CLINICAL REVIEW

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Division/Office	DDLO/OCHEN
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Established/Proper Name	Dasiglucagon injection
(Proposed) Trade Name	Zegalogue
Applicant	Zealand Pharma
Dosage Form(s)	Autoinjector and prefilled syringe
Applicant Proposed Dosing Regimen(s)	0.6 mg/0.6 mL
Applicant Proposed Indication(s)/Population(s)	Treatment of severe hypoglycemia in patients with diabetes ages six years and above
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged six years and above

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Glossary

AC	advisory committee
ADA	anti-drug antibody
AE	adverse event
AI	autoinjector
AR	adverse reaction
BRF	Benefit Risk Framework
C-QTc	concentration-QTc
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHI	congenital hyperinsulinism
CMC	chemistry, manufacturing, and controls
CMH	Cochran Mantel Haenszel
CMQ	Customized MedDRA Query
CRF	case report form
CSR	clinical study report
DCCT	Diabetes Control and Complications Trial
(b) (4)	(b) (4)
DMEPA	Division of Medication Error Prevention and Analysis
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
EOP2	end-of-phase 2 meeting
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FMQ	FDA Medical Query
GCP	good clinical practice
HF	human factors
HS	healthy subjects
ICH	International Council for Harmonization
IM	intramuscular
IMP	investigational medical product
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness

ISR	injection site reaction
ISS	integrated summary of safety
IV	intravenous
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NAbs	neutralizing antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
ND	not determined
NDA	new drug application
NE	not estimable
NME	new molecular entity
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PDO	patient days of observation
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SC	subcutaneous
SMQ	Standardized MedDRA Query
SOC	system organ class
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment emergent adverse event
ULN	upper limit of normal
US	United States

1. Executive Summary

1.1. Product Introduction

Zealand Pharma (hereafter referred to as the Applicant) has developed dasiglucagon for the treatment of severe hypoglycemia in patients with diabetes mellitus ages six years and above. Dasiglucagon is a peptide analog of glucagon where seven amino acid substitutions have been introduced into the native 29 amino acid glucagon peptide chain with the intent of increasing physical and chemical stability in aqueous solution as compared to native glucagon. For the severe hypoglycemia indication, dasiglucagon has been developed for commercialization in two presentations, a prefilled syringe and an autoinjector (AI), for subcutaneous administration into the abdomen, buttock, thigh, and deltoid. The Applicant has proposed one dose for marketing for both adults and pediatrics, 0.6 mg/0.6 mL. There are currently several approved native glucagon products for the treatment of severe hypoglycemia in patients with diabetes; however, there are no currently approved glucagon analogs for any indication. As dasiglucagon is a New Molecular Entity (NME), the Applicant is submitting this New Drug Application (NDA) using the 505(b)(1) approval pathway.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval of dasiglucagon for the treatment of severe hypoglycemia in patients with diabetes ages six years and above. Dasiglucagon (0.6 mg) in comparison to placebo was evaluated in two adequate and well-controlled trials (16137 and 17145) conducted in adults with type 1 diabetes mellitus (T1DM), and one adequate and well-controlled trial (17086) conducted in pediatrics with T1DM. Dasiglucagon demonstrated superiority to placebo in all three trials for the clinically relevant endpoint of time to plasma glucose recovery, defined as the first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose. The evidence from these trials supports the effectiveness of dasiglucagon for the proposed indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Zealand Pharma (i.e. the Applicant) has developed dasiglucagon for the treatment of severe hypoglycemia in patients with diabetes mellitus ages six years and above. Dasiglucagon is a peptide analog of glucagon where seven amino acid substitutions have been introduced into the native 29 amino acid glucagon peptide chain to improve physical and chemical stability in aqueous solution. Glucagon is an endogenous hormone that increases blood glucose by stimulating hepatic glycogenolysis and gluconeogenesis. There are no currently approved glucagon analog products approved in the US or under any foreign regulatory body. Dasiglucagon has been developed for commercialization in two presentations, a prefilled syringe and an autoinjector, for subcutaneous administration.

Severe hypoglycemia is defined as hypoglycemia that causes neurological impairment and requires the assistance from another person to take corrective actions for recovery. Severe hypoglycemia is a medically serious condition that may be associated with sufficient neuroglycopenia to induce seizure and/or coma and can be fatal if untreated. All patients with T1DM and patients with type 2 diabetes mellitus (T2DM) on antihyperglycemic agents, particularly insulin or insulin secretagogues, are at risk for hypoglycemia including severe hypoglycemia. Injectable glucagon products that can be administered by a caregiver are the main treatment options for the treatment of severe hypoglycemia episodes that occur outside of a healthcare setting. Glucagon products intended for the treatment of severe hypoglycemia are, therefore, life-saving drugs for patients with diabetes mellitus. While native glucagon products that require reconstitution prior to injection have been marketed in the United States for decades, two novel presentations have recently been approved and marketed: glucagon for nasal inhalation (Eli Lilly, NDA 210134) and glucagon for injection available in a prefilled syringe and autoinjector (Xeris Pharmaceuticals, NDA 212097).

