Office of Clinical Pharmacology Review

NDA Number	214231
Link to EDR	\\cdsesub1\evsprod\NDA214231
Submission Dates	March 27, 2020; July 20, 2020; July 29, 2020; November 6, 2020
Submission Type	Standard
Brand Name	ZEGALOGUE
Generic Name	Dasiglucagon
Dosage Form and Strength	Solution; 0.6 mg/0.6 mL
Route of Administration	Subcutaneous
Proposed Indication	Treatment of severe hypoglycemia in patients with diabetes aged 6 years and above
Applicant	Zealand Pharma A/S
Associated IND	127866
OCP Review Team	S.W. Johnny Lau, Justin Earp, and Manoj Khurana
OCP Final Signatory	Shirley K. Seo; Director, Division of Cardiometabolic and Endocrine Pharmacology

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1. EXECUTIVE SUMMARY

The applicant (Zealand Pharma) submitted the NDA 214231 for dasiglucagon as an antihypoglycemic agent to treat severe hypoglycemia in patients with type 1 diabetes mellitus (T1DM) aged 6 years and above. Dasiglucagon, a glucagon analog, consists of 29 amino acids but has 7 substituted amino acids that are different from glucagon to improve physical and chemical stability. The applicant developed the dasiglucagon product to be stored either under refrigeration or at room temperature for convenience. . The to-be-marketed dasiglucagon is a ready-to-use aqueous formulation in either a pre-filled syringe or an auto-injector. The dasiglucagon development program consists of pharmacokinetics (PK), tolerability, dose-finding, and pivotal clinical trials in adult and pediatric patients.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology data submitted to support NDA 214231 and found the data acceptable. The application is approvable from a clinical pharmacology perspective for patients with T1DM aged 6 years and above.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Three pivotal trials 16137, 17145, and 17086 provide the pivotal evidence of dasiglucagon effectiveness and safety for patients aged 6 years and above. Patients with T1DM treated with dasiglucagon showed that the median time to increase in blood glucose of 20 mg/dL is about 10 minutes and those treated with placebo is about 40 minutes. The Phase 2 dose finding PK/pharmacodynamic (PD) study provided data for the exposure-response relationship for the primary PD effect of dasiglucagon (as captured via plasma glucose increase from baseline), which supported the single subcutaneous (SC) dose of 0.6 mg.
General dosing instructions	Patients with severe hypoglycemia should subcutaneously inject 0.6 mg dasiglucagon into the abdomen, buttocks, thigh, or upper arm.
Dosing in patient subgroups (intrinsic and extrinsic factors)	None of the patient subgroups such as age (≥ 6 years), body weight (60 – 100 kg), renal impairment, injection site, organ impairments, and concomitant medications have specific dosing recommendations.
Bridge between the to-be-marketed and clinical trial formulations	All phase 3 trials evaluated the to-be-marketed formulation of dasiglucagon.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Dasiglucagon is a glucagon receptor agonist, which increases blood glucose concentration via activating the hepatic glucagon receptors to stimulate glycogen breakdown and release glucose from the liver. Hepatic stores of glycogen are necessary for dasiglucagon to produce an antihypoglycemic effect.

The C_{max} is about 1510 pmol/L (5107 pg/mL)[1] and t_{max} is about 35 minutes upon subcutaneous injection of 0.6 mg dasiglucagon to patients with T1DM. The dasiglucagon apparent volume of distribution and half-life are 47 L and 30 minutes, respectively, upon subcutaneous administration. Dasiglucagon is cleared via proteolytic degradation pathways, similar to glucagon, in the blood, liver, and kidney. Dasiglucagon is excreted via glomerular filtration in the kidneys. After filtration, dasiglucagon is degraded by the proteases in the proximal tubules and the peptide fragments are reabsorbed.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

In patients aged 6 years and above, the recommended dose is 0.6 mg dasiglucagon administered via subcutaneous injection into the abdomen, buttock, thigh, or upper arm.

2.2.2 Therapeutic individualization

No dose adjustment is necessary for age (≥ 6 years), gender, body weight (60 – 100 kg), race, organ impairment, injection site, or drug interaction.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The following is the preliminary labeling recommendations for different sections related to clinical pharmacology:

Section 7 DRUG INTERACTIONS

Deleted the text but added the following table:

[1] To convert the concentration unit of pmol/L to pg/mL for dasiglucagon, multiply the value in pmol/L with 3.382 to convert the value to pg/mL.

Table 3: Clinically Significant Drug Interactions with TRADENAME
Recent

Beta-Blockers	
Clinical Impact:	Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given TRADENAME.
Indomethacin	
Clinical Impact:	In patients taking indomethacin, TRADENAME may lose its ability to raise blood glucose or may even produce hypoglycemia.
Warfarin	
Clinical Impact:	TRADENAME may increase the anticoagulant effect of warfarin.

The table format rather than the proposed text is recommended to improve readability. No interventions are recommended for the concomitant use of beta-blockers, indomethacin, and warfarin because the dasiglucagon dose is for single use only and under conditions of severe hypoglycemia, which is episodic and uncommon in occurrence. The drug interactions listed in Table 3 are based on the generally known information for glucagon and is consistent with other glucagon product labels.

Section 12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose resulting in 5 times the concentration of the 0.6 mg dasiglucagon subcutaneous dose, ZEGALOGUE does not prolong the QT interval to any clinically relevant extent.

The QT-IRT reviewer recommended the above language to be consistent with the Clinical Pharmacology Labeling guidance.

Section 12.3 Pharmacokinetics

Recommended to express the mean peak dasiglucagon concentration as both pg/mL and pmol/L because prescribers may not have access to information on dasiglucagon's molecular weight and the product label does not mention the information. Also, the unit of plasma dasiglucagon concentration in pg/mL helps prescribers better relate to the dasiglucagon dose in mg.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product Development and Regulatory Background

The applicant interacted directly with the FDA through an end of phase 2 meeting (June 2017) and a pre-NDA meeting (November 2019). Besides these major regulatory interactions with the FDA, the sponsor has also been in continuous dialog with the FDA on the development program, both for dasiglucagon and the device component.

The ability to store dasiglucagon both refrigerated and at room temperature for prolonged periods is important to provide patients and caregivers with a portable and convenient treatment option, allowing flexibility in their everyday life while ensuring immediate access to a ready-to-use treatment for episodes of severe hypoglycemia. Thus, the applicant has had interactions with the FDA on the regulatory approach to pursue the dual storage conditions.

The applicant evaluated the therapeutic use of dasiglucagon for the treatment of severe hypoglycemia in a clinical development program consisting of 9 clinical trials (Figure 1).

Phase 1/Clinical pharmacology trials	Phase 2 trials	Phase 3 trials
Healthy volunteers 14013, Part 1 – First in man trial 15007 – Multiple ascending dose trial **17144 – IV/QTc trial** *Patients with T1DM* 14013, Part 2 – First in man trial	*Patients with T1DM* **15126 – PK/PD dose-finding trial**	*Patients with T1DM* **16137 – 1st pivotal trial** **17145 – 2nd pivotal trial** **16136 – Immunogenicity trial** **17084 – Bridging trial** **17086 – Pediatric pivotal trial**

IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; QTc, corrected QT interval;
All are completed trials. Trials providing PK and PD data in this overview are in bold red font.
Source: Modified from Module 2.7.2 Figure 1-1

Figure 1 Overview of Dasiglucagon clinical trials

Due to differences in the formulation of dasiglucagon during the clinical development program, some of the earlier trials (such as Trials 14013 and 15007) are not included in the evaluation of the PK and PD properties of dasiglucagon. In the initial formulation, the excipients (b) (4) (b) (4) were different from those of the drug product intended for the market.

The following trials provide the clinical pharmacology information for the to-be-marketed formulation:

Phase 2 Dose-finding trial 15126

The Phase 2 dose-finding trial 15126 characterized the PK and PD properties of a single SC doses of dasiglucagon (0.1, 0.3, 0.6, and 1.0 mg) in adult patients with type 1 diabetes mellitus (T1DM) in order to determine the optimal dasiglucagon dose for the Phase 3 clinical development program. Trial 15126 also assessed the dasiglucagon dose proportionality via SC administration.

Pivotal trials 16137 and 17145

The PK and PD characteristics of a single SC dose of 0.6 mg dasiglucagon were evaluated as secondary endpoints in these two pivotal Phase 3 trials, 16137 and 17145, in adult patients with T1DM.

Pediatric pivotal trial 17086

In the Phase 3 trial 17086, the PK and PD effects of a single SC dose of 0.6 mg dasiglucagon were evaluated in children (aged 6 to 11 years) and adolescents (aged 12 to 17 years) with T1DM.

All Phase 3 trials evaluated the to-be-marketed formulation of dasiglucagon. The to-be-marketed dasiglucagon is a ready-to-use aqueous formulation in either a pre-filled syringe or an auto-injector. The formulation used in Phase 3 trials was identical to that used in Phase 2 trial, except for a (b) (4) (b) (4), the formulation used in Phase 1 trials was changed prior to the Phase 2 trial.

Bridging trial 17084

This Phase 3 bridging trial 17084 compared the PK and PD effects of a single 0.6 mg dasiglucagon dose from a batch stored under the intended dual storage (refrigerated and at room temperature) relative to a batch stored under refrigerated condition of the to-be-marketed formulation. The exposure of dasiglucagon was about 15% lower for the dual storage condition than that stored under refrigerated condition. However, the glucose response is comparable among the 2 storage conditions.

The applicant assessed the in vitro metabolism of dasiglucagon in human hepatocytes (Studies 15-075 and 15-076), plasma or serum samples (Study 14-001).A total of 498 healthy subjects and patients with T1DM received dasiglucagon in 9 dasiglucagon clinical trials. Four patients had treatment-induced antidrug-antibody (ADA) response (< 1% incidence). The immunogenicity Phase 3 trial 16136 did not show subject with ADA and thus it did not allow follow up of PK and PD sampling to determine the impact of ADAs on efficacy. Of the trials that showed ADA-positive samples, the impact of ADAs on PK and PD is undeterminable due to the lack of dasiglucagon dosing post-development of ADAs. The immunogenicity of dasiglucagon appears low. For details, see Dr. Kristen Pluchino's clinical review in DARRTS.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Table 1 below shows the key pharmacological and pharmacokinetic properties of dasiglucagon.

Dasiglucagon	Characteristics
Dasiglucagon	Consists of 29 amino acids, like glucagon, but has 7 substituted amino acids to improve physical and chemical stability in aqueous environment
Mechanism of action	Dasiglucagon increases blood glucose concentration via activating the hepatic glucagon receptors to stimulate glycogen breakdown and release glucose from the liver
Absolute SC bioavailability[1], %	51
C_{max}, pmol/L (geometric mean) [2]	1266 – 1690 [adult]; 1160 [pediatric]
t_{max}, min (median) [3]	30 – 45 [adult]; 21 [pediatric]
Vz/f, L (geometric mean) [4]	46.6 – 56.6 [adult]; 86.4 [pediatric]
Metabolism*	• cleared mainly in the blood, liver, and kidneys via normal proteolytic degradation pathways • metabolites are not expected to be active on the glucagon receptor with high activity
Excretion	Via filtration thru the kidneys. Following glomerular filtration, peptides are degraded by the proteases present in the proximal tubule and the peptide fragments are reabsorbed
Terminal $t_{1/2}$, min (geometric mean)[5]	28.5 – 34.6 [adult]; 37.4 [pediatric]
SC dose proportionality[6]	$AUC_{0\text{-}360min}$ is proportional to dose in the dose range of 0.1 – 1 mg
Drug interaction[7]	Dasiglucagon does not significantly inhibit CYPs 1A2, 2C9, 2C19, 2D6, and 3A4 with all IC_{50}s > 25 μM.

SC = subcutaneous; C_{max} = maximum plasma dasiglucagon concentration; t_{max} = time C_{max} occurred; V_z/f = apparent volume of distribution; CYP = cytochrome P450

[1]Trial 17144

[2]Trials 15126, 16137, 17145, 16136, and 17084 [adult]; Trial 17086 [pediatric]

[3]Trials 15126, 16137, 17145, 16136, and 17084 [adult]; Trial 17086 [pediatric]

[4]Trials 15126 and 17084

[5]Trials 15126 and 17084[adult]; Trial 17086 [pediatric]

[6]Trial 15126

[7]Study 13-149

* The applicant reported 16 proteolytic metabolites of dasiglucagon. With in vivo rats and dogs studies, the data indicate that dasiglucagon is mainly cleared through the blood, liver, and kidney via proteolytic degradation pathways like that of glucagon.

Source: Reviewer's compilation

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Clinical pharmacology information from Phase 2 dose finding trial (15126), Phase 3 trials in adults (16137 and 17145), and the pediatric Phase 3 trial (17086) provide supportive evidence of effectiveness for dasiglucagon to treat severe hypoglycemia in patients with T1DM aged 6 years and above. These trials consistently demonstrated a significant improvement in PD response parameters ($AUE_{0\text{-}30min}$ and $T_{PG\ increase\ >20mg/dL}$) over placebo for rise in plasma glucose from baseline (see Table 2 below and also Appendix Section 4.2 for details).

