treatment Visit 2						
Yes	NA		NA		x	x.x
No	NA		NA		x	x.x
Reason 1	NA		NA		x	x.x
Reason 2	NA		NA		x	x.x

NA=not applicable.

Table 5: Distribution of protocol deviations
A. Subject-specific protocol deviations by age group

Category	Age Group					
	2.0-<6.0 years (N=X)		6.0-<12.0 years (N=X)		12.0-<18.0 years (N=X)	
	No. of Subjects	No. of Deviations	No. of Subjects	No. of Deviations	No. of Subjects	No. of Deviations
Any Category	xx	xx	xx	xx	xx	xx
Informed consent procedures	xx	xx	xx	xx	xx	xx
Eligibility/exclusion criteria	xx	xx	xx	xx	xx	xx
Missed scheduled study	xx	xx	xx	xx	xx	xx
Scheduled visit/procedure conducted outside of window	xx	xx	xx	xx	xx	xx
Laboratory assessment not performed	xx	xx	xx	xx	xx	xx
Study procedure/ assessment not performed	xx	xx	xx	xx	xx	xx
Procedure/assessment not performed per protocol	xx	xx	xx	xx	xx	xx
Temperature excursion	xx	xx	xx	xx	xx	xx
Specimen excursion	xx	xx	xx	xx	xx	xx
Specimen collected outside of window	xx	xx	xx	xx	xx	xx
Other	xx	xx	xx	xx	xx	xx

Table 5: Distribution of protocol deviations *(continued)*

B. Study-specific protocol deviation by site

Category	No. of Deviations at Each Site							
	Barbara Davis Center for Childhood Diabetes	Women & Children's Hospital of Buffalo	University of Florida Diabetes Institute	Riley Hospital for Children at IU Health	University of Iowa Hospitals and Clinics	Nemours Children's Clinic	Lucile Packard Children's Hospital at Stanford	Yale University School of Medicine
Any Category	xx	xx	xx	xx	xx	xx	xx	xx
Informed consent procedures	xx	xx	xx	xx	xx	xx	xx	xx
Eligibility/exclusion criteria	xx	xx	xx	xx	xx	xx	xx	xx
Missed scheduled study	xx	xx	xx	xx	xx	xx	xx	xx
Scheduled visit/procedure conducted outside of window	xx	xx	xx	xx	xx	xx	xx	xx
Laboratory assessment not performed	xx	xx	xx	xx	xx	xx	xx	xx
Study procedure/ assessment not performed	xx	xx	xx	xx	xx	xx	xx	xx
Procedure/assessment not performed per protocol	xx	xx	xx	xx	xx	xx	xx	xx
Temperature excursion	xx	xx	xx	xx	xx	xx	xx	xx
Specimen excursion	xx	xx	xx	xx	xx	xx	xx	xx
Specimen collected outside of window	xx	xx	xx	xx	xx	xx	xx	xx
Other	xx	xx	xx	xx	xx	xx	xx	xx

Listing 1: Listing of protocol deviations by site									
Site	**Date Deviation identified**	**Subject-specific Deviation?**	**Subject ID**	**Treatment Group**	**Deviation Category**	**Deviation Description**	**Resulted in Subject Termination?**	**Deviation Severity**	**Deviation Resolution**

Table 6: Demographic and baseline clinical characteristics by age group			
	Age Group		
	2.0-<6.0 years (N=X)	**6.0-<12.0 years (N=X)**	**12.0-<18.0 years (N=X)**
Age, years			
N	x	x	x
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x
[Min-Max]	[xx.x-xx.x]	[xx.x-xx.x]	[xx.x-xx.x]
Gender – n (%)			
Male	x (x.x)	x (x.x)	x (x.x)
Female	x (x.x)	x (x.x)	x (x.x)
Ethnicity – n (%)			
Hispanic or Latino	x (x.x)	x (x.x)	x (x.x)
Not Hispanic or Latino	x (x.x)	x (x.x)	x (x.x)
Race – n (%)			
White	x (x.x)	x (x.x)	x (x.x)
Black/African American	x (x.x)	x (x.x)	x (x.x)
Native Hawaiian/Other Pacific Islander	x (x.x)	x (x.x)	x (x.x)
Asian	x (x.x)	x (x.x)	x (x.x)
American Indian/Alaskan Native	x (x.x)	x (x.x)	x (x.x)
Multi-Racial	x (x.x)	x (x.x)	x (x.x)

Table 6: Demographic and baseline clinical characteristics by age group			
	Age Group		
	2.0-<6.0 years (N=X)	**6.0-<12.0 years (N=X)**	**12.0-<18.0 years (N=X)**
Body Mass Index[a], kg/m^2			
N	x	x	x
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x
[Min-Max]	[xx.x-xx.x]	[xx.x-xx.x]	[xx.x-xx.x]
Duration of Type 1 Diabetes, years			
N	x	x	x
Mean (SD)	xx.xxx (xx.xxx)	xx.xxx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.xx	xx.xx	xx.xx
[Min-Max]	[xx.xx-xx.xx]	[xx.xx-xx.xx]	[xx.xx-xx.xx]
Hemoglobin A1c, %			
N	x	x	x
Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
Median	xx.x	xx.x	xx.x
[Min-Max]	[xx.x-xx.x]	[xx.x-xx.x]	[xx.x-xx.x]
Primary Insulin Modality – n (%)			
Insulin pump	x (x.x)	x (x.x)	x (x.x)
Insulin injections	x (x.x)	x (x.x)	x (x.x)
Both pump and injections	x (x.x)	x (x.x)	x (x.x)