To provide substantial evidence of effectiveness, two adequate and well-controlled trials (16137 and 17145) were conducted in adults with T1DM, and one adequate and well-controlled trial (17086) was conducted in pediatrics with T1DM. In these trials, hypoglycemia was artificially induced with a hypoglycemic clamp procedure to a target plasma glucose between 45-60 mg/dL (adults) or between 54-80 mg/dL (pediatrics), and the ability of dasiglucagon to increase blood glucose versus a placebo injection was assessed. As the likelihood of a serious complication from a severe hypoglycemic episode increases with the duration and severity of neuroglycopenia, the time to resolution of the event is of key clinical importance. To this end, the pre-specified primary endpoint was the time to plasma glucose recovery, defined as the first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose. Dasiglucagon demonstrated superiority to placebo in all three trials (all log-rank test 2-sided p-values <0.001) and demonstrated a median time to glucose recovery of 10 minutes (95% CI: 10, 10) and 10 minutes (95% CI: 8, 12) in trials 16137 and 17145 compared to 40 minutes (95% CI 30, 40) and 35 minutes (20, upper limit not estimable) with placebo, respectively. The median time to glucose recovery in pediatric trial 17086 was 10 minutes (95% CI: 8, 12) with

dasiglucagon versus 30 minutes (20, upper limit not estimable) with placebo. Despite aiming to enroll pediatric subjects down to 6 years of age, the youngest subjects enrolled in trial 17086 were 7 years old; however, the robust efficacy data in combination with the lack of a specific safety concern in the younger pediatric cohort support extrapolation of the conclusions regarding safety and effectiveness to subjects 6 years old to support the proposed indication. Additionally, dasiglucagon demonstrated superiority to placebo for all secondary endpoints: the proportion of subjects obtaining plasma glucose recovery within 30, 20, 15, and 10 minutes after investigational product injection without administration of rescue IV glucose (four separate endpoints), and plasma glucose change from baseline at 30, 20, 15, and 10 minutes after investigational product injection or at the time of rescue (four separate endpoints). Sensitivity analyses performed by the Applicant confirmed the robustness of the primary efficacy analyses. There were no important efficacy-by-subpopulation interactions.

Adult trial 16137 and pediatric trial 17086 also included an active comparator treatment arm, wherein subjects received a single 1.0 mg injection of GlucaGen (Novo Nordisk, NDA 020918). While no formal statistical comparison between dasiglucagon and GlucaGen was carried out, the inclusion of GlucaGen in these trials allows for the informal comparison of dasiglucagon to another glucagon product approved for the treatment of severe hypoglycemia. Subjects administered GlucaGen demonstrated a median time to glucose recovery of 12 minutes (95% CI: 10, 12) and 10 minutes (95% CI: 8, 12) in trials 16137 and 17086, respectively. Therefore, dasiglucagon is similar to GlucaGen with regard to the endpoint of time to plasma glucose recovery from hypoglycemia.

There are additional potential benefits of dasiglucagon intended for the treatment of severe hypoglycemia. Dasiglucagon has been developed for administration via a prefilled syringe or autoinjector device. As noted previously, time to resolution of neuroglycopenia is of primary clinical importance for the treatment of severe hypoglycemia. Published literature from studies conducted with other glucagon products that do not require reconstitution demonstrate a faster time to administration as compared to glucagon products that require reconstitution.[1-3] While not directly assessed in the clinical development program, it can be reasoned that dasiglucagon may also allow for faster time to administration similar to other glucagon products that also do not require reconstitution. Additionally, medication errors have been reported with glucagon products that require reconstitution, such as injecting diluent only, injecting with an empty syringe, or injecting an insufficient dose due to incorrect reconstitution, all errors that are of considerable risk given the life-threatening nature of severe hypoglycemia.[3,4] These types of medication errors would not be expected to occur with use of dasiglucagon.

The safety profile of dasiglucagon was assessed via review of safety data from adult placebo-controlled efficacy trials (placebo-controlled pool) and with a secondary pool comprised of all adult subjects with T1DM exposed to doses of dasiglucagon ≥ 0.6 mg (broad pool). Adverse events that occurred in ≥2% of adult subjects and greater than with placebo in the placebo-controlled safety data pool included gastrointestinal events

(most commonly, nausea, vomiting, and diarrhea), headache, and injection site pain. Events were non-serious, transient, and generally resolved without intervention. These events are consistent with events that would be anticipated with glucagon receptor agonism or with use of an injectable product and are also expected pharmacodynamic effects based on nonclinical data. Hemodynamic events, such as hypotension, were observed at an incidence of 2.3% and 5.9% in dasiglucagon and GlucaGen exposed-subjects, respectively, in an analysis utilizing the broad pool, a finding that is in accordance with published literature and labeling for approved native glucagon products. Pediatric trial 17086 was evaluated independently and there were no important differences in safety between the adult and pediatric populations, or between pediatric subjects given dasiglucagon versus GlucaGen.

As dasiglucagon is a glucagon analog, there is the potential for increased immunogenicity compared to native glucagon. Therefore, the Applicant conducted trial 16136 in 111 subjects (of which 57 subjects were exposed to dasiglucagon) to assess the immunogenic potential of dasiglucagon after repeated dosing and the subsequent impact of anti-drug antibodies (ADAs) on the pharmacokinetics (PK) and pharmacodynamics (PD) of dasiglucagon. However, no subjects in this trial developed ADAs, and thus further PK/PD analysis could not be completed. The Applicant also provided ADA analyses from a pool of all dasiglucagon-exposed subjects where ADA assessments were performed (498 subjects, including trial 16136) that demonstrated an incidence of ADA formation of <1% (four ADA-positive subjects; one of these with neutralizing antibodies of no apparent clinical consequence). Based on the available data, the immunogenic potential of dasiglucagon appears low. Standard postmarket surveillance is appropriate to monitor the risk of immunogenicity.

If approved, dasiglucagon would be the first glucagon analog marketed for any indication, and therefore, we have not been afforded the opportunity for post-marketing experience with the class. Importantly, however, information presented in this submission indicates that the safety profile of dasiglucagon is consistent with the well-characterized safety profile of native glucagon. Standard surveillance is sufficient for general safety monitoring in the postmarket setting.