Table 2. Summary of dasiglucagon PK and PD parameters as observed from different trials

Trial	$AUC_{0\text{-}30\ min}$, pM*h	$AUC_{0\text{-}inf}$, pM*h	C_{max}, pmol/L	$t_{1/2}$, min	$AUE_{0\text{-}30\ min}$, mg*h/dL	$T_{PG\ increase\geq 20mg/dL}$, min
15126	413 (36.8)	2610 (13.8)	1510 (28.2)	28.5 (25.2)	21.1 (6.1)	9 (6 – 16)§
16137	—	1770 (31.2)#	1280 (37.7)	—	21.0 (5.26)	10 (10 – 10)
17145	—	1780 (31.6) #	1350 (38.2)	—	19.9 (8.41)	9.3 (7.8 – 10.3)
17086	376 (78.1)	1850 (45.1)	1160 (61.2)	37.4 (37.4)	22.8 (6.13)	10 (8 – 12)

$AUC_{0\text{-}30\ min}$, $AUC_{0\text{-}inf}$, C_{max} , and $t_{1/2}$ are in geometric mean (CV%); $AUE_{0\text{-}30\ min}$, in mean (SD); $T_{PG\ increase\geq 20mg/dL}$ in median (95% CI); # = $AUC_{0\text{-}120\ min}$, pM*h; § = $T_{PG\ increase\geq 20mg/dL}$ in median (range)

Source: Reviewer's compilation

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing of 0.6 mg dasiglucagon administered via SC injection into the abdomen, buttock, thigh, or upper arm to patients 6 years of age and above is appropriate for the proposed indication from a clinical pharmacology perspective.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No dose adjustment is necessary for age, gender, body weight, race, organ impairments, injection site, or drug interaction. The applicant did not conduct dedicated studies for organ impairment (renal and hepatic) or for drug interactions. However, dasiglucagon is intended for single use to treat severe hypoglycemia. Population PK analysis and simulations showed that the dasiglucagon exposure of a patient with renal impairment relative to that of a typical male or female aged ≥ 24 years, weighing 78 kg with eGFR of 95 mL/min/1.73 m^2 is estimated to be 1.05, 1.16, and 1.25 for mild, moderate, and severe renal impairment, respectively (see Appendix 4.3 Population PK analysis). While body weight was observed to be the main covariate affecting dasiglucagon exposure, the PK, PD, and efficacy data from clinical trials support that the proposed single 0.6

mg SC dose provides adequate efficacy coverage for the broad body weight range in patients 6 years and above.

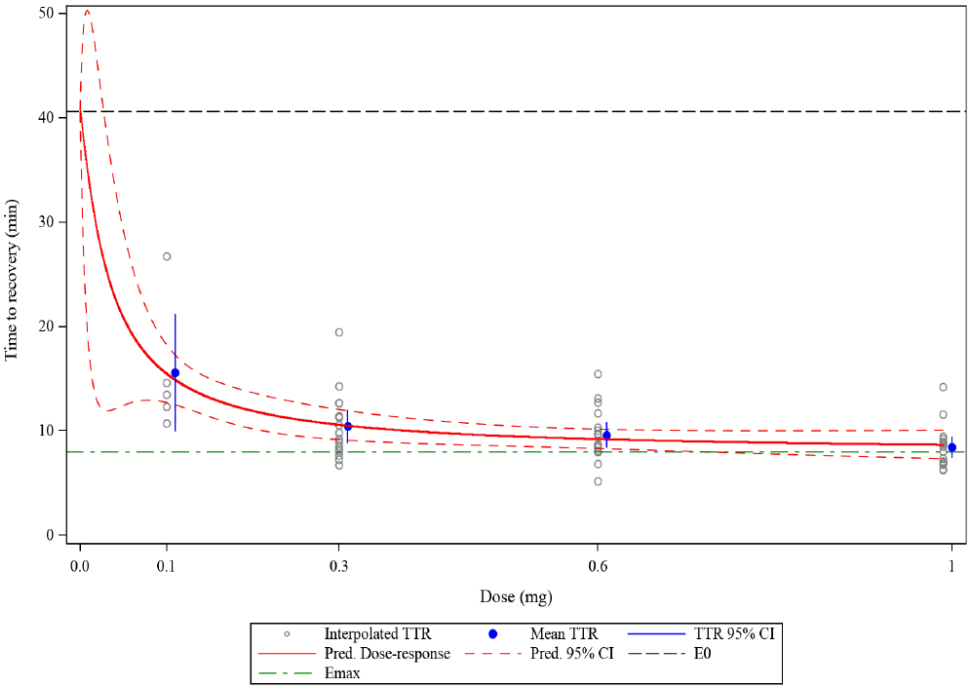
3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

In vitro Study 13-149 showed that dasiglucagon does not significantly inhibit CYPs 1A2, 2C9, 2C19, 2D6, and 3A4 isozymes in human liver microsomes with all IC_{50} values > 25 µM. The geometric mean C_{max} of 0.6 mg dasiglucagon SC injection is 1510 pmol/L (Trial 15126). Assuming a competitive inhibition, the K_i value for inhibiting CYPs equals $IC_{50}/2$ as 12.5 µM. The R value according to the In Vitro Drug Interaction guidance is 1.000121 and is < 1.02. As a result of these in vitro findings, the applicant did not conduct dedicated clinical drug-drug interaction studies.

3.3.5 Is the proposed product specification for the dasiglucagon content (b) (4) acceptable to account for the loss in stability due to dual storage under refrigeration and at room temperature?

Yes. The recommended dose is 0.6 mg dasiglucagon and the proposed product specification for the dual storage condition for 12 months is (b) (4)% of the original dasiglucagon content. Thus, (b) (4)% of the recommended dose is (b) (4) mg. The applicant developed a model of SC dasiglucagon dose and time to increase glucose 20 mg/dL from baseline in blood according to Trial 15126.

Figure 2. Model prediction of mean time to recovery as a function of dasiglucagon dose



TTR = time to recovery
Source: Submission on July 29, 2020

Table 3 below shows the predicted glucose recovery time and the difference in predicted glucose recovery time to the 0.6 mg dose.

Dasiglucagon Subcutaneous Dose, mg	Predicted Mean Recovery Time (95% Confidence Interval), minutes	Predicted Mean Difference in Recovery Time versus 0.6 mg, minutes	95% Confidence Interval (CI) of the Predicted Mean Difference in Recovery Time versus 0.6 mg, minutes*
0.6	9.21 (8.28, 10.14)	0	
0.46	9.63 (8.61, 10.65)	0.42	-0.93, 1.76
0.44	9.71 (8.65, 10.76)	0.50	-0.87, 1.87
0.42	9.80 (8.70, 10.90)	0.59	-0.82, 1.99
0.40	9.90 (8.75, 11.04)	0.68	-0.76, 2.12

* The confidence intervals are derived from the standard errors of the predicted means.
Source: Submission on July 29, 2020

The 95% CI for the difference in recovery time contains zero. Thus, the recovery times for the lower doses are not significantly different from that of 0.6 mg. The upper bound of the CI for the difference in recovery time is 2.12 minutes for the 0.4 mg dose. Considering the benefit of the to-be-marketed dasiglucagon product being ready-to-use without the need to reconstitute, this may justify the very small delay (~0.6 minutes) of anti-hypoglycemia effect.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The applicant used a bioanalytical method that consisted of offline solid phase extraction (SPE) followed by online SPE and a liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) with multiple reaction monitoring to measure dasiglucagon in human plasma samples. The applicant used a stable labeled internal standard in all validation studies and actual clinical trials. Table 4 shows the validation of the dasiglucagon bioanalytical method. To convert the concentration unit of pmol/L to pg/mL for dasiglucagon, multiply the value in pmol/L with 3.382 to convert the value to pg/mL.

Table 4. Summary of assay validations for dasiglucagon in human plasma samples

Method	LLOQ (nmol/L)	ULOQ (nmol/L)	Inter-assay CV (%)	Inter-assay bias (%)	Validation study
LC-MS/MS	0.010	1.0	2.9 – 12.4	-5.5 – 11.0	14-170
LC-MS/MS	0.010	1.0	2.76 – 4.7	-13.7 – 3.0	15-170
LC-MS/MS	0.020	1.0	3.5 – 16.9	-2.3 – -0.3	17-063

Source: Module 2.7.1's Table 1-2

LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; CV = coefficient of variation

Table 5 shows the performance of the bioanalytical assay to determine dasiglucagon in human plasma for key clinical trials.

Table 5. Performance of the dasiglucagon bioanalytical assay in human plasma for key clinical trials

	Trial 15126	**Trial 16137**	**Trial 17084**	**Trial 17086**	**Trial 17144**	**Trial 17145**
Standard curve performance	Cumulative bias: -2.2 – 2% Cumulative precision: ≤ 9.5% CV	Cumulative bias: -2.4 – 1.9% Cumulative precision: ≤ 4.7% CV	Cumulative bias: -2.3 – 3% Cumulative precision: ≤ 7.7% CV	Cumulative bias: -2.5 – 1% Cumulative precision: ≤ 8.9% CV	Cumulative bias: -1.1 – 0.8% Cumulative precision: ≤ 8.4% CV	Cumulative bias: -2.5 – 2% Cumulative precision: ≤ 7.3% CV
QC performance	Cumulative bias: -4.3 – 5.7% Cumulative precision: ≤ 6.6% CV	Cumulative bias: -6.0 – 4.3% Cumulative precision: ≤ 8.1 % CV	Cumulative bias: -7.7 – 2% Cumulative precision: ≤ 13.4% CV	Cumulative bias: 4 – 7% Cumulative precision: ≤ 11.5% CV	Cumulative bias: -0.3 – 1.3% Cumulative precision: ≤ 10.2% CV	Cumulative bias: 2 – 3% Cumulative precision: ≤ 8.9% CV
Incurred sample reanalysis	Performed on 10.9% trial samples; 100% of samples met pre-specified criteria	Performed on 10.3% trial samples; 80.3% of samples met pre-specified criteria	Performed on **8%** trial samples; 90.2% of samples met pre-specified criteria	Performed on 10% trial samples; 95% of samples met pre-specified criteria	Performed on 10.7% trial samples; 83.9% of samples met pre-specified criteria	Performed on 11.8% trial samples; 97.1% of samples met pre-specified criteria
Study sample stability	182 days at -80°C	188 days at -80°C	188 days at -80°C	227 days at -80°C	188 days at -80°C	188 days at -80°C

Source: Reviewer's compilation of the file "Summary-biopharm-app-4-2.pdf" for Module 2.7.1

The applicant reanalyzed 8% of the clinical samples for Trial 17084, whereas the Bioanalytical Method Validation Guidance recommends 10% to be reanalyzed. Trial 17084 is the bridging trial for the dual storage condition. Nevertheless, the passing rate of 90.2% for incurred sample reanalysis for Trial 17084 is consistent with the Bioanalytical Method Validation Guidance. Overall, the bioanalytical method validation of dasiglucagon is acceptable.

For the 3 pivotal clinical trials (16137, 17145, and 17086), the applicant used the US FDA-approved glucose analyzer Yellow Springs Instrument (YSI) 2300, Yellow Springs Instruments, Yellow Springs, OH to measure the glucose concentration in plasma samples at central laboratories.

The applicant used a radioimmunoassay and used the ^{125}I-labelled glucagon as a tracer for the quantitative determination of glucagon in plasma samples. The ^{125}I-labelled glucagon and the sample-derived glucagon competed for binding to a glucagon-specific antibody. The complex of the antibody and glucagon was precipitated through a secondary antibody. The measured radioactivity in the sample was inversely correlated with the concentration of glucagon. The lower limit of quantification (LLOQ) was determined to be 4.7 pmol/L.

The stability of glucagon samples stored at -30°C ± 10°C was assessed through testing aliquots of EDTA plasma containing aprotinin. Aprotinin increased the stability of rapidly degrading proteins such as glucagon, enabling them to be more accurately measured in plasma samples. The samples of EDTA plasma containing glucagon and aprotinin were stored for up to 24 months and then assessed at 5 time points. The data for EDTA-plasma samples with aprotinin stored at -30°C ± 10°C for up to 24 months demonstrated a high stability of glucagon. Thus, glucagon samples from the dasiglucagon clinical trials can be stored for up to 24 months at -30°C ± 10°C without loss of stability.

4.2 Clinical PK and/or PD Assessments

Table 5 shows the clinical trials that the applicant conducted to support NDA 214231. All Phases 2 and 3 clinical trials were conducted in patients with T1DM. All Phase 1 trials were conducted in healthy volunteers except Part B of Trial 14013 was conducted in patients with T1DM.