Table 6: Demographic and baseline clinical characteristics by age group			
	Age Group		
	2.0-<6.0 years (N=X)	**6.0-<12.0 years (N=X)**	**12.0-<18.0 years (N=X)**
Average Daily Insulin Dose for Pumpers, total units			
N	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Number of Injections Per Day for Injectors			
N	x	x	x
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx
[Min-Max]	[xx-xx]	[xx-xx]	[xx-xx]
Clinical Site – n (%)			
Barbara Davis Center for Childhood Diabetes	x (x.x)	x (x.x)	x (x.x)
Women & Children's Hospital of Buffalo	x (x.x)	x (x.x)	x (x.x)
University of Florida Diabetes Institute	x (x.x)	x (x.x)	x (x.x)
Riley Hospital for Children at IU Health	x (x.x)	x (x.x)	x (x.x)
University of Iowa Hospitals and Clinics	x (x.x)	x (x.x)	x (x.x)
Nemours Children's Clinic	x (x.x)	x (x.x)	x (x.x)
Lucile Packard Children's Hospital at Stanford	x (x.x)	x (x.x)	x (x.x)
Yale University School of Medicine	x (x.x)	x (x.x)	x (x.x)

[a] Calculated as weight in kilograms divided by height in meters squared.
SD=standard deviation.

Efficacy Data

Table 7: Plasma glucose before and 30 minutes after administration of G-Pen™ by age group				
	Plasma Glucose (mg/dL) Mean (SD), median, [min – max]			
Age Group	**Baseline**	**30 minutes**	**Change**	***P*-value[a]**
2.0-<6.0 years (N=X)	xx.x (xx.x), xx, [xx-xx]	xxx.x (xxx.x), xxx, [xxx-xxx]	xxx.x (xxx.x), xxx, [xxx-xxx]	x.xxx
6.0-<12.0 years (N=X)	xx.x (xx.x), xx, [xx-xx]	xxx.x (xxx.x), xxx, [xxx-xxx]	xxx.x (xxx.x), xxx, [xxx-xxx]	x.xxx
12.0-<18.0 years (N=X)	xx.x (xx.x), xx, [xx-xx]	xxx.x (xxx.x), xxx, [xxx-xxx]	xxx.x (xxx.x), xxx, [xxx-xxx]	x.xxx

[a] *P*-value computed using *t*-test for testing whether the change in glucose from baseline to 30 minutes is zero.
SD= standard deviation.

Table 8: Plasma glucose before and 30 minutes after administration of G-Pen™ in the 12.0-<18.0 year-old age group at a dose of 0.5 mg				
	Plasma Glucose (mg/dL) Mean (SD), median, [min – max]			
Age Group	**Baseline**	**30 minutes**	**Change**	***P*-value[a]**
12.0-<18.0 years (N=X)	xx.x (xx.x), xx, [xx-xx]	xxx.x (xxx.x), xxx, [xxx-xxx]	xxx.x (xxx.x), xxx, [xxx-xxx]	x.xxx

[a] *P*-value computed using *t*-test for testing whether the change in glucose from baseline to 30 minutes is zero.
SD= standard deviation.

Table 9: Plasma glucose $AUC_{0\text{-}90m}$, C_{max}, T_{max}, and time to increase by ≥25 mg/dL from baseline by age group							
Age Group	**G-Pen™ Dose**	**Summary Statistics**	**C_{max} (mg/dL)**	**T_{max} (min)**	**$AUC_{0\text{-}90m}$ (min*mg/dL)**	**Baseline-adjusted $AUC_{0\text{-}90m}$ (min*mg/dL)**	**Time to increase by ≥25 mg/dL from baseline**
2.0-<6.0 years	**0.5 mg**	**N**	x	x	x	x	x
		Mean (SD)	xxx.x (xxx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xx.x (xx.x)
		Median	xxx	xx	xxx	xxx	xx
		[Min-Max]	[xxx-xxx]	[xx-xx]	[xxx-xxx]	[xxx-xxx]	[xx-xx]
6.0-<12.0 years	**0.5 mg**	**N**	x	x	x	x	x
		Mean (SD)	xxx.x (xxx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xx.x (xx.x)
		Median	xxx	xx	xxx	xxx	xx
		[Min-Max]	[xxx-xxx]	[xx-xx]	[xxx-xxx]	[xxx-xxx]	[xx-xx]
12.0-<18.0 years	**1.0 mg**	**N**	x	x	x	x	x
		Mean (SD)	xxx.x (xxx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xx.x (xx.x)
		Median	xxx	xx	xxx	xxx	xx
		[Min-Max]	[xxx-xxx]	[xx-xx]	[xxx-xxx]	[xxx-xxx]	[xx-xx]

AUC= area under the curve; C_{max}= maximum plasma concentration; T_{max}= time to maximum plasma concentration; SD= standard deviation.

Table 10: Plasma glucose $AUC_{0\text{-}90m}$, C_{max}, T_{max}, and time to increase by ≥25 mg/dL from baseline by treatment dose for subjects aged 12.0-<18.0						
G-Pen™ Dose	**Summary Statistics**	**C_{max} (mg/dL)**	**T_{max} (min)**	**$AUC_{0\text{-}90m}$ (min*mg/dL)**	**Baseline-adjusted $AUC_{0\text{-}90m}$ (min*mg/dL)**	**Time to increase by ≥25 mg/dL from baseline**
1.0 mg	**N**	x	x	x	x	x
	Mean (SD)	xxx.x (xxx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xx.x (xx.x)
	Median	xxx	xx	xxx	xxx	xx
	[Min-Max]	[xxx-xxx]	[xx-xx]	[xxx-xxx]	[xxx-xxx]	[xx-xx]
0.5 mg	**N**	x	x	x	x	x
	Mean (SD)	xxx.x (xxx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xx.x (xx.x)
	Median	xxx	xx	xxx	xxx	xx
	[Min-Max]	[xxx-xxx]	[xx-xx]	[xxx-xxx]	[xxx-xxx]	[xx-xx]

AUC= area under the curve; C_{max}= maximum plasma concentration; T_{max}= time to maximum plasma concentration; SD= standard deviation.