Overall, there is a favorable benefit-risk profile for dasiglucagon for the treatment of severe hypoglycemia in patients with diabetes mellitus aged six years and above, and I recommend approval of this NDA. The benefit of correction of neuroglycopenia expected with the clinically meaningful increase in plasma glucose, which is potentially life-saving, far outweighs temporary gastrointestinal intolerability and transient hemodynamic changes with limited clinical significance. The safety and effectiveness in children under 6 years of age have not been established, and a PREA PMR will be issued to study dasiglucagon in this age group.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe hypoglycemia is defined by the American Diabetes Association and the Endocrine Society as a hypoglycemic event requiring assistance of another person for recovery.[5] • Episodes may be associated with sufficient neuroglycopenia to induce seizure, coma, or death. The mortality rate reported in the literature from severe hypoglycemia in T1DM ranges from 4-10%.[5,6] The likelihood of a serious complication from a severe hypoglycemic episode increases with the duration and severity of neuroglycopenia. Therefore, the time to resolution of the event is of key clinical importance. • Severe hypoglycemia is more likely to occur in patients with T1DM than T2DM. Event rates for severe hypoglycemia for patients with T1DM range from 115 to 320 events per 100 patient-years.[5] Severe hypoglycemia in patients with T2DM has been shown to occur at rates of 35 to 70 events per 100 patient-years. In T2DM, hypoglycemia is more likely to occur in the context of treatment with a sulfonylurea or insulin.[7] • Certain persons with diabetes, such as those with poorly controlled diabetes, the elderly, and patients with lower socioeconomic status, are at increased risk of severe hypoglycemia.[8-10] Additionally, patients managing their diabetes with intensive insulin therapy with the goal of obtaining optimal glycemic control may be at increased risk of an event.[11]	Severe hypoglycemia in patients with diabetes mellitus is a medically serious condition that can be fatal if untreated. All patients with T1DM, and some patients with T2DM on antihyperglycemic agents, particularly insulin or insulin secretagogues, are at risk of experiencing an event. Certain vulnerable populations, such as patients of lower socioeconomic status and the elderly, are at increased risk. Additionally, severe hypoglycemia can be a barrier to obtaining optimal glycemic control for some patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Outpatient treatments for severe hypoglycemia include five approved native glucagon products that are marketed in various formulations, including glucagon for nasal inhalation and several injectable options. Of the injectable options, there is currently one marketed native glucagon that is available in a prefilled syringe and AI; all other glucagon products require reconstitution prior to administration. • Intravenous glucose can be administered by a healthcare professional.	As severe hypoglycemia typically occurs outside of a healthcare setting, currently approved rescue glucagon products are the main treatment options available at this time.
Benefit	• In two adult phase 3 trials (16137 and 17145) and one pediatric phase 3 trial (17086) designed to evaluate children ages ≥6 to <18, dasiglucagon demonstrated the ability to raise blood glucose levels significantly faster than placebo during an insulin-induced hypoglycemic clamp procedure. In the adult trials, the median time to glucose recovery was 10 minutes in the dasiglucagon groups, versus 35 to 40 minutes in the placebo groups. In the pediatric trial, the median time to glucose recovery was 10 minutes with dasiglucagon versus 30 minutes with placebo. These differences were statistically significant. • All subjects treated with dasiglucagon in adult trials 16137 and 17145 trials achieved glucose recovery within the pre-defined observation period (i.e., 45 minutes), with the exception of one adult patient (0.9%) who was administered rescue IV glucose approximately 10 minutes post-dose (see Subject (b) (6) for additional information regarding this subject). In contrast, ~72% of subjects in the placebo groups of the adult trials recovered within 45 minutes, and two (4%)	Dasiglucagon demonstrated the ability to increase blood glucose in adults and pediatrics with insulin-induced hypoglycemia. Availability in a prefilled syringe/AI that can be stored at room temperature offers additional benefits related to ease of administration, convenience, and potentially a faster time to administration and fewer medication errors as compared to glucagon products that require reconstitution. Children with T1DM using insulin therapy are at risk for severe hypoglycemia, and therefore a PREA PMR for children ages ≥1 to <6 will be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	received rescue IV glucose. Data from pediatric trial 17086 were similar; all pediatric subjects treated with dasiglucagon achieved glucose recovery within 45 minutes as compared to 64% of subjects achieving recovery in the placebo group. • Dasiglucagon will be available in a prefilled syringe/AI. It can be stored at room temperature for a period of up to 12 months. • Efficacy in children under age 6 has not been established.	
Risk and Risk Management	• The safety of dasiglucagon was evaluated in both adult and pediatric subjects. The most frequent treatment emergent adverse events in the safety database (i.e., the placebo-controlled pool) occurring in ≥2% of subjects were nausea, vomiting, headache, diarrhea, and injection site pain. • Hemodynamic events were observed at a low incidence (2.3%; broad pool analysis), which is in accordance with published literature and labeling for approved native glucagon products. • No subjects developed ADAs in immunogenicity trial 16136 and therefore the clinical consequence of ADA formation is unknown at this time. Nonetheless, the immunogenic potential of dasiglucagon appears low, with <1% (4 of 498 subjects) of dasiglucagon-exposed subjects having developed ADAs in the clinical development program. Loss of efficacy due to neutralizing antibodies is a theoretical concern at this time. • The development program was not designed to assess rare safety events. • The long-term safety, for example safety of repeated dosing over years, is unknown.	Nausea, vomiting, and diarrhea were observed in 57%, 25%, and 5% of subjects in the dasiglucagon group compared to 4%, 4% and 2% of subjects in the placebo group, respectively, in the placebo-controlled safety pool. Headache was also observed in 11% of dasiglucagon treated subjects as compared to 4% with placebo. All events were non-serious, transient, and generally resolved without intervention (some subjects received an antiemetic to treat nausea during trials). No adverse events lead to subject withdrawal from placebo-controlled studies, although withdrawal may be unexpected due to the single-dose trial design. Hemodynamic events (such as hypotension, hypertension, bradycardia, and presyncope) were also non-serious, transient, and generally resolved without intervention. Overall, while it is to be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		expected that about half of subjects will experience a gastrointestinal event, and a smaller number of subjects (~2%) may experience a hemodynamic event, based on the data presented in this application, events are expected to be transient without requiring intervention. Relevant safety information regarding the adverse events characterized in this application can be adequately communicated through product labeling. Standard postmarking surveillance appears appropriate for the monitoring of adverse reactions or potential immunogenicity-related events, such as loss of efficacy due to the development of ADAs or increased hypoglycemia due to neutralizing antibodies.