Table 5. Clinical trials that support NDA 214231

Type of study	Study ID and location	Location of trial in eCTD	Objectives of the study	Study design and type of control	Test products Dose regimen Administration route	Number of subjects randomized and dosed	Healthy subjects or diagnosis of patients	Duration of treatment
Studies within the indication of treatment of severe hypoglycemia								
Phase 1 First in man	Trial 14013	5.3.3.1	Evaluate safety, tolerability, PK and PD	Randomized, double-blind, active-controlled	Part 1 Dasiglucagon 0.01, 0.1, 0.3, 1 and 2 mg SC and 0.3, 1 and 2 mg IM using vial and syringe. GlucaGen 1 mg in all cohorts Part 2 Dasiglucagon 0.7 mg IM GlucaGen 1.0 mg IM	Part 1 64 Part 2 20	Part 1 Healthy subjects Part 2 Patients with T1DM	Single SC or IM dose
Phase 1b Multiple ascending doses	Trial 15007	5.3.3.1	Evaluate safety, tolerability, PK and PD	Randomized, double-blind, placebo-controlled	Dasiglucagon 0.1, 0.3 and 1.0 mg SC using vial and syringe Placebo SC	24	Healthy subjects	5 repeated doses
Phase 1 IV/QTc	Trial 17144	5.3.3.1	Evaluate safety, tolerability and bioavailability	Randomized, double-blind, placebo-controlled	Dasiglucagon 0.6 mg SC using a PFS Dasiglucagon 0.03, 0.1, 0.3, 0.6, and 1.5 mg IV Placebo IV	60	Healthy subjects	Single SC or IV dose
Phase 2 Dose-finding	Trial 15126	5.3.4.2	Dose-finding, characterization of PK/PD, and evaluation of safety	Randomized, double-blind, active-controlled Group 1 Parallel-group Groups 2-4 Crossover	Dasiglucagon 0.1, 0.3, 0.6 and 1.0 mg SC using a PFS GlucaGen 0.5 mg and 1.0 mg SC	58	Patients with T1DM	Single dose
Phase 3 1st pivotal	Trial 16137	5.3.5.1	Evaluate efficacy and safety	Randomized, double-blind, placebo-controlled, parallel group	Dasiglucagon 0.6 mg SC using a PFS Placebo SC GlucaGen 1.0 mg SC	168	Patients with T1DM	Single dose
Phase 3 2nd pivotal	Trial 17145	5.3.5.1	Evaluate efficacy and safety	Randomized, double-blind, placebo-controlled, parallel group	Dasiglucagon 0.6 mg SC using an auto-injector Placebo SC	44	Patients with T1DM	Single dose
Phase 3 Pediatric pivotal	Trial 17086	5.3.5.1	Evaluate efficacy and safety	Randomized, double-blind, placebo-controlled, parallel group	Dasiglucagon 0.6 mg SC using a PFS Placebo SC GlucaGen 1.0 mg SC[2]	41	Pediatric patients with T1DM[3]	Single dose
Phase 3 Immuno-genicity	Trial 16136	5.3.5.1	Evaluate immunogenicity	Randomized, double-blind, active-controlled, parallel group	Dasiglucagon 0.6 mg SC using a PFS GlucaGen 1.0 mg SC	111	Patients with T1DM	3 consecutive weekly doses
Phase 3 Bridging	Trial 17084	5.3.5.1	Evaluate efficacy and safety of two dasiglucagon batches[1]	Randomized, double-blind, crossover	Dasiglucagon[1] 0.6 mg SC using a PFS	90	Patients with T1DM	Single doses of two dasiglucagon batches

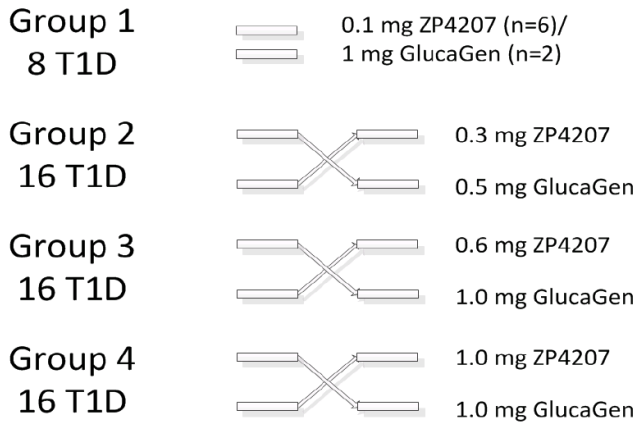
Studies providing supportive safety data								
Phase 2 Pump feasibility	Trial 16051	5.3.5.4	Evaluate safety and tolerability	Randomized, open-label, crossover	Dasiglucagon or Lilly Glucagon delivered via pump (dosed according to blood glucose control algorithm)	12	Patients with T1DM	Two 1-day treatment periods of up to 8 hours each
Phase 2 Low-dose range	Trial 16098	5.3.5.4	Evaluate PK, PD, safety and tolerability	Randomized, double-blind, active-controlled, crossover	Dasiglucagon 0.03, 0.08, 0.2 and 0.6 mg SC Lilly Glucagon 0.03, 0.08 and 0.2 mg SC	23	Patients with T1DM	Multiple fixed doses

Source: Modified table of Module 5.2

Trial 15126 in Adult Patients with T1DM (A randomized, double-blind trial of single doses of ZP4207 (dasiglucagon*) administered s.c. to hypoglycemic Type 1 diabetic patients to describe the pharmacokinetics and pharmacodynamics of ZP4207 as compared to marketed glucagon)

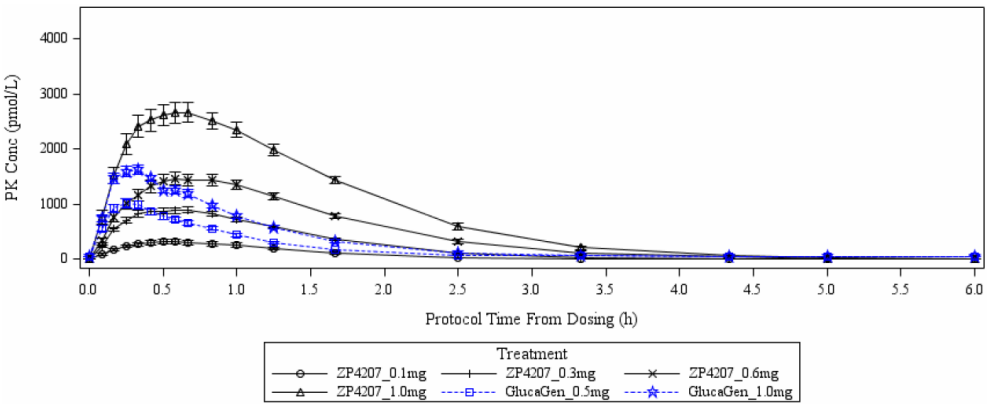
This was a Phase 2, single-center, randomized, double-blind within groups, single dose parallel trial in Group 1 and cross-over trial in Groups 2, 3, and 4 in patients with T1D. Figure 3 shows the schematic of Trial 15126's design. The sponsor collected serial blood samples predose and postdose to determine the dasiglucagon, glucagon, and glucose concentrations in plasma.

Figure 3. Schematic of Trial 15126



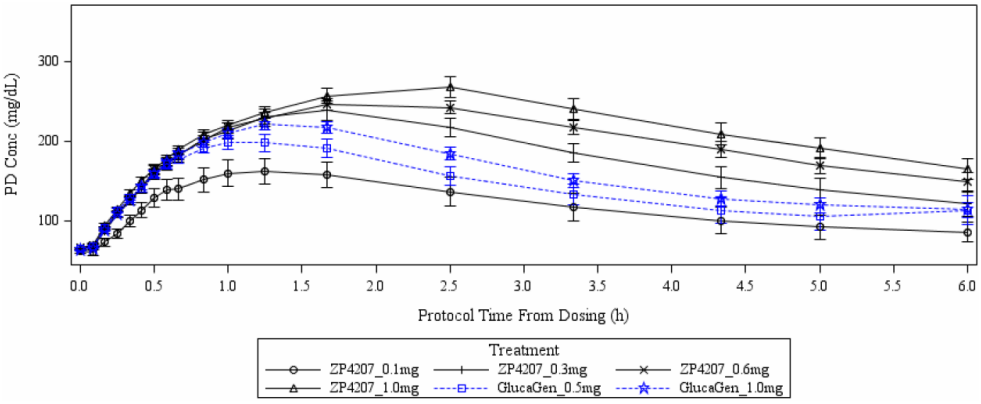
Source: Trial 15126's study report Figure 9.1

Figure 4. Mean (with standard error of mean) plasma concentration profiles following single SC doses of dasiglucagon (ZP4207) and GlucaGen



Source: Trial 15126's report Figure 14.2.2.3.2

Figure 5. Mean (with standard error of mean) plasma glucose concentration profiles following single SC doses of dasiglucagon (ZP4207) and GlucaGen



Source: Trial 15126's report Figure 14.2.4.3.2

Table 6. Dose proportionality of SC dasiglucagon

Parameter	Treatment / Comparison	Slope	95% CI
$AUC_{0\text{-}30min}$	Overall	0.885	(0.7403; 1.0292)
$AUC_{0\text{-}360min}$	Overall	1.029	(0.9667; 1.0904)
$AUC_{0\text{-}inf}$	Overall	1.030	(0.9683; 1.0916)
C_{max}	Overall	0.888	(0.7791; 0.9972)

Source: Trial 15126's report Table 11-5

The applicant used the Power model to assess dose proportionality of SC dasiglucagon. Table 6 shows the results of ANOVA analysis for the slope of log dasiglucagon PK parameter vs. log dasiglucagon dose plots. Dose-proportionality was indicative as the 95% CI of the slope included "1". Thus, the SC dasiglucagon PK is dose-proportional between 0.1 mg – 1 mg.

The PK profiles in Figure 4 show rather rapid increases in plasma dasiglucagon concentrations upon SC administrations. For example, the dasiglucagon C_{max} was 1570 pM (mean) and t_{max} was 35 minutes (median) for the 0.6 mg SC dose (see Table 7).

Table 7. Summary statistics of dasiglucagon PK parameters as arithmetic mean (standard deviation) but median (range) for t_{max}

Treatment Dose No. of patients	$AUC_{0\text{-}30min}$ [pmol*h/L]	$AUC_{0\text{-}360min}$ [pmol*h/L]	$AUC_{0\text{-}inf}$ [pmol*h/L]	C_{max} [pmol/L]	t_{max} [h]	$t_{½}$ [h]
ZP4207						
0.1mg N = 5	99.4 (32.0)	451 (123)	451 (123)	334 (113)	0.500 (0.500-0.583)	0.431 (0.088)
0.3 mg N = 16	302 (78.9)	1360 (166)	1360 (166)	976 (208)	0.625 (0.333-0.833)	0.429 (0.073)
0.6 mg N = 16	444 (163)	2630 (368)	2640 (365)	1570 (445)	0.583 (0.500-1.67)	0.490 (0.136)
1.0 mg N = 16	884 (307)	4800 (697)	4810 (696)	2800 (767)	0.625 (0.333-0.833)	0.538 (0.169)
Treatment Dose No. of patients	$AUC_{0\text{-}30min,BL}$ [pmol*h/L]	$AUC_{0\text{-}360min,BL}$ [pmol*h/L]	$AUC_{0\text{-}inf,BL,Truncated}$ [pmol*h/L]	$C_{max,BL}$ [pmol/L]	t_{max} [h]	$t_{½,BL,Truncated}$ [h]
GlucaGen						
0.5 mg N = 17	375 (104)	939 (177)	895 (169)	1100 (307)	0.250 (0.167-0.583)	0.370 (0.068)
1.0 mg N = 33	600 (180)	1660 (315)	1630 (311)	1720 (526)	0.333 (0.167-0.833)	0.418 (0.131)

Note: As the glucagon assay captures exogenous administered glucagon (GlucaGen) and endogenous glucagon, GlucaGen $AUC_{0\text{-}30min}$, $AUC_{0\text{-}360min}$ and C_{max} are shown calculated from baseline-adjusted data whereas $AUC_{0\text{-}inf}$ and $t_{1/2}$ are displayed as calculated from baseline-adjusted and truncated GlucaGen profiles with a cut-off at 2.5 hours.

Source: Trial 15126's synopsis

Table 8. Summary statistics of plasma glucose PD parameters as arithmetic mean (standard deviation) but median (range) for t_{max}, $T_{PG≥70mg/dL}$, and $T_{PG\ increase≥20mg/dL}$

Treatment Dose No. of patients	$AUE_{0\text{-}30min}$ [mg*h/dL]	AUE [mg*h/dL]	CE_{30min} [mg/dL]	CE [mg/dL]	t_{max} [h]	$T_{PG≥70mg/dL}$ [min]	$T_{PG\ increase≥20mg/dL}$ [min]
ZP4207							
0.1 mg N = 5	12.9 (5.21)	344 (149)	66.1 (23.8)	102 (33.7)	1.25 (0.833-1.67)	10.0 (2.00-17.0)	14.0 (11.0-27.0)
0.3 mg N = 16	20.9 (6.13)	666 (247)	93.4 (23.7)	174 (44.6)	1.67 (1.00-2.50)	6.00 (0.000-13.0)	10.0 (7.00-20.0)
0.6 mg N = 17	21.1 (6.10)	788 (165)	98.2 (25.0)	190 (32.2)	1.67 (1.67-4.33)	6.00 (0.000-9.00)	9.00 (6.00-16.0)
1.0 mg N = 16	24.1 (5.18)	895 (213)	100 (20.3)	209 (40.2)	2.50 (1.67-2.50)	6.00 (0.000-9.00)	9.00 (7.00-15.0)
GlucaGen							
0.5 mg N = 17	22.1 (5.48)	462 (273)	93.5 (21.4)	142 (42.6)	1.00 (0.667-5.00)	6.00 (0.000-9.00)	10.0 (6.00-13.0)
1.0 mg N = 33	21.9 (5.74)	566 (232)	96.5 (21.9)	166 (42.5)	1.25 (0.833-6.12)	7.00 (0.000-10.0)	10.0 (5.00-15.0)