Figure 2: Plasma glucose over time by age group

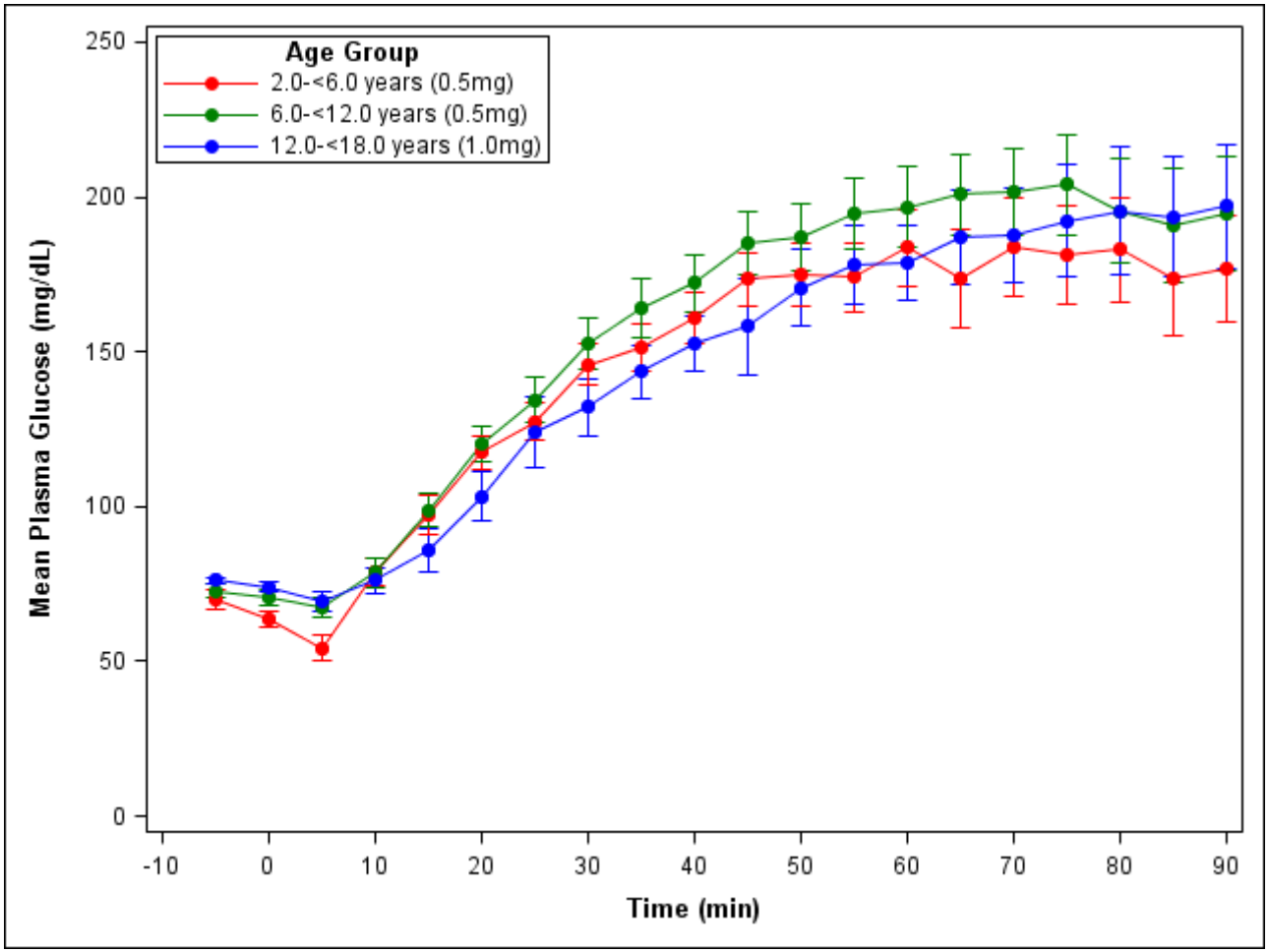


Figure 3: Plasma glucose over time by treatment dose for subjects aged 12.0-<18.0