1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Severe hypoglycemia is defined by the American Diabetes Association and the Endocrine Society as an episode of hypoglycemia that causes neurological impairment and requires the assistance from another person to actively administer carbohydrates, glucagon, or take other corrective actions for recovery.[5] Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. Severe hypoglycemia is a medically significant and potentially life-threatening complication of diabetes treatment that, if left untreated, can lead to seizures, coma, or death. The mortality rate reported in the literature from severe hypoglycemia in T1DM ranges from 4-10%.[5,6]

In patients with diabetes mellitus, hypoglycemia is caused by imperfect insulin replacement, which is exacerbated by compromised counterregulatory hormone defects, including loss of glucagon response to hypoglycemia that may occur soon after diagnosis.[12] Current treatment options for severe hypoglycemia include intravenous dextrose, which requires administration by a medical professional in a healthcare setting, and administration of exogenous glucagon, which can be administered by a caregiver outside of a healthcare setting. As most events of severe hypoglycemia occur outside of a healthcare setting, administration of exogenous glucagon by a non-medical professional is the most common treatment for severe hypoglycemia.

Severe hypoglycemia occurs more frequently in patients with T1DM but can also occur in patients with T2DM taking antihyperglycemic agents, particularly insulin or insulin secretagogues. While event rates are not precisely established, severe hypoglycemia remains a relatively frequent complication of diabetes, ranging from 115 to 320 events per 100 patient-years in patients with T1DM.[5] In patients with T2DM, event rates range from 35 to 70 per 100 patient-years; however, because T2DM is much more prevalent than T1DM, severe hypoglycemia remains a significant problem.

Severe hypoglycemia is a barrier to obtaining optimal glycemic control and has been associated with increased morbidity and mortality in patients with diabetes.[13] As demonstrated by the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy in patients with T1DM aimed at achieving near-normal glucose levels is effective at reducing long-term microvascular complications (i.e., retinopathy, nephropathy, and neuropathy). Importantly however, the frequency of severe hypoglycemia and the subset of episodes involving coma or seizure were both threefold higher in the treatment arm undergoing intensive insulin therapy in the DCCT as compared to conventional therapy.[11] Underscoring the seriousness of these events, current American Diabetes Association Guidelines note that less stringent HbA1c goals

may be appropriate for patients with a history of severe hypoglycemia.[14] Additionally, fear of hypoglycemia has been shown to influence patients' adherence to prescribed treatment regimens leading to sub-optimal glycemic control, which could increase long-term complications due to diabetes.[15,16]

While all patients with T1DM and some patients with T2DM are at risk of experiencing severe hypoglycemia, certain populations are at increased risk for events. Young children who may not be able to communicate their symptoms and diabetes management needs, as well as patients with poor glycemic control, which is known to be pronounced during adolescence, may be at increased risk for experiencing an event.[10] In older adults with long-standing T1DM, greater hypoglycemia unawareness and glucose variability are associated with an increased risk of severe hypoglycemia.[8] Events in older adults may also have other serious consequences; for example, severe hypoglycemia has been associated with a higher risk of hip fractures, potentially due to falls during hypoglycemic events.[17] Low socioeconomic status has also been associated with increased incidence of severe hypoglycemia.[9]

In summary, severe hypoglycemia is a serious medical condition with significant impact on patient quality of life, morbidity, and mortality.

2.2. Analysis of Current Treatment Options

Currently available treatments for severe hypoglycemia are limited to intravenous dextrose, exogenous glucagon, or oral carbohydrates. Intravenous dextrose requires administration by trained personnel typically within a healthcare setting. As most events of severe hypoglycemia occur outside of a healthcare setting, and as patients with severe hypoglycemia are often unconscious and unable to consume carbohydrates safely, exogenous glucagon is the main treatment option because it can be administered by a caregiver in an outpatient setting. The goal of glucagon treatment is to increase blood glucose levels rapidly to the point where the patient regains sufficient cognitive function to consume oral carbohydrates safely. There are currently five approved glucagon products indicated for the treatment of severe hypoglycemia in patients with diabetes (Table 1). Of the five products, one product (Baqsimi) is administered intranasally, while all other treatments are administered via injection. Gvoke is the only glucagon injection available in a prefilled syringe/AI (the glucagon in Gvoke is stabilized in dimethyl sulfoxide (DMSO)). All other glucagon products for injection require reconstitution prior to use.