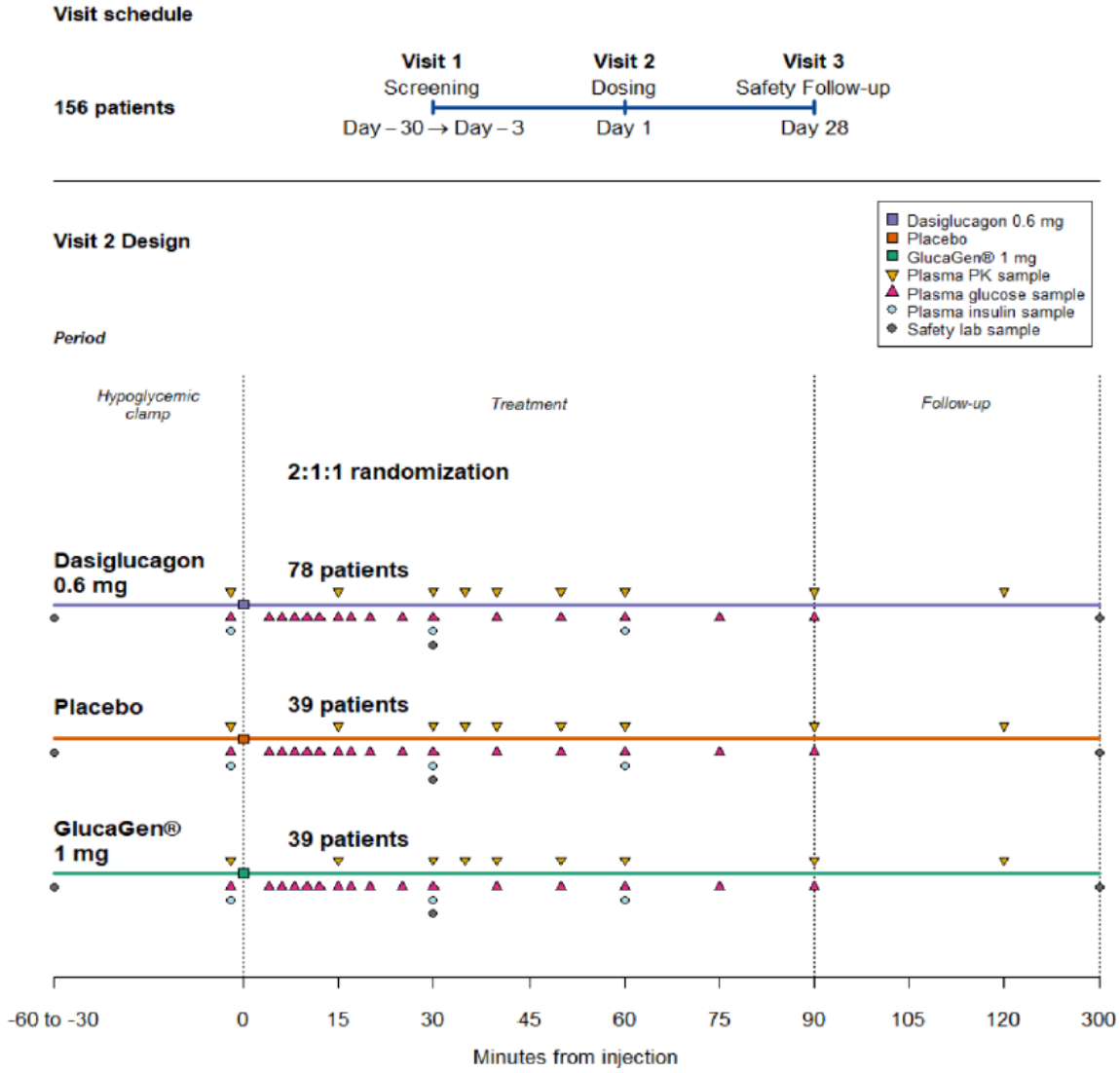
$AUE_{0\text{-}30min}$ and AUE = area under the plasma glucose (PG) excursions above baseline from 0-30 minutes and 0-last available measurement; CE_{30min} = PG excursion at 30 minutes; CE = maximum PG excursion; t_{max} = time to maximum PG excursion; $T_{PG≥70mg/dL}$ = time to achieve a PG of ≥70 mg/dL; $T_{PG\ increase≥20mg/dL}$ = time to achieve a PG increase of ≥20 mg/dL

Source: Trial 15126's synopsis

Figure 5 shows the PD data for the different doses of dasiglucagon and GlucaGen treatments. For example, the SC 0.6 mg dasiglucagon treatment and SC 1 mg GlucaGen treatment resulted in increases of plasma glucose and the area under the observed plasm glucose-time curve ($AUE_{0\text{-}30min}$) for the dasiglucagon and GlucaGen treatments were 21.1 and 20.4 mg*h/dL, respectively (see Table 8).

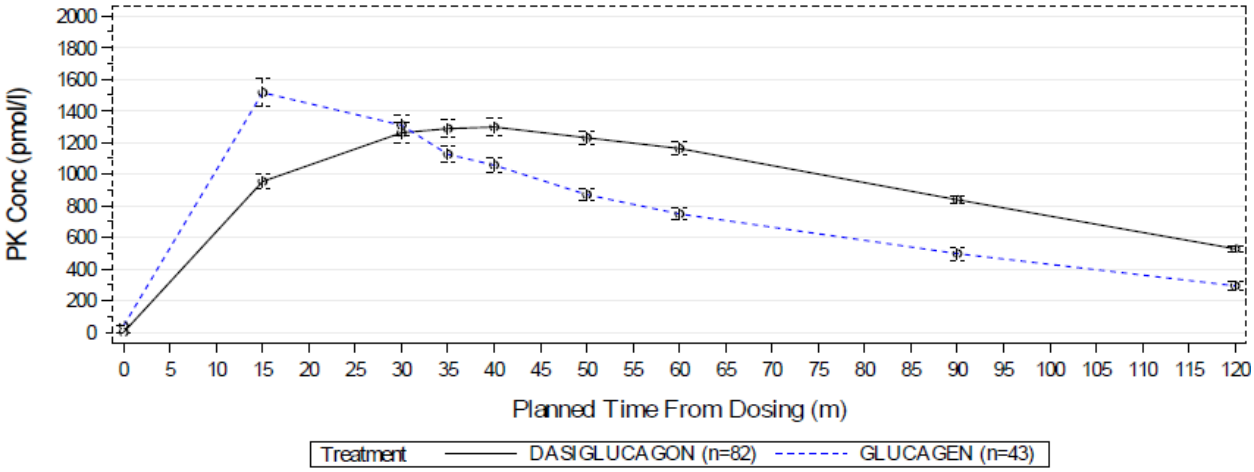
Trial 16137 in Adult Patients with T1DM (A Phase 3, randomized, double-blind, parallel trial to confirm the clinical efficacy and safety of dasiglucagon in the rescue treatment of hypoglycemia in patients with type 1 diabetes mellitus (T1DM) compared to placebo and with reference to GlucaGen®)

This was a Phase 3, randomized, double-blind, parallel trial to confirm the clinical efficacy and safety of dasiglucagon in the rescue treatment of hypoglycemia in adult patients with T1DM compared to placebo and with reference to GlucaGen. Figure 6 below shows the schematic of Trial 16137.



Source: Trial 16137's report Figure 9-1.

Figure 7. Mean (with standard error of mean) plasma concentration profiles following single SC doses of dasiglucagon (0.6 mg) and GlucaGen (1 mg)

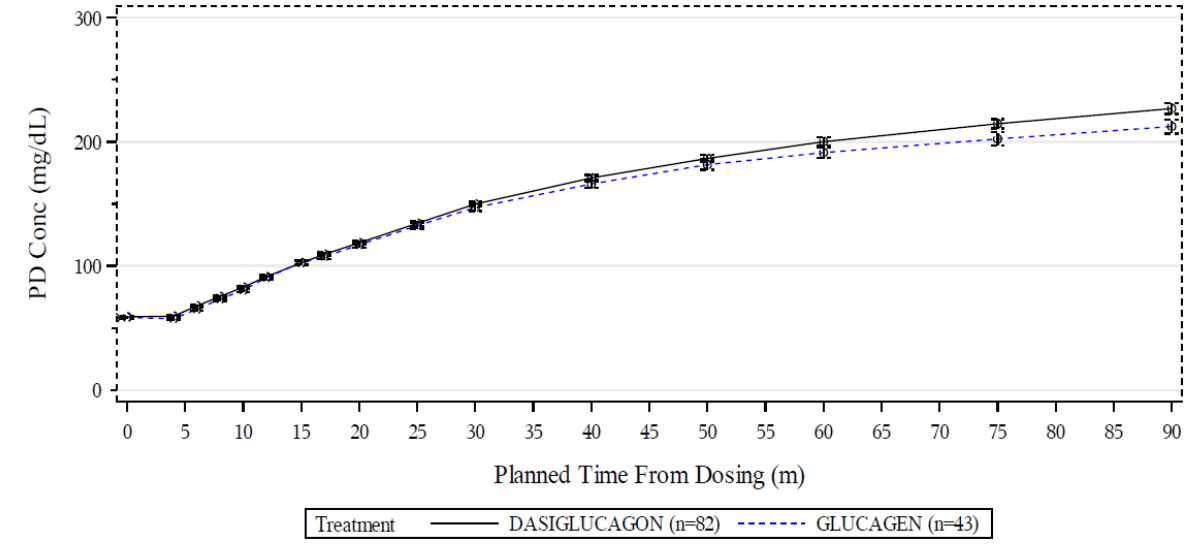


Source: Trial 16137's report Figure 14.2.2.1

Figure 7 shows the PK data for the dasiglucagon and GlucaGen treatments. The dasiglucagon C_{max} was 1280 pM (geometric mean) and t_{max} was 40 minutes (median) upon a single subcutaneous 0.6 mg dasiglucagon injection.

Figure 8 shows the PD data for the dasiglucagon and GlucaGen treatments. The SC 0.6 mg dasiglucagon treatment resulted in a rise from baseline (mean 58.9 mg/dL) in plasma glucose, which was apparent on average within 5 minutes of injection, to about 220 mg/dL by the last observation time of 90 minutes. The area under the observed plasm glucose-time curve ($AUE_{0\text{-}30min}$) for the dasiglucagon and GlucaGen treatments were 21 mg*h/dL and 20.4 mg*h/dL, respectively, and higher than that of the placebo (3.57 mg*h/dL) (see Table 10)

Figure 8. Mean (with standard error of mean) plasma glucose concentration profiles following single SC doses of dasiglucagon (0.6 mg) and GlucaGen (1.0 mg)



Source: Trial 16137's report Figure 14.2.2.2

Table 9. Summary statistics of dasiglucagon PK and GlucaGen PK

PK Parameter	Category/ Statistic	Dasiglucagon (N=82)	GlucaGen (N=43)
$AUC_{0\text{-}90min}$ (pmol*h/L)	N	82	43
	Mean (SD)	1520 (518)	1350 (372)
	Geometric mean	1430	1300
	CV (%)	34.2	27.5
	Median	1470	1320
	Min, Max	587, 2850	475, 2080
Cmax (pmol/L)	N	82	43
	Mean (SD)	1380 (519)	1570 (542)
	Geometric mean	1280	1490
	CV (%)	37.7	34.5
	Median	1330	1470
	Min, Max	530, 2990	722, 3160
Tmax (h)	N	82	43
	Mean (SD)	0.669 (0.158)	0.312 (0.117)
	Geometric mean	0.651	0.295
	CV (%)	23.6	37.6
	Median	0.670	0.250
	Min, Max	0.250, 1.00	0.230, 0.670

Source: Trial 16137's report Table 14.2.12.1

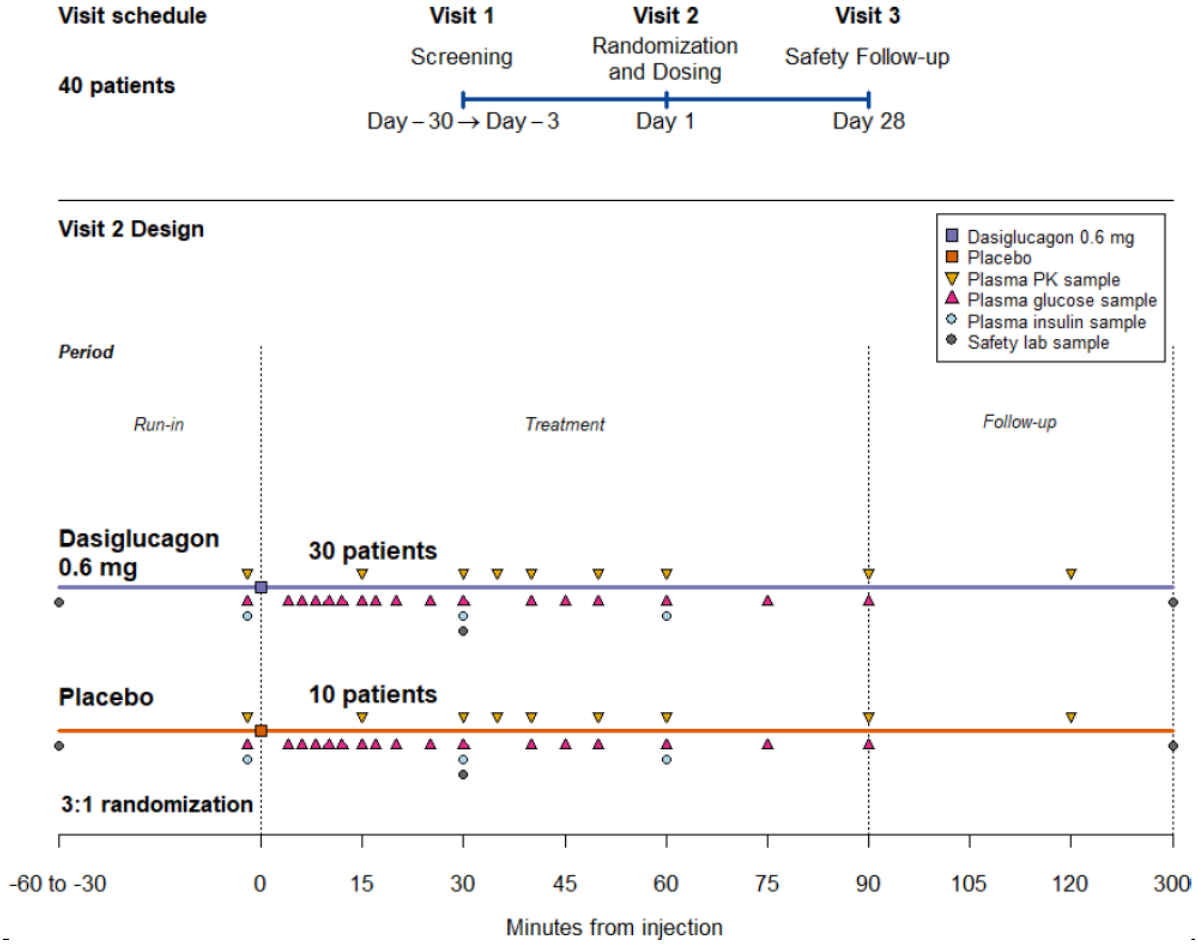
Table 10. Plasma Glucose Response as $AUE_{0\text{-}30min}$