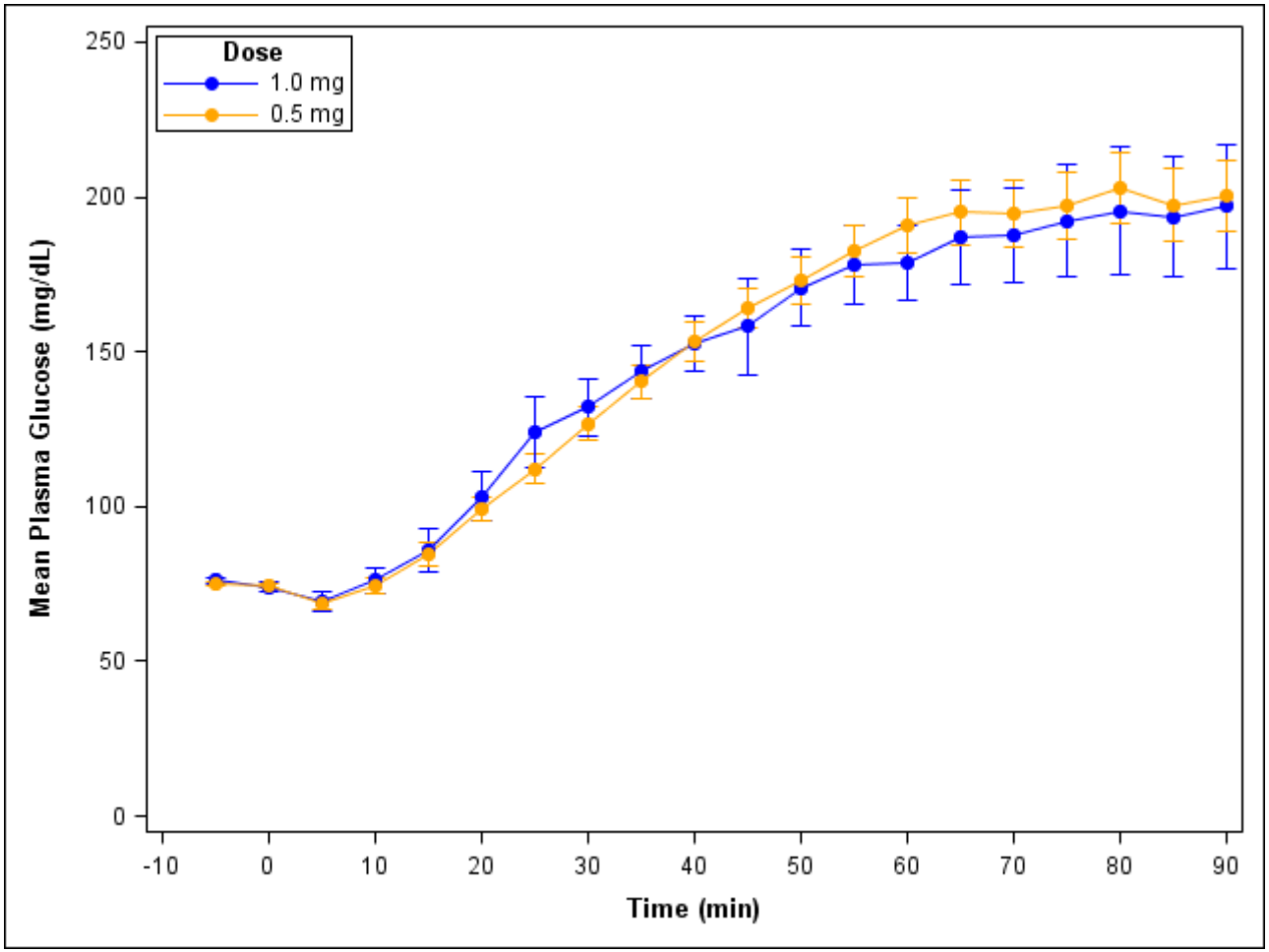


Table 11: Plasma glucose over time by age group and by treatment dose for subjects aged 12.0-<18.0

Plasma Glucose, mg/dL Mean (SD)		**Time (min)**																			
Age Group	**G-Pen™ Dose**	**-5**	**0**	**5**	**10**	**15**	**20**	**25**	**30**	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**
2.0-<6.0 years (N=X)	0.5 mg	xx.x (xx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
6.0-<12.0 years (N=X)	0.5 mg	xx.x (xx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
12.0-<18.0 years (N=X)	1.0 mg	xx.x (xx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
12.0-<18.0 years (N=X)	0.5 mg	xx.x (xx.x)	xx.x (xx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)

SD= standard deviation.

Safety Data

Table 12: Number and percentage of subjects experiencing adverse events by MedDRA® system organ class and preferred term, and treatment dose

Non-treatment emergent adverse events (non-TEAE)

MedDRA® System Organ Class (SOC)	MedDRA® Preferred Term (PT)	G-Pen™ Dose			
		0.5 mg (N=X)		1.0 mg (N=X)	
		n	%	n	%
Any SOC	Any PT	xx	x.x	x	x.x
[SOC 1]	Any PT	xx	x.x	x	x.x
	[PT 1]	xx	x.x	x	x.x
	[PT 2]	xx	x.x	x	x.x
[SOC 2]	Any PT	xx	x.x	x	x.x
	[PT 1]	xx	x.x	x	x.x
	[PT 2]	xx	x.x	x	x.x

[1]Note: This table presents number and percentage of subjects. A subject is only counted once per PT. A subject may have multiple PTs.
[2]Any SAE occurred will be summarized in the footnote.

Table 12: Number and percentage of subjects experiencing adverse events by MedDRA® system organ class and preferred term, and treatment dose *(continued)*

Treatment emergent adverse events (TEAE)

MedDRA® System Organ Class (SOC)	MedDRA® Preferred Term (PT)	G-Pen™ Dose			
		0.5 mg (N=X)		1.0 mg (N=X)	
		n	%	n	%
Any SOC	Any PT	xx	x.x	x	x.x
[SOC 1]	Any PT	xx	x.x	x	x.x
	[PT 1]	xx	x.x	x	x.x
	[PT 2]	xx	x.x	x	x.x
[SOC 2]	Any PT	xx	x.x	x	x.x
	[PT 1]	xx	x.x	x	x.x
	[PT 2]	xx	x.x	x	x.x

[1]Note: This table presents number and percentage of subjects. A subject is only counted once per PT. A subject may have multiple PTs.
[2]Any SAE occurred will be summarized in the footnote.

Table 13: Severity of adverse events and their relatedness to study by MedDRA® system organ class and preferred term, and treatment dose

Non-treatment emergent adverse events (non-TEAE)

MedDRA® System Organ Class (SOC)	MedDRA® Preferred Term (PT)	G-Pen™ Dose																							
		0.5 mg (N=X)												1.0 mg (N=X)											
		Severity						Relatedness						Severity						Relatedness					
		Mild		Moderate		Severe		Study Drug		Study Device		Study Procedure		Mild		Moderate		Severe		Study Drug		Study Device		Study Procedure	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
[SOC 1]	Any PT	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 1]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 2]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
[SOC 2]	Any PT	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 1]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 2]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x

[1]Note: This table presents number and percentage of subjects. A subject is only counted once per PT and is summarized according to their highest severity and closest relationship. A subject may have multiple PTs.

[2]Any SAE occurred will be summarized in the footnote.