Table 1. FDA Approved Glucagon Treatments for Severe Hypoglycemia

Brand Name (NDA)	Manufacturer	Route of Administration	Formulation
Baqsimi (210134)	Eli Lilly	Intranasal	Powder
Gvoke (212097)	Xeris Pharmaceuticals	SC	Solution
GlucaGen (020918)	Novo Nordisk	SC, IM, IV	Powder for reconstitution
Glucagon (201849)	Fresenius Kabi	SC, IM, IV	Powder for reconstitution
Glucagon (020928)	Eli Lilly	SC, IM, IV	Powder for reconstitution

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dasiglucagon has not been previously approved for any indication. (b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

The following section outlines selected interactions between the Agency and the Applicant relevant to this NDA with a focus on areas related to the clinical development program.

PIND 127866

The Applicant submitted PIND 127866 on September 15, 2015 requesting discussion with the Agency regarding various aspects of the development program for dasiglucagon to support a future 505(b)(2) application. Prior to submission of PIND 127866, the Applicant completed a phase 1, first-in-human trial (14013) in the European Union (EU). In the PIND written feedback, FDA noted that dasiglucagon is considered a new molecular entity (NME) and therefore the Agency's previous findings of safety and/or effectiveness for other marketed native glucagon products is likely not appropriate to support a future 505(b)(2) application. Additionally, the Agency recommended that prior to initiating phase 3 studies, a PK/PD study be conducted to evaluate the PK/PD profile of dasiglucagon at a minimum of three dose levels (b) (4) (b) (4).

IND 127866 Opening Study

The Applicant submitted the IND for dasiglucagon on January 23, 2017. The IND opening study was a phase 3 trial to assess the immunogenicity of dasiglucagon (16136). In this submission, the Applicant provided information regarding two additional trials that have been completed in the EU: a phase 1 multiple dose trial in healthy subjects (15007) and a phase 2 dose-finding trial (15126) that was recommended by the Agency in PIND 127866. Several non-hold comments were provided to the Applicant in the safe to proceed letter, including a recommendation that hemodynamic events be considered as adverse events of special interest in the clinical development program.

Fast Track Designation Request

The Applicant submitted a request for Fast Track designation on January 23, 2017. The request was subsequently denied on April 13, 2017 on the basis that the clinical development program was not designed to evaluate whether the product would fulfill an unmet need for patients experiencing severe hypoglycemia compared to currently available glucagon therapies.

End-of-Phase 2 (EOP2) Meeting

An EOP2 meeting was held on June 29, 2017. Topics included the appropriateness of the proposed regulatory pathway as well as the adequacy of the CMC, nonclinical, and clinical documentation to support the proposed phase 3 clinical development program and an NDA for the (b) (4) indications pursued at that time (treatment of severe hypoglycemia (b) (4)). The following points summarize salient aspects from the EOP2 written feedback and/or discussion:

- Proposed Regulatory Pathway: The Agency reiterated that the 505(b)(2) pathway does not appear to be appropriate and strongly recommend the Applicant consider the 505(b)(1) pathway.
- Clinical Endpoint: The Agency requested the Applicant consider the clinical relevance the proposed endpoint (defined as plasma glucose concentration ≥70 mg/dL or a glucose increase of ≥20 mg/dL within 30 minutes after treatment) beyond the fact that other approved glucagon products may have used these cutoffs. FDA noted that a time to event (e.g. time to first increase of plasma glucose ≥20 mg/dL from baseline) primary endpoint may be more clinically relevant and meaningful given the life-threatening nature of severe hypoglycemia.
- Study Population: The Agency recommended that the Applicant enroll subjects with T1DM versus T2DM as the product is more likely to be used in this population, and this approach would avoid potential confounding of results with endogenous insulin production during the clamp study.
- Comparators: The Agency stated that it is not necessary from a regulatory or clinical standpoint for the Applicant to use GlucaGen as a comparator, and recommended the

Applicant consider a placebo-controlled trial.

- QT: FDA stated that the Applicant should evaluate the impact of dasiglucagon on QT prolongation.
- (b) (4)

Reviewer comment: The Applicant incorporated key FDA recommendations, such as the proposed endpoint, selection of a T1DM patient population, and comparison of dasiglucagon to placebo into their phase 3 studies.

Initial Pediatric Study Plan (iPSP)

The Applicant submitted the agreed iPSP Version 4.0 on May 29, 2018, which stated that dasiglucagon would be evaluated in pediatric patients down to 6 years of age for the initial NDA. The Applicant further stated that it was their intention to request a deferral until after approval of the NDA for the conduct of a pediatric trial for the age group ≥1 year to <6 years of age. The Applicant stated their intention to request a waiver in pediatric patients <1 year of age.

Pre-NDA Meeting

A pre-NDA meeting was held November 19, 2019. The following bullets summarize salient aspects from the pre-NDA written feedback and/or discussion:

- The Applicant and FDA agreed to proposed intrinsic and extrinsic factors for efficacy and safety subgroup analyses.
- The Applicant's proposed data pooling strategy was discussed. The Agency noted that it would not be appropriate to pool trials of different designs (parallel and crossover) and randomization ratios. Cochran Mantel Haenszel (CMH) weighting was discussed as an appropriate method to account for bias when combining studies of different randomization ratios (Simpson's paradox).

Reviewer comment: The Applicant has submitted information in this NDA per the agreements reached between the Agency and the Applicant in the pre-NDA meeting held November 19, 2019.

3.3. Foreign Regulatory Actions and Marketing History

Dasiglucagon is not currently marketed in any country.

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

4.1. Office of Scientific Investigations (OSI)

For details refer to the OSI review by Dr. Cynthia Kleppinger dated November 23, 2020.