Pharmacodynamic Parameter	**Category/ Statistic**	**Dasiglucagon (N=82)**	**Placebo (N=43)**	**GlucaGen® (N=43)**
$AUE_{0\text{-}30min}$ (mg*h/dL)	Mean (SD)	21.0 (5.26)	3.57 (2.86)	20.4 (5.49)
	Median	20.5	3.21	20.6
	Min, max	6.47, 31.8	0.0, 12.5	9.75, 32.9

Source: Trial 16137's report Table 11-5

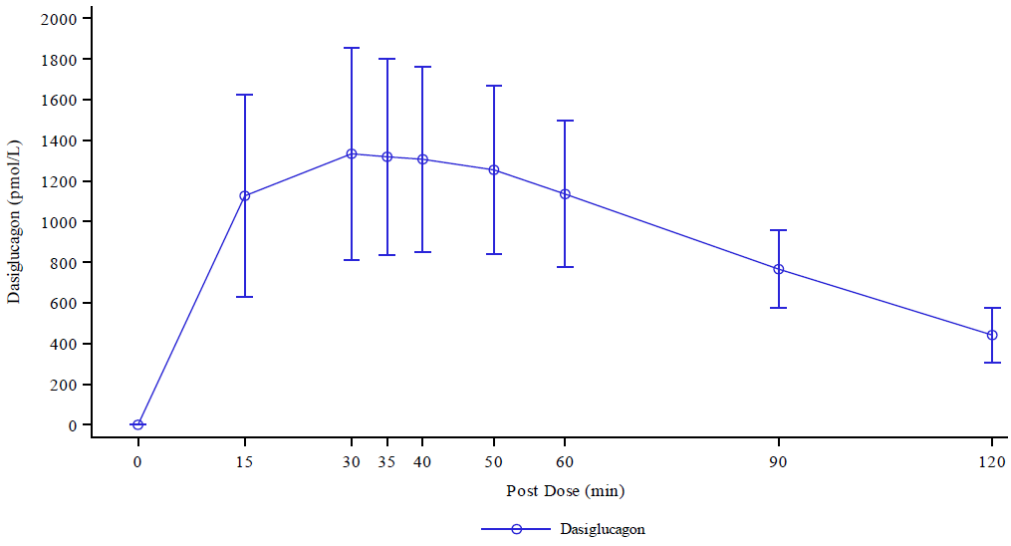
Trial 17145 in Adult Patients with T1DM (A randomized, double-blind, parallel-group trial to confirm the clinical efficacy and safety of dasiglucagon in the rescue treatment of hypoglycemia in subjects with type 1 diabetes)

Figure 9 below shows the schematic of Trial 17145



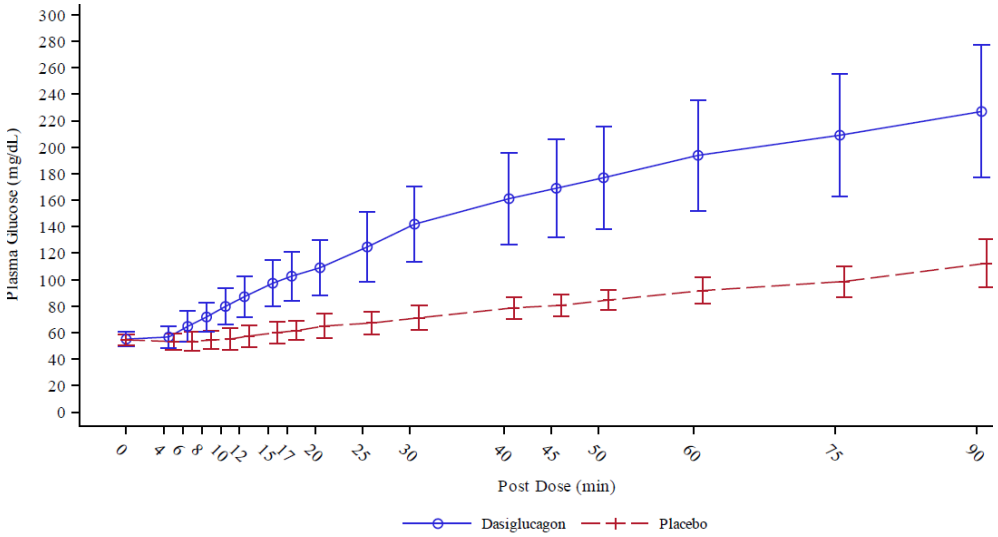
Source: Trial 17145's report Figure 2-1

Figure 10. Mean (with standard error of mean) plasma concentration profiles following single SC doses of dasiglucagon



Source: Trial 17145's report Figure 11-5

Figure 11. Mean (SD) plasma glucose concentration profiles following single SC doses of dasiglucagon and placebo



Source: Trial 17145's report Figure 14.2.2.2

Table 11. Summary statistics of dasiglucagon PK

Parameter Statistics	Treatment 0.6 mg Dasiglucagon (N=34)
$AUC_{0\text{-}90mins}$ (hr*pmol/L)	
n	34
Mean (SD)	1560 (506)
SE	86.7
Median	1560
Min, Max	757, 2800
Geometric Mean (SE)	1480 (85.2)
% CV of Geo. Mean	34.6
$AUC_{0\text{-}120mins}$ (hr*pmol/L)	
n	34
Mean (SD)	1860 (549)
SE	94.2
Median	1860
Min, Max	950, 3150
Geometric Mean (SE)	1780 (94.1)
% CV of Geo. Mean	31.6
Cmax (pmol/L)	
n	34
Mean (SD)	1440 (511)
SE	87.6
Median	1440
Min, Max	643, 2710
Geometric Mean (SE)	1350 (85.6)
% CV of Geo. Mean	38.2
Tmax (min)	
n	34
Mean (SD)	35.6 (10.4)
SE	1.79
Median	35
Min, Max	15, 60
Geometric Mean (SE)	33.8 (2.02)
% CV of Geo. Mean	35.9

Source: Trial 17145's report Table 14.2.9

The PK profiles in Figure 10 show rather rapid increases in plasma dasiglucagon concentrations upon SC administrations. The dasiglucagon C_{max} was 1440 pM (mean) and t_{max} was 35 minutes (median) for the 0.6 mg SC dose (see Table 11).

Table 12. Plasma glucose response as $AUE_{0\text{-}30min}$

Parameter Statistics	Treatment 0.6 mg Dasiglucagon (N=34)	Placebo (N=10)
$AUE_{0\text{-}30mins}$ (hr*mg/dL)		
n	34	10
Mean (SD)	19.9 (8.41)	2.67 (3.06)
SE	1.44	0.968
Median	19.3	3.22
Min, Max	-0.01, 34.7	-1.45, 6.89
n	33	6
Geometric Mean (SE)	18.7 (1.49)	4.62 (0.658)
% CV of Geo. Mean	48.1	36

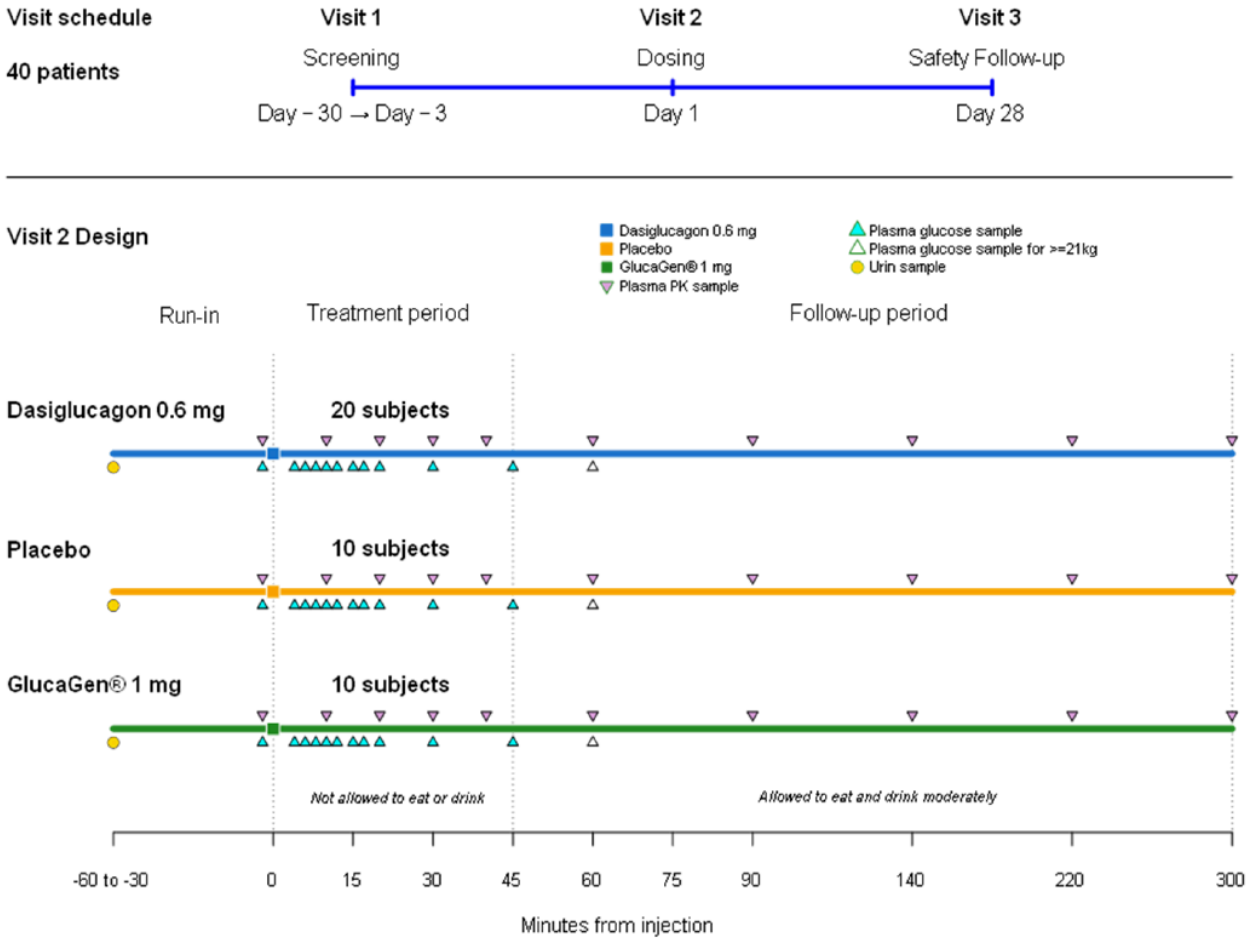
Source: Trial 17145's report Table 14.2.6

Figure 11 shows the PD data for the dasiglucagon and placebo treatments. The SC 0.6 mg dasiglucagon treatment resulted in increases of plasma glucose and the area under the observed plasm glucose-time curve ($AUE_{0\text{-}30min}$) for the dasiglucagon and placebo treatments were 19.9 and 2.67 mg*h/dL, respectively (see Table 12).