Table 14: Severity of adverse events and their relatedness to study by MedDRA® system organ class and preferred term, and treatment dose *(continued)*

Treatment emergent adverse events (TEAE)

MedDRA® System Organ Class (SOC)	MedDRA® Preferred Term (PT)	G-Pen™ Dose																							
		0.5 mg (N=X)												1.0 mg (N=X)											
		Severity						Relatedness						Severity						Relatedness					
		Mild		Moderate		Severe		Study Drug		Study Device		Study Procedure		Mild		Moderate		Severe		Study Drug		Study Device		Study Procedure	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
[SOC 1]	Any PT	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 1]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 2]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
[SOC 2]	Any PT	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 1]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x
	[PT 2]	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x	xx	xx.x

[1]Note: This table presents number and percentage of subjects. A subject is only counted once per PT and is summarized according to their highest severity and closest relationship. A subject may have multiple PTs.

[2]Any SAE occurred will be summarized in the footnote.

Listing 2: Abnormality in the physical examination evaluation at screening			
Subject ID	**Age Group**	**Physical Exam**	**Abnormal Finding**

Table 15: Vital signs before and after administration of G-Pen™ by age group and by treatment dose for subjects aged 12.0-<18.0

Age Group: 2.0-<6.0 years (N=X)

	Time					Change from Baseline[a]	
	Baseline	**30 minutes**	**60 minutes**	**120 minutes**	**180 minutes**	**Max Increase**	**Max Decrease**
Heart Rate, beats/min							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Systolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Diastolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]

SD= standard deviation; BP= blood pressure.
[a] Positive value indicates an increase from baseline and negative value indicates a decrease.

Table 14: Vital signs before and after administration of G-Pen™ by age group and by treatment dose for subjects aged 12.0-<18.0

Age Group: 6.0-<12.0 years (N=X)

	Time					Change from Baseline[a]	
	Baseline	**30 minutes**	**60 minutes**	**120 minutes**	**180 minutes**	**Max Increase**	**Max Decrease**
Heart Rate, beats/min							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Systolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Diastolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]

SD= standard deviation; BP= blood pressure.
[a] Positive value indicates an increase from baseline and negative value indicates a decrease.

Table 14: Vital signs before and after administration of G-Pen™ by age group and by treatment dose for subjects aged 12.0-<18.0 *(continued)*

Age Group: 12.0-<18.0 years with a dose of 1.0 mg (N=X)

	Time					Change from Baseline[a]	
	Baseline	**30 minutes**	**60 minutes**	**120 minutes**	**180 minutes**	**Max Increase**	**Max Decrease**
Heart Rate, beats/min							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Systolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Diastolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]

SD= standard deviation; BP= blood pressure.
[a] Positive value indicates an increase from baseline and negative value indicates a decrease.

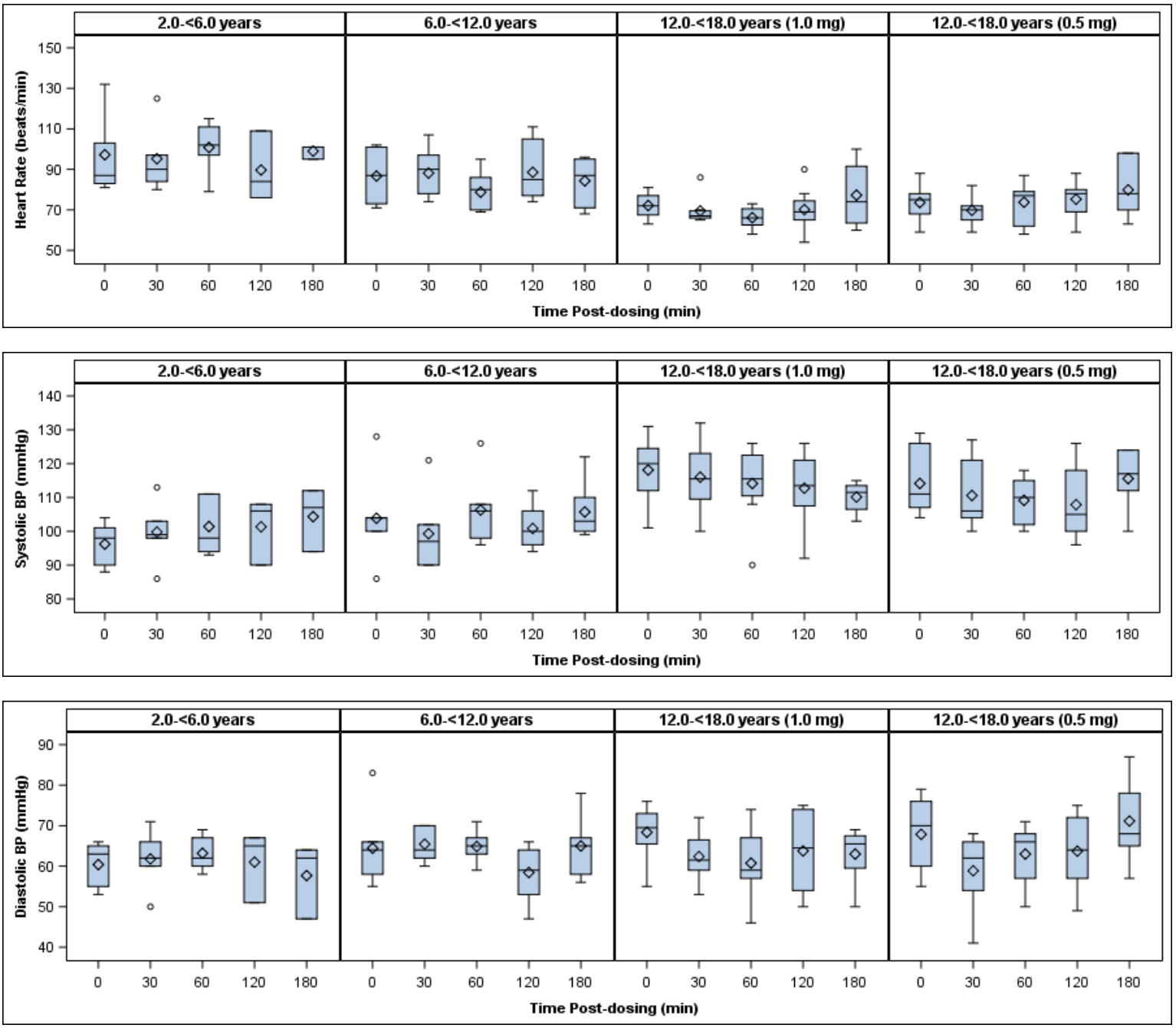
Table 14: Vital signs before and after administration of G-Pen™ by age group and by treatment dose for subjects aged 12.0-<18.0 *(continued)*