Inspections were requested for the three phase 3 trials (16137, 17145, 17086) being used to support the safety and efficacy of this NDA. The inspection included two domestic sites (representing three clinical trial sites) in addition to the Applicant.

OSI identified regulatory deficiencies in one clinical site (AMCR Institute, site 005) with 23 enrolled pediatric subjects in 17086. At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for not always obtaining the permission of both parents as per 21 CFR 50.53. Twenty of the 36 screened subjects did not have parental consent from both parents prior to screening procedures (all subjects that underwent dosing at Visit 2 did have the consent of both parents prior to that procedure). The violation should not impact safety and efficacy analyses.

The inspection of the second domestic site (ProSciento, Inc., site 14 for trial 16137 and site 101 for trial 17145) revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

While onsite inspections occurred at both domestic sites, the COVID-19 global pandemic limited the Office of Regulatory Affairs' ability to conduct a foreign onsite good clinical practice (GCP) inspection for the Applicant site located in Denmark. As a result, a remote regulatory assessment of Zealand Pharma source records was performed. The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Overall, based on the inspections of the two domestic clinical sites and the remote regulatory assessment of the Applicant foreign site, the inspectional findings support validity of data as reported by the Applicant under this NDA.

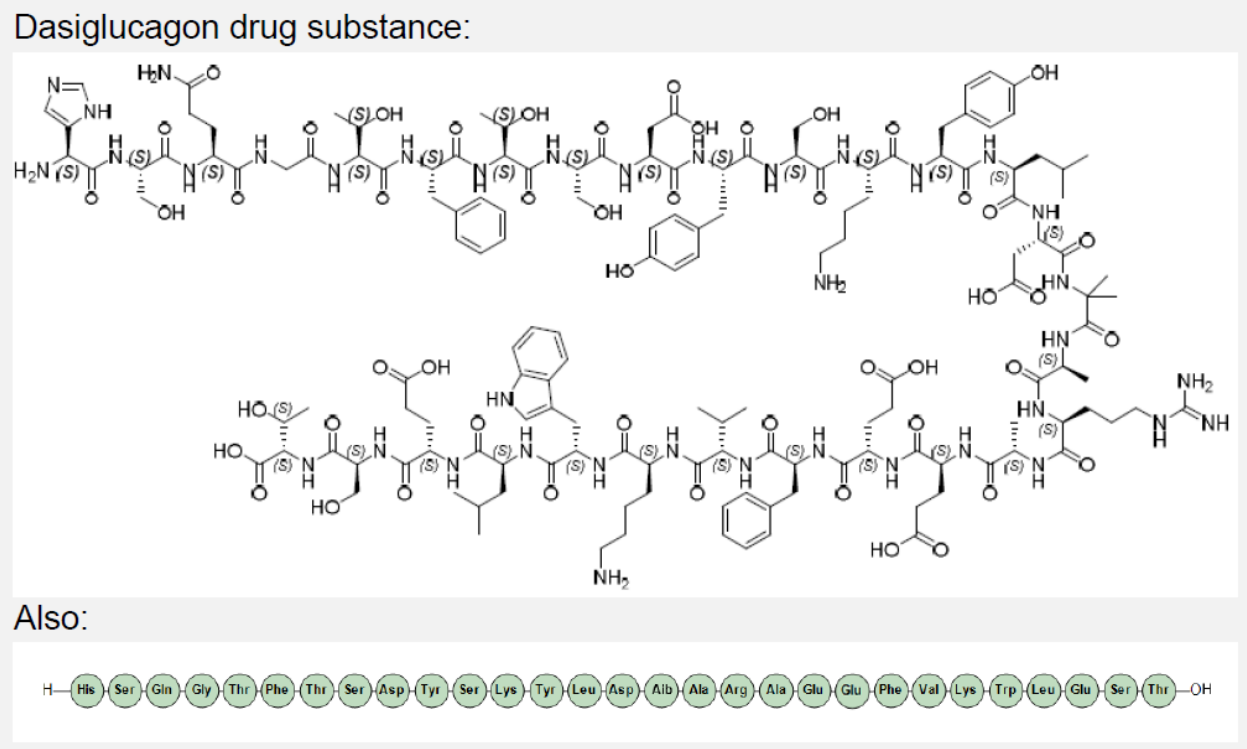
4.2. Product Quality

For details refer to the Office of Product Quality (OPQ) review by Dr. Muthukumar Ramaswamy dated November 27, 2020.

Drug Substance

Dasiglucagon is a synthetic 29-amino acid peptide (Figure 1). The molecular formula and molecular weight are $C_{152}H_{222}N_{38}O_{50}$ and 3381.6 g/mol (mean mass), respectively. Dasiglucagon is an amorphous powder and is freely soluble in water. Dasiglucagon is synthesized by (b) (4) (b) (4)

Figure 1. Chemical Structure of Dasiglucagon



Source: Quality review memorandum

Drug Product

The proposed drug product, dasiglucagon injection, 0.6 mg/0.6 mL is a clear, colorless, sterile, aqueous solution packaged in a 1.0 mL single-dose prefilled syringe or autoinjector. Each mL contains 1.0 mg of dasiglucagon (provided as dasiglucagon hydrochloride) solubilized in (b) (4) tromethamine (tris buffer), sodium chloride, and water for injection. The final pH of the formulation is adjusted with hydrochloric acid or sodium hydroxide to 6.5. The composition of the proposed commercial product is the same as the one used during phase 3 trials.

Microbiology

The microbiological controls used in the drug product manufacturing process, including (b) (4) (b) (4) drug product specifications for sterility, container closure integrity, endotoxin, (b) (4)

validation, depyrogenation and component sterilization, media fill studies, hold times, and post-approval stability commitments, were reviewed. The proposed microbiological controls were concluded to be adequate to support the NDA.