Trial 17086 in Pediatric Patients with T1DM (A phase 3, randomized, double-blind, placebo- and active-controlled, parallel-arm trial to assess the efficacy, safety, and pharmacokinetics of dasiglucagon relative to placebo and GlucaGen® when administered as a rescue therapy for severe hypoglycemia in children with T1DM treated with insulin)

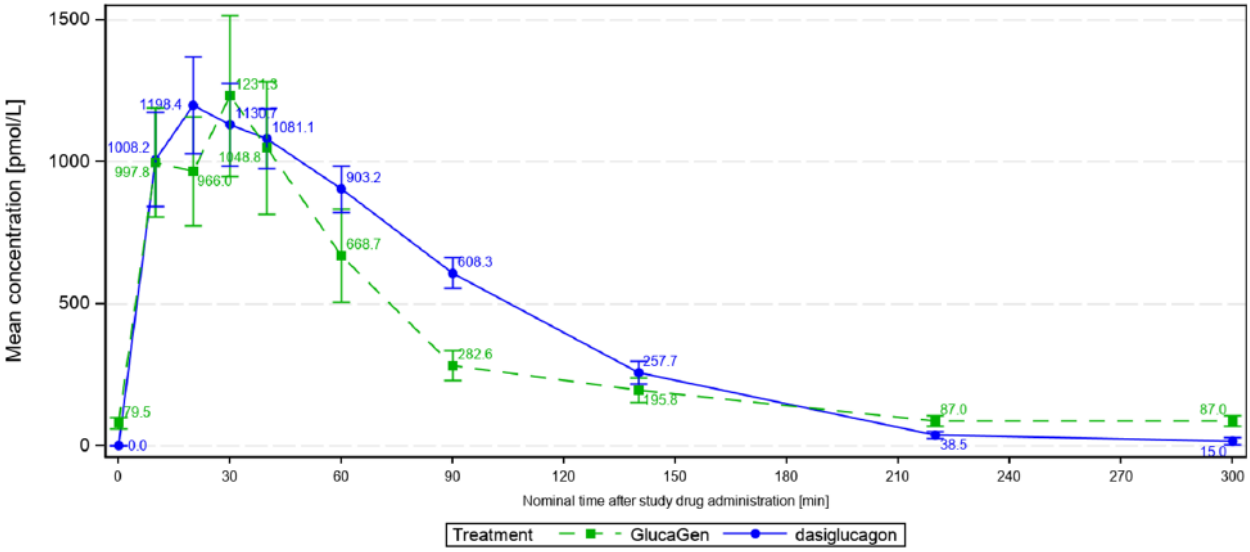
Figure 12 below shows the schematic of Trial 17086

Figure 12 Trial 17086 Design



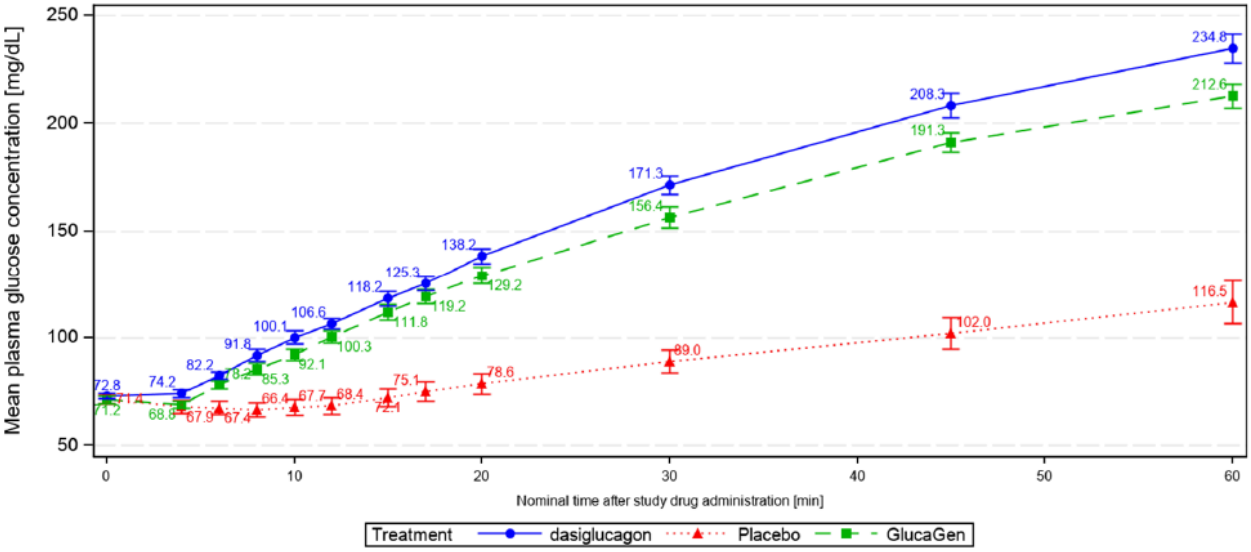
Source: Trial 17086's report Figure 9.1

Figure 13. Mean (with standard error of mean) plasma concentration profiles following single SC doses of dasiglucagon



Source: Trial 17086's report Figure 11.5

Figure 14. Mean (with standard error of mean) plasma glucose concentration profiles following single SC doses of dasiglucagon, GLUCAGEN, and placebo



Source: Trial 17086's report Figure 11.7

Table 13. Summary statistics of dasiglucagon PK and GlucaGen PK

Parameter[1]		Dasiglucagon (N=20)	GlucaGen® (N=10)
$AUC_{0\text{-}30min}$ (h•pmol/L)	Median	413	356
	Min-max	88.7-1340	147-902
	Geom. mean	376	376
	Geom. mean CV %	78.1	63.3
$AUC_{0\text{-}300min}$ (h•pmol/L)	Median	1900	1180
	Min-max	709-4440	599-3250
	Geom. mean	1810	1370
	Geom. mean CV %	44.8	72.7
C_{max} (pmol/L)	Median	1160	979
	Min-max	359-3410	376-2660
	Geom. mean	1160	1120
	Geom. mean CV %	61.2	80
T_{max} (h)	Median	0.35	0.333
	Min-max	0.167-1.5	0.167-0.5
	Geom. mean	0.476	0.328
	Geom. mean CV %	58.9	41.8
$AUC_{0\text{-}inf}$ (h•pmol/L)	Median	1920	1250
	Min-max	719-4450	715-3590
	Geom. mean	1850	1530
	Geom. mean CV %	45.1	70.3
MRT (h)	Median	1.21	1.85
	Min-max	0.777-2.31	1.36-2.44
	Geom. mean	1.27	1.86
	Geom. mean CV %	29.5	21.1
λ_z (/h)	Median	1.07	0.544
	Min-max	0.515-2.1	0.296-0.67
	Geom. mean	1.11	0.504
	Geom. mean CV %	37.4	27.2
$t_{½}$ (h)	Median	0.647	1.27
	Min-max	0.329-1.35	1.03-2.34
	Geom. mean	0.623	1.38
	Geom. mean CV %	37.4	27.2
CL/f (L/h)	Median	92.7	229
	Min-max	39.9-247	80.1-401
	Geom. mean	96.1	188
	Geom. mean CV %	45.1	70.3
V_z/f (L)	Median	77.4	348
	Min-max	36.1-245	143-943
	Geom. mean	86.4	373
	Geom. mean CV %	62.2	81.1

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Geom. mean	86.4
Geom. mean CV %	62.2

Baseline correction was not applied for GlucaGen pharmacokinetic assessments, and the influence of endogenous glucagon is therefore not accounted for in the pharmacokinetic parameter calculations.
Source: Trial 17086's synopsis

Figure 13 shows rather rapid increase in plasma dasiglucagon concentrations upon 0.6 mg SC administration. The dasiglucagon C_{max} was 1160 pM (geometric mean) and t_{max} was 21 minutes (median) for the 0.6 mg SC dose (see Table 13).

Table 14. Plasma glucose response as $AUE_{0\text{-}30min}$

Parameter		Dasiglucagon (N=20)	Placebo (N=11)	GlucaGen® (N=10)
$AUE_{0\text{-}30min}$ (mmol•h/L)	Mean (±SD)	22.83 (±6.126)	1.81 (±4.641)	19.66 (±3.410)
	Median	22.44	1.46	20.11
	Min-max	10.9-34.1	-6.3-9.1	13.8-24.1

Source: Trial 17086's synopsis

Figure 14 shows the PD data for the dasiglucagon, GlucaGen, and placebo treatments. The SC 0.6 mg dasiglucagon treatment and GlucaGen treatment resulted in increases of plasma glucose and the area under the observed plasm glucose-time curve ($AUE_{0\text{-}30min}$) for the dasiglucagon, GlucaGen, and placebo treatments were 22.83, 19.66, and 1.81 mg*h/dL, respectively (see Table 14).

4.3 Population PK and/or PD Analyses

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW FOR NDA 214231, DASIGLUCAGON

RESULTS OF APPLICANT'S ANALYSIS

Population Pharmacokinetic Modeling Review

The Applicant submitted the following 3 Population Pharmacokinetic (PPK) Reports to support the approval of dasiglucagon to treat severe hypoglycemia in patients with type 1 diabetes mellitus (T1DM) aged 6 years and above:

- 16-147
- 17-094
- 19-077

Report 16-147 is also for the population PK/PD modeling and simulation of dasiglucagon in patients with T1DM. **Error! Reference source not found.**5 below shows the studies assessed in these 3 PPK reports.

Trial Type	Trial	Number	Dose Regimen
Dose finding	15126	54	Single doses of 0.1, 0.3, 0.6 and 1 mg of dasiglucagon. Injection site: abdomen. Pre-filled syringe
Immunogenicity	16136	57	3 consecutive 0.6 mg doses of dasiglucagon. Injection site: abdomen. Pre-filled syringe
1st pivotal	16137	82	0.6 mg single dose of dasiglucagon. Injection sites: abdomen, thigh or buttocks. Pre-filled syringe.
Dual storage	17084	90	2 consecutive 0.6 mg doses of dasiglucagon of 2 batches. Injection site: abdomen. Pre-filled syringe
Pediatric pivotal	17086	20	0.6 mg single dose of dasiglucagon. Injection sites: abdomen or thigh. Pre-filled syringe
2nd pivotal	17145	34	0.6 mg single dose of dasiglucagon. Injection sites: buttocks or deltoid. Auto injector

Number = Number of subjects with available dasiglucagon PK

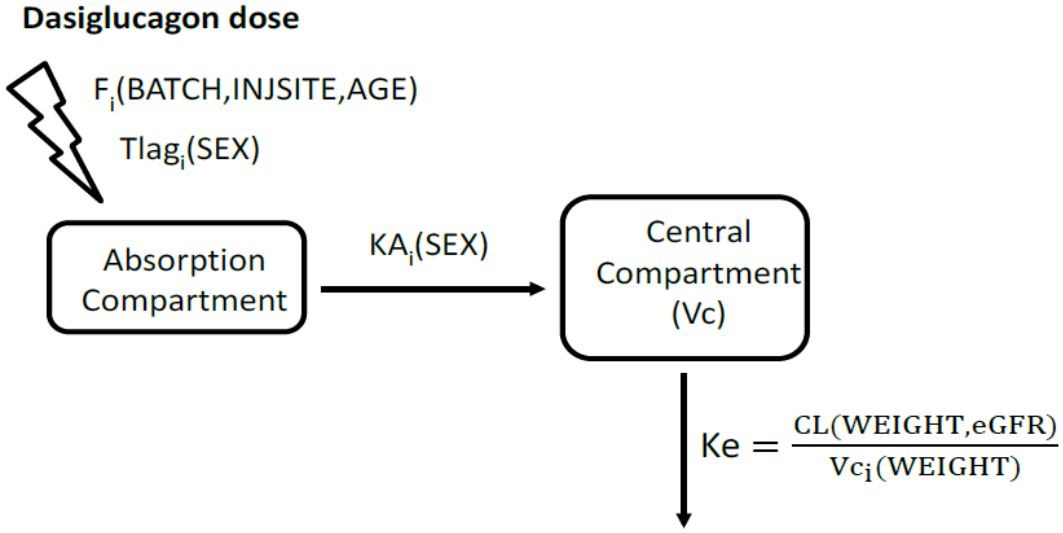
Source: Review's compilation

The applicant used the data from the dose-finding trial (15126) to develop the PPK model as reflected in Report 16-147. The applicant then used this PPK model and updated it with allometric scaling to support the pediatric dose of 0.6 mg dasiglucagon (Report 17-094). Report 19-077 reflects the establishment of the final PPK model through all 7 trials shown in Table 1.

Reviewer's Comments: *This PPK review will focus on Report 19-077 because it is the updated final PPK model.*

Figure 15 shows the structure of the Applicant's final PPK model.

Figure 15. Structures for Dasiglucagon PPK Model for Patients with T1DM.



F is the bioavailability. T_{lag} is the lag time. Ka is the absorption rate constant. Vc is the central compartment volume. Ke is the elimination rate constant. CL is the clearance.
Source: Population PK Report 19-077's Figure 4.

Dasiglucagon concentration after subcutaneous (SC) administration in adult and pediatric subjects was characterized through a 1-compartment model with first-order delayed absorption and first-order linear elimination.

Rates of Drug absorption and elimination:

$$\frac{d}{dt}A_1 = -KA_i(\text{SEX}) \cdot A_1$$
$$\frac{d}{dt}A_2 = KA_i(\text{SEX}) \cdot A_1 - \left(\frac{CL(WEIGHT, eGFR)}{Vc_i(WEIGHT)}\right) \cdot A_2$$

Calculation of drug concentration:

$$\text{C} = \frac{A_2}{V_c} \cdot \left(1 + \varepsilon_{prop}\right) + \varepsilon_{add}$$

Residual error:
The proportional and additive residual errors were independent and normally distributed with mean=0 and variance σ^2:

$$\begin{bmatrix}\varepsilon_{prop} \\ \varepsilon_{add}\end{bmatrix} = N\left(\begin{bmatrix}0\\0\end{bmatrix}, \begin{bmatrix}\sigma^2_{prop} & 0 \\ 0 & \sigma^2_{add}\end{bmatrix}\right)$$

Population PK parameters:

$$KA_i(SEX) = TVKA \cdot \left(1 + b_1 \cdot (SEX = Female)\right) \cdot \exp(\eta_{KA,i})$$

$$CL(WEIGHT, eGFR) = TVCL \cdot \left(\frac{WEIGHT}{78}\right)^{0.75} \cdot \left(\frac{eGFR}{95.16}\right)^{b_2}$$

$$Vc_i(WEIGHT) = TVVc \cdot \left(\frac{WEIGHT}{78}\right) \cdot \exp(\eta_{Vc,i})$$

$$F_i(BATCH, INJSITE, AGE) = F_{BATCH} \cdot F_{INJSITE} \cdot F_{AGE} \cdot \exp(\eta_{F,i})$$

$$F_{BATCH} = 1 + b_3 \cdot (BATCH = Dual\ storage)$$

$$F_{INJSITE} = 1 + b_4 \cdot (INJSITE = Thigh) + b_5 \cdot (INJSITE = buttock\ or\ deltoid)$$

$$F_{AGE} = 1 + b_6 \cdot (AGE - b_7) \cdot I(AGE < b_7)$$

b_7=Age knot point separating the two linear pieces of the piece-wise linear relationship between F and AGE

$$T_{lag,i} = TVTlag \cdot \exp(\eta_{Tlag,i})$$

Subject specific random effects (η) are independent and log-normally distributed with mean=0 and variance ω^2:

$$Diag(\omega^2_{KA}, \omega^2_{Vc}, \omega^2_F, \omega^2_{Tlag})$$

A1=dasiglucagon amount in absorption compartment; A2=dasiglucagon amount in central compartment; Tlag=absorption lag time; C=dasiglucagon concentration; CL=clearance; eGFR=estimated glomerular filtration rate; KA=absorption rate constant; ke=elimination rate constant; PK=pharmacokinetic; Vc=central compartment

Table 16 shows the parameter estimates for the final dasiglucagon PPK model.