Age Group: 12.0-<18.0 years with a dose of 0.5 mg (N=X)

	Time					Change from Baseline[a]	
	Baseline	**30 minutes**	**60 minutes**	**120 minutes**	**180 minutes**	**Max Increase**	**Max Decrease**
Heart Rate, beats/min							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Systolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]
Diastolic BP, mmHg							
N	x	x	x	x	x	x	x
Mean (SD)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)	xxx.x (xxx.x)
Median	xxx	xxx	xxx	xxx	xxx	xxx	xxx
[Min-Max]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]	[xxx-xxx]

SD= standard deviation; BP= blood pressure.
[a] Positive value indicates an increase from baseline and negative value indicates a decrease.

Figure 4: Vital signs before and after administration of G-Pen™ by age group and by treatment dose for subjects aged 12.0-<18.0



BP= blood pressure.

Table 16: Incidence of any injection site discomfort by age group and by treatment dose for subjects aged 12.0-<18.0							
Age Group	G-Pen™ Dose	Incidence of Any Injection Site Discomfort[a]					
		10 minutes		30 minutes		180 minutes	
		n	%	n	%	n	%
2.0-<6.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x
6.0-<12.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x
12.0-<18.0 years (N=X)	1.0 mg	x	x.x	x	x.x	x	x.x
12.0-<18.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x

[a] Any injection site discomfort is defined as Faces Pain Scale – Revised (FPS-R) score >0.

Table 17: Incidence of erythema after administration of G-Pen™ by age group and by treatment dose for subjects aged 12.0-<18.0							
Age Group	G-Pen™ Dose	Incidence of Erythema[a]					
		10 minutes		30 minutes		180 minutes	
		n	%	n	%	n	%
2.0-<6.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x
6.0-<12.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x
12.0-<18.0 years (N=X)	1.0 mg	x	x.x	x	x.x	x	x.x
12.0-<18.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x

[a] Erythema formation is defined as Modified Draize Scale score for erythema >0.

Table 18: Incidence of edema after administration of G-Pen™ by age group and by treatment dose for subjects aged 12.0-<18.0							
Age Group	G-Pen™ Dose	Incidence of Edema[a]					
		10 minutes		30 minutes		180 minutes	
		n	%	n	%	n	%
2.0-<6.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x
6.0-<12.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x
12.0-<18.0 years (N=X)	1.0 mg	x	x.x	x	x.x	x	x.x
12.0-<18.0 years (N=X)	0.5 mg	x	x.x	x	x.x	x	x.x

[a] Edema formation is defined as Modified Draize Scale score for edema >0.

Figure 5: Local tolerability by age group and by treatment dose for subjects aged 12.0-<18.0