Expiration Date & Storage Conditions

The application contains up to 36 months of long-term stability data (5°C/60% RH), 12 months of long-term stability data (25°C/60% RH), and three months of accelerated stability data (40°C/65% RH) for six stability batches manufactured at (b) (4) L scale. The product is sensitive to light and should not be frozen. Based on available stability data, an expiration period of 36 months will be granted when the product is stored at 2°C to 8°C (36°F to 46°F). During the 36-month period, the drug product can be stored at room temperature (25°C, 77°F) for a single period of up to 12 months in the protective case (referred to as 'dual storage conditions'). In the labeling, patients will be instructed to record the date when the product was removed from the refrigerator in the space provided on the protective case and discard the product either after 12 months at room temperature or after the expiration date stated on the product, whichever occurs first.

Unlike glucagon, dasiglucagon is relatively stable to agitation stress and does not fibrillate (b) (4)

4.3. Clinical Microbiology

Refer to the product quality review in section 4.2.

4.4. Nonclinical Pharmacology/Toxicology

For details refer to the Pharmacology/Toxicology review by Dr. Patricia Brundage dated November 23, 2020.

Pharmacology

Dasiglucagon exhibited comparable in vitro potency to native glucagon with regard to glucagon receptor agonism in humans and nonclinical species. The absence of activity at any of the 239 G-protein coupled receptors evaluated suggests a lack of off-target activity. In the rat, dog, and rabbit, single SC doses of dasiglucagon induced increases in blood glucose, similar to glucagon. Safety pharmacology studies assessing the effects of single SC doses of dasiglucagon on cardiovascular, neurological, and respiratory function did not identify any significant clinical safety concerns. Dasiglucagon caused tachycardia in dogs at clinically relevant exposures (1X clinical exposure; C_{max} basis); however, this finding is in accordance with established positive

inotropic and chronotropic effects of glucagon receptor agonism. In vitro evaluation of eight human cardiac ion channels (including hERG) indicated that dasiglucagon has a low potential for QT prolongation in vivo.

Toxicology

Repeat-dose studies were conducted in Crl:CD1(ICR) mice for up to 13 weeks (3 months), Wistar rats for up to 26 weeks (6 months) and beagle dogs for up to 39 weeks (9 months) duration. As no single-dose SC toxicity studies were conducted, the 28-day toxicity studies in the rat and dog are considered the pivotal studies for the proposed acute use for the treatment of severe hypoglycemia.

In the rat and the dog, dasiglucagon caused treatment-related effects in the heart, gastrointestinal system (dog only), kidney, and liver, which are attributable to the pharmacodynamic activity of the drug due to the expression of glucagon receptors in these organs. Transient freezing absences, in which animals go into a sleeping-like state and remain either motionless or exhibit a slow movement towards a resting place, were observed in rats following repeated daily dosing, and increased in frequency with dose. The transient freezing absences occurred within an hour after dosing and appeared to be related to the peak plasma exposures of dasiglucagon. A NOAEL of 0.05 mg/kg/day (1X [adults] and 2X [children] clinical exposure; C_{max} basis) was established for the transient freezing absences in a 28-day follow-up study in rats with 0.25 mg/kg/day (8X [adults] and 10X [children] clinical exposure; C_{max} basis) eliciting sporadic transient freezing absences after six days of daily dosing. Native glucagon (5 mg/kg) was shown to elicit similar freezing absences indicating that the freezing absences are likely related to glucagon receptor agonism. Additionally, dasiglucagon did not elicit transient freezing absences, or similar findings in the mouse, rabbit, or dog, and similar findings have not been observed clinically. Overall, as freezing episodes were only observed upon repeat dosing in rats, episodes were also observed with native glucagon, and as these findings have not been observed in the clinical development program for dasiglucagon, which included doses of dasiglucagon up to 2.0 mg, additional monitoring in the postmarket setting for these events does not appear warranted.

Reproductive and developmental toxicity were assessed in fertility and embryonic and fetal development animal studies. Dasiglucagon had no effects on reproductive performance or fertility indices in male and female rats at exposures up to 364 to 625 times clinical exposure. Dasiglucagon was not teratogenic in the rat at doses up to the high dose of 24 mg/kg/day (709X clinical exposure) or in rabbits at the low dose (7X clinical exposure). Additionally, dasiglucagon was not found to be mutagenic or clastogenic. Carcinogenicity studies were not required to support this application. See Dr. Brundage's nonclinical review for additional details.

4.5. Clinical Pharmacology

For details refer to the Clinical Pharmacology review by Dr. Johnny Lau dated December 10, 2020.