Table 16. Parameter Estimates of Applicant's PPK Model.

Parameters	Symbol#	Final Model Estimates		Bootstrap estimates		
		Value	95% CI	Mean	95% CI	
CL (L/hr)		65.3	[63.5; 67.2]	65.1	[63.1; 67.1]	
Vc (L)		33.2	[30.4; 36.3]	33.1	[30; 36.4]	
KA (hr^{-1})		1.13	[1.05; 1.21]	1.12	[1.02; 1.22]	
T_{lag} (minutes)		0.47	[0.33; 0.68]	0.48	[0.30; 0.65]	
BATCH-F: Dual storage vs regular (ratio)	$1 + b_3$	0.866	[0.836; 0.89]	0.866	[0.838; 0.889]	
Weight exponent for CL		0.75 (Fixed)		0.75 (Fixed)		
Weight exponent for Vc		1 (Fixed)		1 (Fixed)		
INJSITE-F						
Thigh vs abdomen (ratio)	1 + b4	0.69	[0.62; 0.75]	0.68	[0.63; 0.75]	
Buttocks/deltoid vs abdomen (ratio)	1 + b5	0.86	[0.80; 0.91]	0.86	[0.80; 0.91]	
AGE-F : Age_{kp} (years)	b_7	24	[24.0; 24.0]*	24	[20.9; 27.2]*	
Age > kp: 1						
Age ≤ kp: $1 + \theta$*(Age-Age_{kp})	b_6	0.0275	[0.0182; 0.0369]	0.0272	[0.0165; 0.0466]	
SEX-KA: Female vs Male (ratio)	$1 + b_1$	1.29	[1.23; 1.35]	1.29	[1.20; 1.39]	
eGFR-CL: $(eGFR/95.16)^{\theta}$	b_2	0.19	[0.08; 0.31]	0.19	[0.07; 0.29]	
Random effects						**Shrinkage (%)**
IIV on Vc (CV%)		37	[30.8; 42.5]	36.7	[31.1; 42.8]	21.5
IIV on KA (CV%)		26.8	[22.8; 30.3]	26.8	[22.4; 31.0]	29.6
IIV on T_{lag} (CV%)		163	[111; 224]	159	[111; 238]	40.8
IIV on F (CV%)		20.9	[18.5; 23]	20.4	[18.3; 22.7]	4.6
Residual error						
Proportional (CV%)		42.3	[40.7; 43.9]	42.2	[40.3; 44.2]	--
Additive (pmol/L)		19	[14.1; 23.8]	19.1	[13.4; 33.1]	10

AGE-F=age effect on F, Agekp=age knot point in the piece-wise linear relationship between F and age, BATCH-F=batch effect on F, CI=confidence interval, CL=clearance, CV=coefficient of variation, eGFR=estimated glomerular filtration rate, eGFR-CL=eGFR effect on CL, F=relative bioavailability, IIV=interindividual variability, INJSITE-F=injection site effect on F, KA=absorption rate constant; kp=knot point, SEX-KA=sex effect on KA, Tlag=absorption lag time, Vc=central volume of distribution.
Source: Population PK Report 19-077's Table 12.

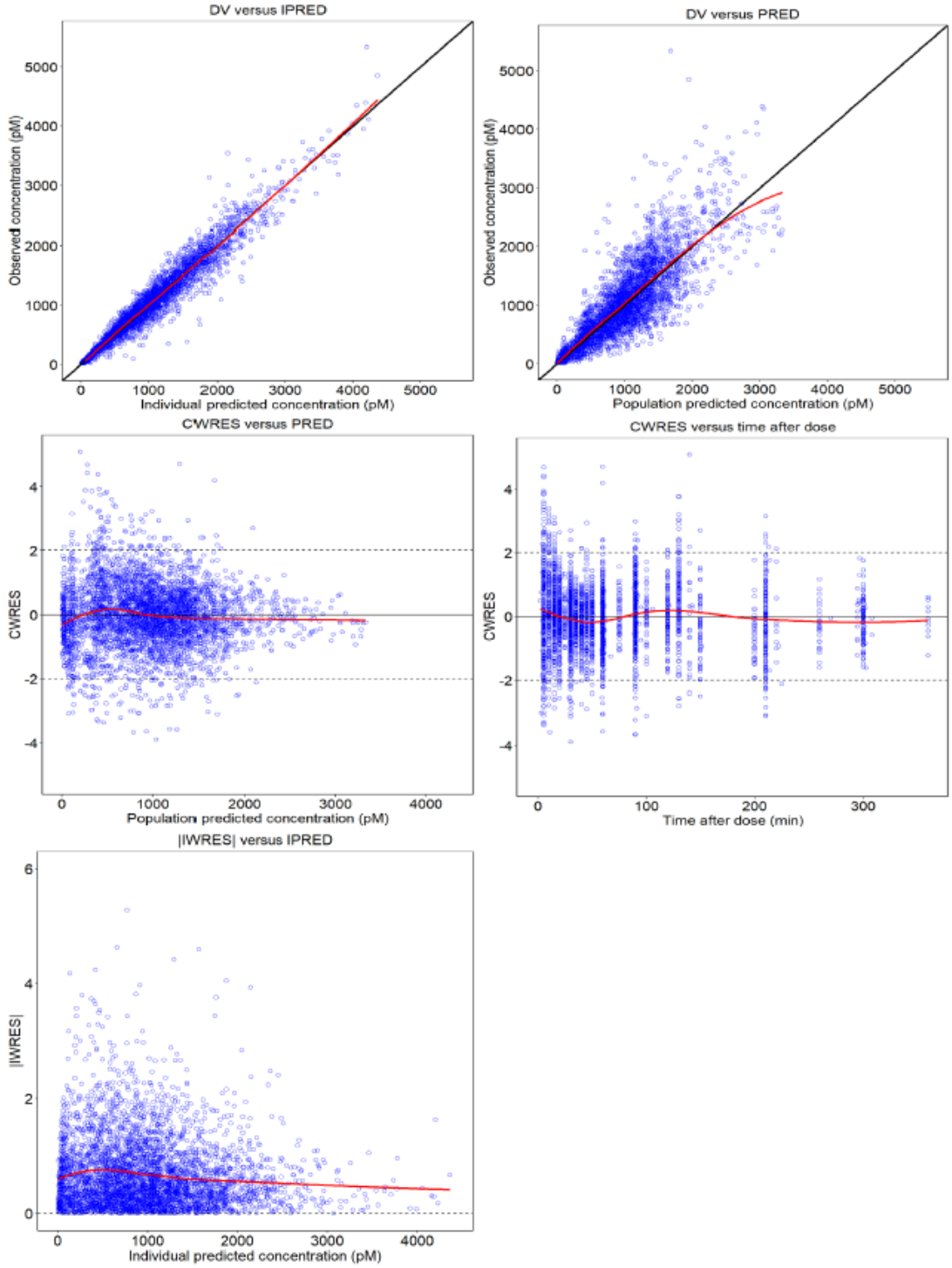
The PPK parameters KA, CL, V, F and Tlag were estimated with acceptable precision for descriptive PK purposes. The η-shrinkage was low for F (4.6%), acceptable for Vc (21.5%) and KA (29.6%) and high for Tlag

(40.8%). The ε-shrinkage was low (10%). The parametric estimates and bootstrap estimates from the final PPK model are consistent. The bootstrap estimates were based on 450 successfully converged bootstrap replicates (out of 500). The 95% CI of all parameter estimates does not include zero.

The estimated bioavailability was lower in pediatric subjects than in adult subjects, and lower after thigh, buttock and deltoid injections than after abdominal injection. The estimated F was 69% (95% CI: 62%-75%) for thigh injection vs abdominal injection and 86% (95% CI: 80%-91%) for buttocks and deltoid injections vs abdominal injection. The estimated F for the batch reflecting storage at the intended dual storage conditions was 87% (84%-89%) relative to batches stored at refrigerated conditions. The KA was predicted 29% (95% CI: 23%-35%) higher in female subjects compared to male subjects.

Figure shows the goodness-of-fit (GOF) plots for dasiglucagon's final PPK model.

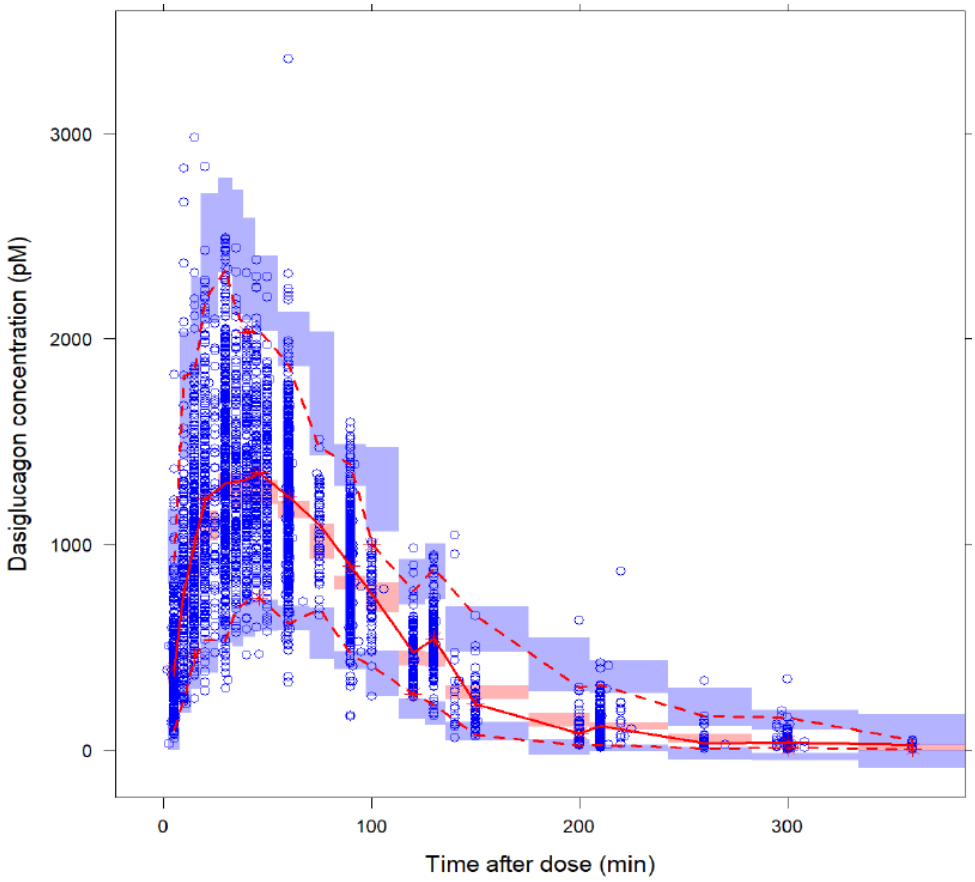
Figure 16. GOF Plots for Dasiglucagon's Final PPK Model.



Dots are individual data points and solid red lines are smoothed LOESS lines. The solid black lines in the 2 plots in the 1st row are lines of identity. The dashed lines in the 2 plots in the 2nd row show the boundaries of the CWRES ± 2 interval.
CWRES=conditional weighted residuals, DV=dependent variable (dasiglucagon concentration), GOF=goodness of fit, IPRED=individual predictions, |IWRES|=absolute values of individual weighted residuals, PRED=population predictions.
Source: Population PK Report 19-077's Figure 8.

Figure shows the prediction-corrected visual predictive checks (VPC) for the final PPK model of dasiglucagon.

Figure 17. Prediction-Corrected VPC for Applicant's Final PPK Model for Dasiglucagon.



Source: Population PK Report 19-077's Figure 11.

Blue dots are observed data points; red solid line is the observed median; red dashed lines are observed p5 and p95. The pink area is the 95% prediction interval (PI) of the simulated median, and purple areas are the 95%PI of the simulated p5 and p95 based on 500 replicates. VPC=visual predictive check

Reviewer's Comments: *The GOF and VPC plots demonstrate reasonable agreement between the observed concentrations and model predictions for descriptive PK purposes and establishing exposure metrics for the PK/PD model..*

Figure 18 below shows the relative effect of covariates on dasiglucagon exposure.

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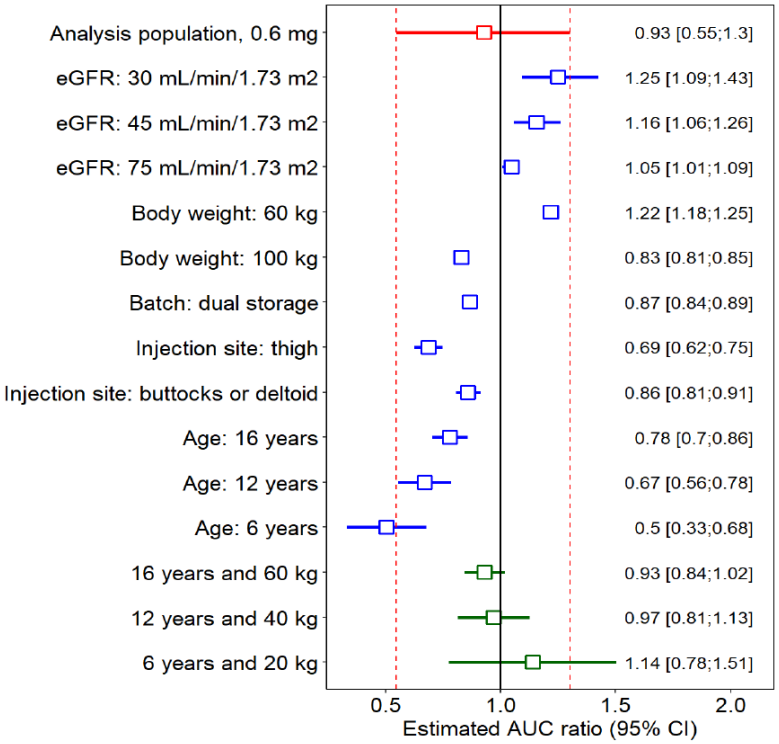
Figure 18 The relative effect of covariates on dasiglucagon exposure.