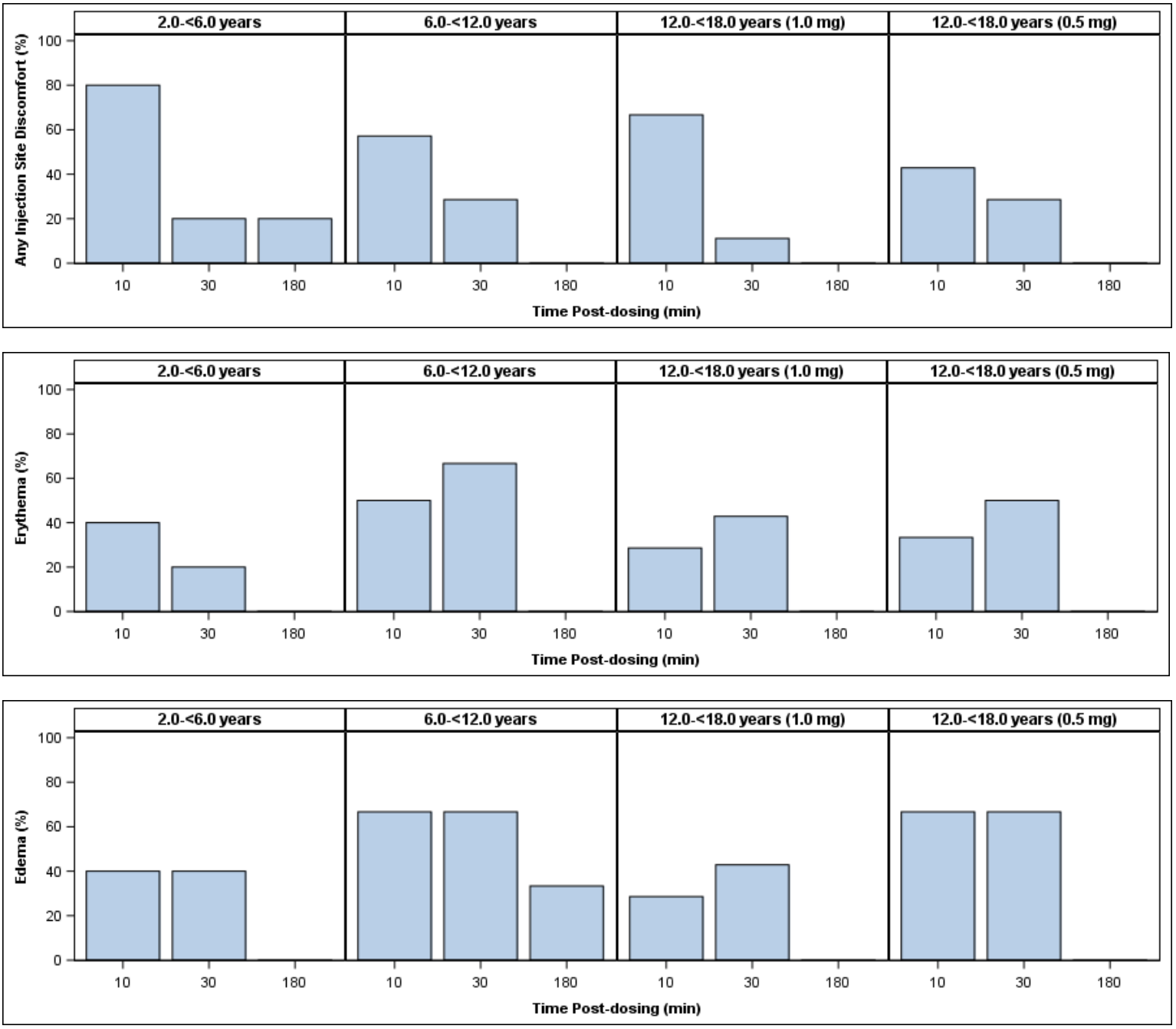


Table 19: Time of onset and duration of discomfort and discomfort description by age group and by treatment dose for subjects aged 12.0-<18.0				
	2.0-<6.0 years (N=X[a,b])	**6.0-<12.0 years (N=X[a])**	**12.0-<18.0 years with 1.0 mg (N=X[a])**	**12.0-<18.0 years with 0.5 mg (N=X[a])**
Time of Onset, minute				
N	x	x	x	x
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median	xx	xx	xx	xx
[Min-Max]	[xx-xx]	[xx-xx]	[xx-xx]	[xx-xx]
Duration – n (%)				
< 1 minute	x (x.x)	x (x.x)	x (x.x)	x (x.x)
1-2 minutes	x (x.x)	x (x.x)	x (x.x)	x (x.x)
3-5 minutes	x (x.x)	x (x.x)	x (x.x)	x (x.x)
6-9 minutes	x (x.x)	x (x.x)	x (x.x)	x (x.x)
10-15 minutes	x (x.x)	x (x.x)	x (x.x)	x (x.x)
16-30 minutes	x (x.x)	x (x.x)	x (x.x)	x (x.x)
30-120 minutes	x (x.x)	x (x.x)	x (x.x)	x (x.x)
121-180 minutes	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Discomfort Description [c]				
Pain (e.g. throbbing, soreness, muscle ache) – n (%)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Itching – n (%)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Tingling, twitching, or numbness – n (%)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Irritation (e.g. burning, stinging) – n (%)	x (x.x)	x (x.x)	x (x.x)	x (x.x)

[a] Only those who reported having at least one discomfort post-injection are included in the table.
[b] X subjects are not applicable because they are too young for comprehension.
[c] A subject may report more than one discomfort.

Listing 3: Pregnancies and outcomes										
Subject ID	**Age group**	**G-Pen™ dose**	**Number of Embryos, Fetuses, and/or Infants**	**Outcome**	**Congenital Anomaly?**	**Gestational Age (weeks and days)**	**Gender**	**Weight (lbs)**	**Length (in)**	**Head Circumference (cm)**

Appendix II: PHARMACOKINETIC ANALYSIS CONDECUTED BY Integrated Medical Development, New jersey USA

1 PK Analysis Population

There is only one population for PK analysis. It is defined as all subjects randomized.

2 PK Endpoints

The following PK endpoints will be analyzed:

- C_{Max}, maximum concentration of G-Pen Glucagon
- T_{Max}, the time when maximum concentration of G-Pen Glucagon reached
- $AUC_{0\text{-}120min}$, area under the curve of G-Pen Glucagon from 0 to 120 minutes

3 Analysis variables

3.1 Handling of the missing values

The PK samples are drawn blood at -5, 0, 10, 20, 30, 45, 60, 90, 120, and 180 minutes post dose, with ±2 minutes per collection for the samples from -5 and 0 minutes, and ±5 minutes for later samples. The following procedures will be applied to handle any missing values of the PK:

- If PK at time 0 minute (T_0) is missing, then PK at -5 minute will be substituted. If both -5 minute and 0 minute PK are missing, then the PK at later minutes will be used to impute the PK at 0 minute. In such case, linear imputation will be used.
- If PK at 120 minute is missing, then cubic imputation will be used to impute the PK at 120 minute. Exception: if PK at 120 minute is missing and the last available PK is the Cmax, i.e, PK never comes down, and then no imputation will be done.
- All other missing PK values will not be imputed

3.2 Calculation of the PK variables

The following PK analysis variables will be calculated as the data handle procedures described above (section 3.1). If 2 draws of the PK at time 0 were done, the average of two will be used for time 0.

3.2.1 C_{Max}

C_{Max} is defined as the maximum concentration of G-Pen Glucagon after time 0 minute.

3.2.2 T_{Max}

T_{Max} is defined as time (min) when maximum concentration of G-Pen Glucagon reached after T_0. If there are multiple C_{Max} following the injection, T_{Max} will be the first time when C_{Max} is reached. Actual time instead of protocol time will be used.

3.2.3 $AUC_{0\text{-}120min}$

$AUC_{0\text{-}120min}$ is calculated using Trapezoidal rule from T_0 to T_{120}. Actual time instead of protocol time will be used.

4 Statistical Analysis

The three PK variables defined in section 3.2 will be analyzed descriptive for the age groups and doses (2.0-<6.0yr 0.5mg, 6.0-<12.0yr 0.5mg, 12.0-<18.0yr 1mg, and 12.0-<18.0yr 0.5mg). Mean, standard deviation, median, minimum and maximum will be presented.