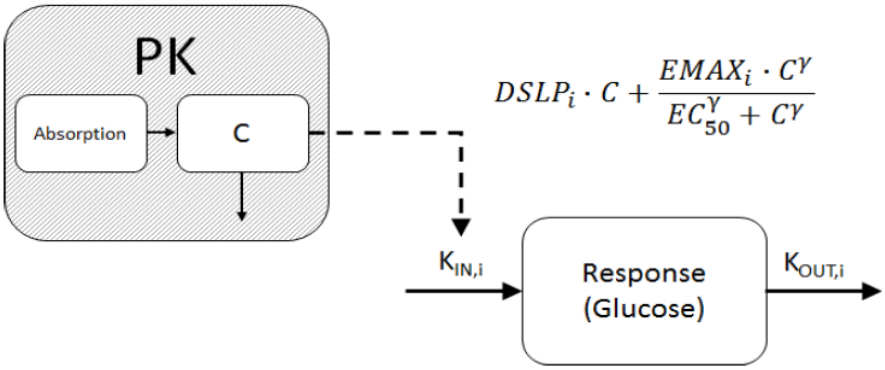
Source: Report 19-077's Figure 7

4.4 Exposure-Response Analyses

Population Pharmacokinetic-Pharmacodynamic (PKPD) Model

Figure 19 shows the final PKPD model for dasiglucagon.

Figure 19. Structure of the final PKPD model. The dasiglucagon concentrations are predicted by the final population PK model.



Source: Population PK Report 16-147's Figure 7.

$$Glu = Glu_i + Glu_i \cdot \varepsilon$$

$$\frac{d\,Glu_i}{dt} = K_{IN,Eff,i} - K_{OUT,i} \cdot Glu_i, Glu_i(0) = BASE$$

$$K_{IN,eff,i} = K_{IN,i} \cdot \left(1 + \frac{EMAX_i \cdot C^{\gamma}}{EC_{50}{}^{\gamma} + C^{\gamma}}\right) + DSLP_i \cdot C$$

$$K_{IN,i} = PLAT_i \cdot K_{OUT,i},$$

$$K_{OUT,i} = TVK_{OUT} \cdot \exp(\eta_1),$$

$$EMAX_i = TVEMAX \cdot \exp(\eta_2),$$

$$PLAT_i = TVPLAT \cdot \exp(\eta_3),$$

$$DSLP_i = TVDSLP + \eta_4$$

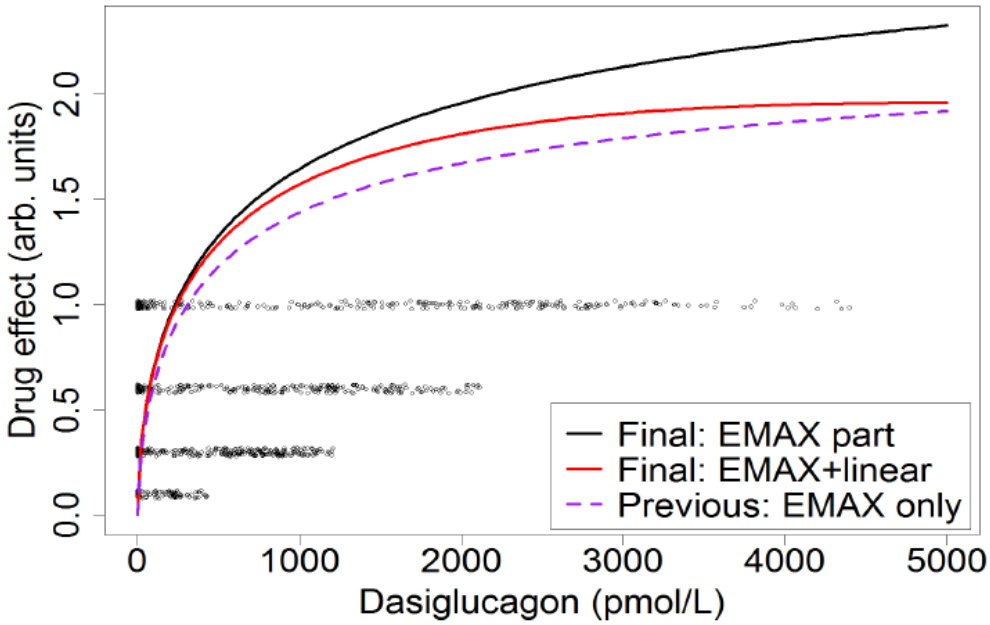
$$\begin{bmatrix}\eta_1\\ \eta_2\\ \eta_3\\ \eta_4\end{bmatrix} \sim N\left(0, \begin{matrix}\omega_{11} & 0 & 0 & 0\\ 0 & \omega_{22} & \omega_{23} & 0\\ 0 & \omega_{23} & \omega_{33} & 0\\ 0 & 0 & 0 & \omega_{44}\end{matrix}\right), \varepsilon \sim N(0, \sigma^2)$$

Glu is the observed glucose concentration described by the model-predicted individual glucose concentration, Glui, and a proportional residual error model with variance σ^2. A population baseline, BASE, was estimated representing glucose concentration in the induced hypoglycemic state at time zero. Individual glucose elimination rate (KOUT,i), maximal effect of the sigmoid EMAX component of the PKPD relation (EMAXi; with Hill factor, γ), glucose steady state concentration (PLATi, plateau), and slope of the linear component of the PKPD relation (DSLPi) was estimated by the model.

The individual estimated EMAXi and PLATi were highly (negatively) correlated, and estimation of an off-diagonal element (ω_{23}) of the variance-covariance matrix was necessary in order to adequately describe the inter- individual variability in the data. Without dasiglucagon exposure (C=0), the model predicts a glucose concentration of BASE at time zero. Over time, this concentration exponentially approaches steady state, PLATi, with time constant, KOUT,i. Thus, this model, starts from a non-steady state hypoglycemic level. In a model starting at steady state, the initial condition would be defined as KIN/KOUT.

The PKPD relation estimated with a previous model including a standard sigmoidal EMAX model. Figure 20 shows that the impact of the linear component (DSLP) is to create a flatter plateau at high exposures compared to the EMAX component only. Also, the steepness at low exposures was greater in the final model than predicted by the previous model. The addition of the linear component to the PKPD relation led to a statistically significant improvement in model fit compared to a model including a sigmoid EMAX relation only: p=0.0019 and p=0.0018 when adding the fixed and random effects in 2 successive steps (2 x 1 df).

Figure 20. PKPD relation estimated by the combined linear and sigmoid EMAX component in the final model (red) compared to the contribution from the EMAX component only (black) and a previous sigmoid EMAX model (purple). Black markers show predicted dasiglucagon concentration at the PD sampling time points at the dose level corresponding to the position on the ordinate axis.



Source: Population PK Report 16-147's Figure 7.

Table 17 shows the PKPD model parameters.

Table 17. PKPD model parameter estimates with relative standard errors (RSE) and bootstrap confidence intervals

Parameter	NONMEM parameter	Parameter estimate (%RSE)[$]	Bootstrap 95%CI[#]	Untransformed parameter[$]
BASE	THETA1	1.238 (1%)	[1.215 ; 1.261]	3.449 mmol/L
KOUT	THETA2	-3.857 (1%)	[-3.939 ; -3.776]	0.02113 /min
EMAX	THETA3	3.173 (31%)	[1.807 ; 8.969]	3.173
EC50	THETA4	6.782 (10%)	[5.846 ; 9.922]	881.7 pmol/L
GAM	THETA5	-0.5405 (29%)	[-0.9547 ; -0.3219]	0.5825
PLAT	THETA6	1.736 (5%)	[1.532 ; 1.884]	5.672 mmol/L
DSLP	THETA7	-7.341 (99%)	[-24.02 ; 10.05]	-7.341
EPS	SIGMA.1.1.	0.003346 (10%)	[0.002652 ; 0.003947]	0.05785
ETA1 (KOUT)	OMEGA.1.1.	0.07298 (19%)	[0.04818 ; 0.1081]	0.2702
ETA2 (EMAX)	OMEGA.2.2.	0.5033 (26%)	[0.3132 ; 0.866]	0.7094
ETA2x3	OMEGA.3.2.	-0.3092 (24%)	[-0.5182 ; -0.1926]	-0.92
ETA3 (PLAT)	OMEGA.3.3.	0.2245 (24%)	[0.1334 ; 0.3884]	0.4738
ETA4 (DSLP)	OMEGA.4.4.	280.4 (131%)	[15.69 ; 2205]	16.74
OFV	**OBJ**	**123**	**[-69.92 ; 262.6]**	**123**

$: Random effects are shown as variances and covariances in the parameter estimate column, and sd and correlation in the untransformed parameter column. #: Out of 500 replicates, 48 runs with minimization terminated were skipped when calculating the bootstrap results and 14 runs with estimates near a boundary were skipped when calculating the bootstrap results Source: Population PK Report 16-147's Table 9.

Figure 21. VPC showing glucose response stratified by treatment arm. Solid (dashed) curves show median (5th and 95th percentile) of observed data; red (blue) shaded areas show the 95% CI of the simulated median (outer percentile bands) based on 1000 replicates.

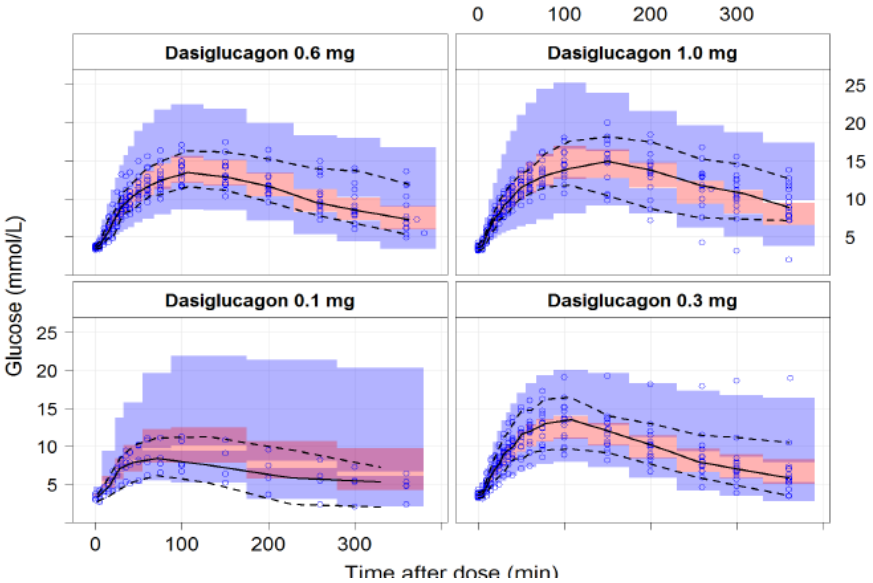
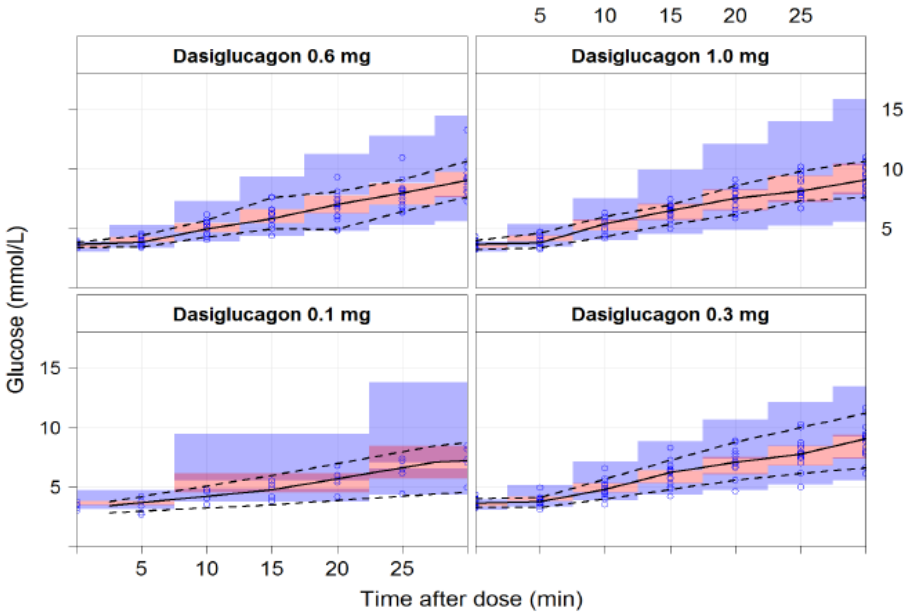


Figure 22. VPC showing glucose response in the first 30 minutes after dose, stratified by treatment arm. Solid (dashed) curves show median (5th and 95th percentile) of observed data; red (blue) shaded areas show the 95% CI of the simulated median (outer percentile bands) based on 1000 replicates.



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