Individual figures of each subject each dose will be presented. Mean G-Pen Glucagon vs protocol time point will be presented for each age group and doses. Protocol time point will be used to allow aggregation.

5 Planned Output Table of Content

Tables	14.2.1.1	Glucagon : Cmax by age and dose
	14.2.1.2	Glucagon : Tmax by age and dose
	14.2.1.3	Glucagon : AUC0-120 by age and dose
Listing	16.2.5.1	PK profile for each subject
	16.2.5.2	PK Cmax, Tmax, AUC for each subject
Figure	14.4.1.1.subjid	Individual Glucagon profile of each subject
	14.4.1.2	average Glucagon vs time for each age group and dose

6 Mock-ups Tables/Listings/Figures

Table 14.2.1.1 Glucagon: Cmax by age and dose

Glucagon: Cmax				
CATEGORY	**2-6yr 0.5mg**	**6-12yr 0.5mg**	**12-18yr 1mg**	**12-18yr 0.5mg**
N	6	6	6	6
Mean(SD)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)
Min, Median, Max	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)

Table 14.2.1.2 Glucagon: Tmax by age and dose

Glucagon: Tmax				
CATEGORY	**2-6yr 0.5mg**	**6-12yr 0.5mg**	**12-18yr 1mg**	**12-18yr 0.5mg**
N	6	6	6	6
Mean(SD)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)
Min, Median, Max	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)

Table 14.2.1.3 Glucagon: AUC0-120 by age and dose

Glucagon: Auc0-120				
CATEGORY	**2-6yr 0.5mg**	**6-12yr 0.5mg**	**12-18yr 1mg**	**12-18yr 0.5mg**
N	6	6	6	6
Mean(SD)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)
Min, Median, Max	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)	x.x(x.xx)

Listing 16.2.5.1 Glucagon of each subject

PATIENT ID	Actual Date/Time	Protocol Time	Glucagon
xxxx	Xx/xx/xxxx xx:xx	-5	xx
xxxx	Xx/xx/xxxx xx:xx	0	xx
xxxx	Xx/xx/xxxx xx:xx	10	xx
xxxx	Xx/xx/xxxx xx:xx	20	xx

Listing 16.2.5.2 Glucagon Cmax, TMax, AUC of each subject

PATIENT ID	CMax	TMax	AUC01-20
xxxx	xx	xx	xx
xxxx	xx	xx	xx
xxxx	xx	xx	xx
xxxx	xx	xx	xx

Figure 14.4.1.1.xxxx Glucagon at each time points

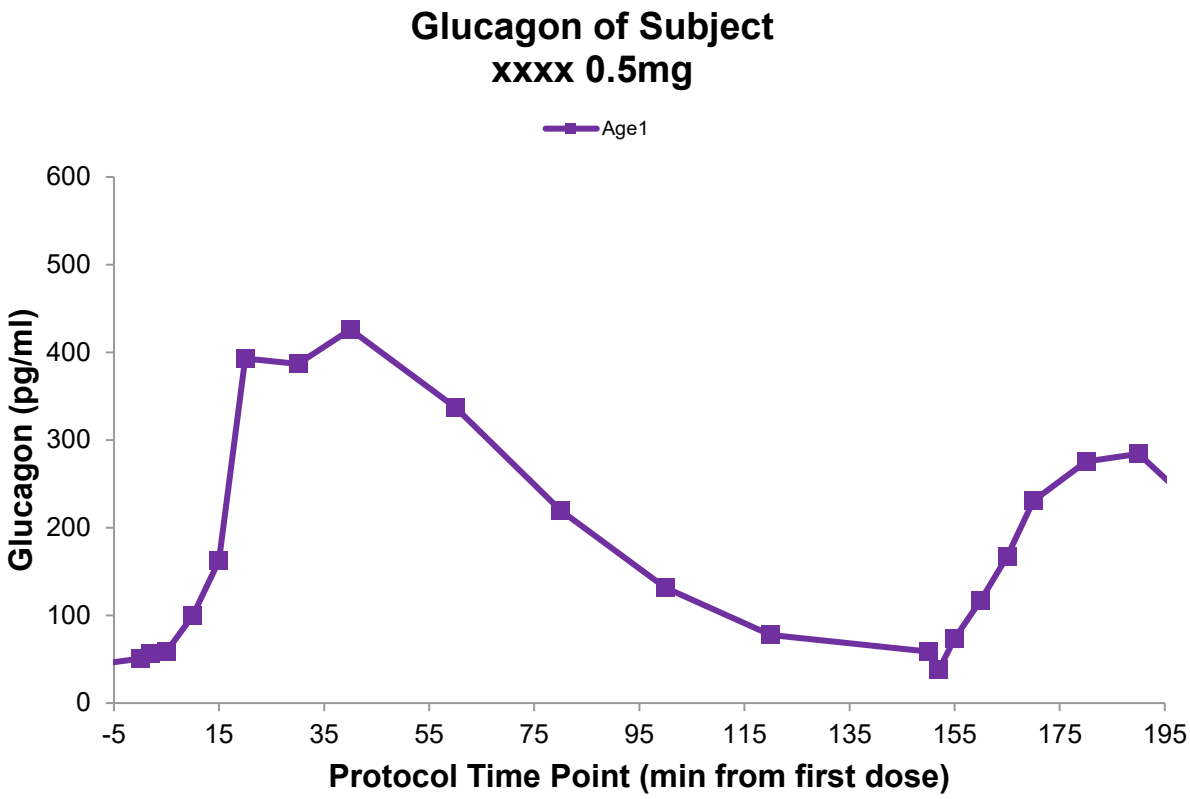


Figure 14.4.1.2 Mean Glucagon at each time points for age/dose group