Overview

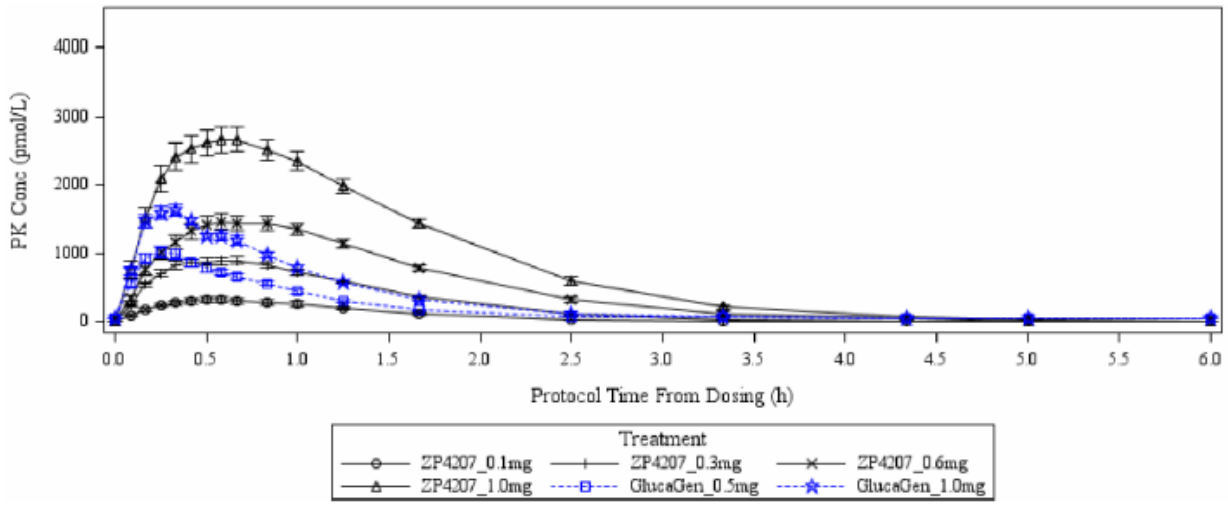
The following trials provide information relevant to the clinical pharmacology assessment of dasiglucagon: 15126, 16137, 17145, 17086, and 17084 (see Table 2 for a summary of each trial). Salient aspects of the clinical pharmacology program per the Applicant and Dr. Lau's review are summarized below.

Dose-Finding Trial 15126

The phase 2 dose finding trial 15126 was a randomized, double-blind evaluation of single doses of dasiglucagon and GlucaGen administered to subjects with T1DM with insulin-induced hypoglycemia in a clamp procedure. This trial characterized the PK/PD properties of a single SC dose of 0.1, 0.3, 0.6, and 1.0 mg dasiglucagon and 0.5 and 1.0 mg GlucaGen. This trial also assessed dose proportionality of dasiglucagon between 0.1 to 1.0 mg.

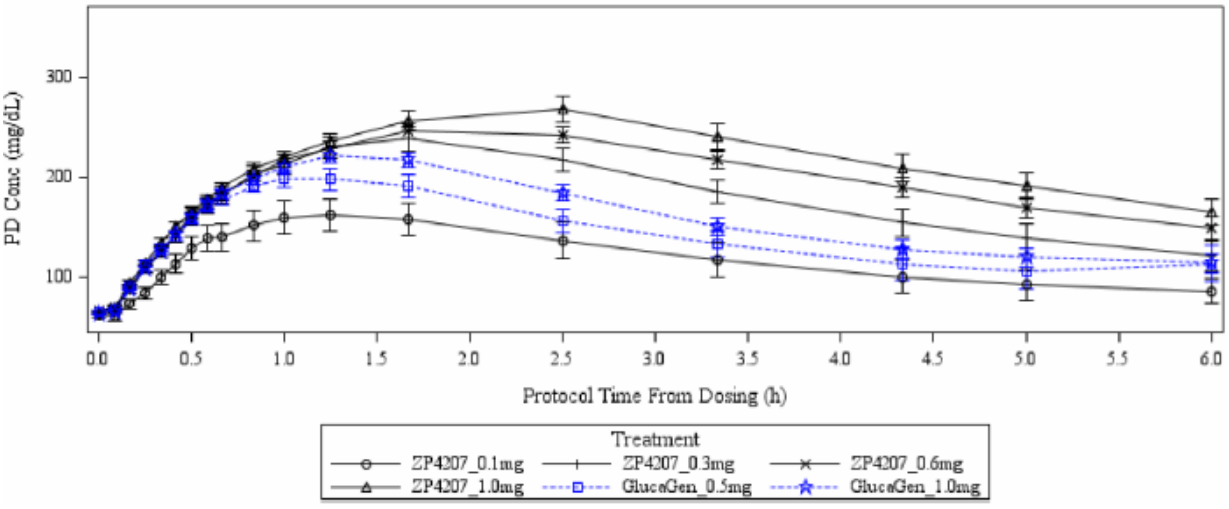
Figures 2 and 3 demonstrate the PK and PD characterization, respectively, in trial 15126. The PK profiles in Figure 2 show an increase in plasma dasiglucagon concentrations upon SC administration, with a 0.6 mg dose (the proposed to-be-marketed dose) of dasiglucagon demonstrating a C_{max} of 1570 pM (mean) and a t_{max} of 35 minutes (median). Figure 3 shows the PD data for the different doses of dasiglucagon and GlucaGen. The 0.6 mg dasiglucagon dose exhibited similar PD properties to 1.0 mg GlucaGen (e.g., $AUE_{0\text{-}30min}$ of 21.1 and 21.9 mg*h/dL for 0.6 mg dasiglucagon and 1.0 mg GlucaGen, respectively). Trial 15126 also demonstrated that PK is dose-proportional between 0.1 mg – 1 mg (see Tables 6-8 of Dr. Lau's memorandum for additional information regarding PK/PD characterization in 15126).

Figure 2. Plasma Concentration Profiles Following Single SC Doses of Dasiglucagon and GlucaGen – Trial 15126



Abbreviations: ZP4207: dasiglucagon
Source: Trial 15126's report Figure 14.2.2.3.2

Figure 3. Plasma Glucose Concentration Profiles Following Single SC Doses of Dasiglucagon and GlucaGen – Trial 15126



Abbreviations: ZP4207: dasiglucagon
Source: Trial 15126's report Figure 14.2.4.3.2

PK and PD Characterization – Phase 3 Trials Supporting Efficacy and Safety

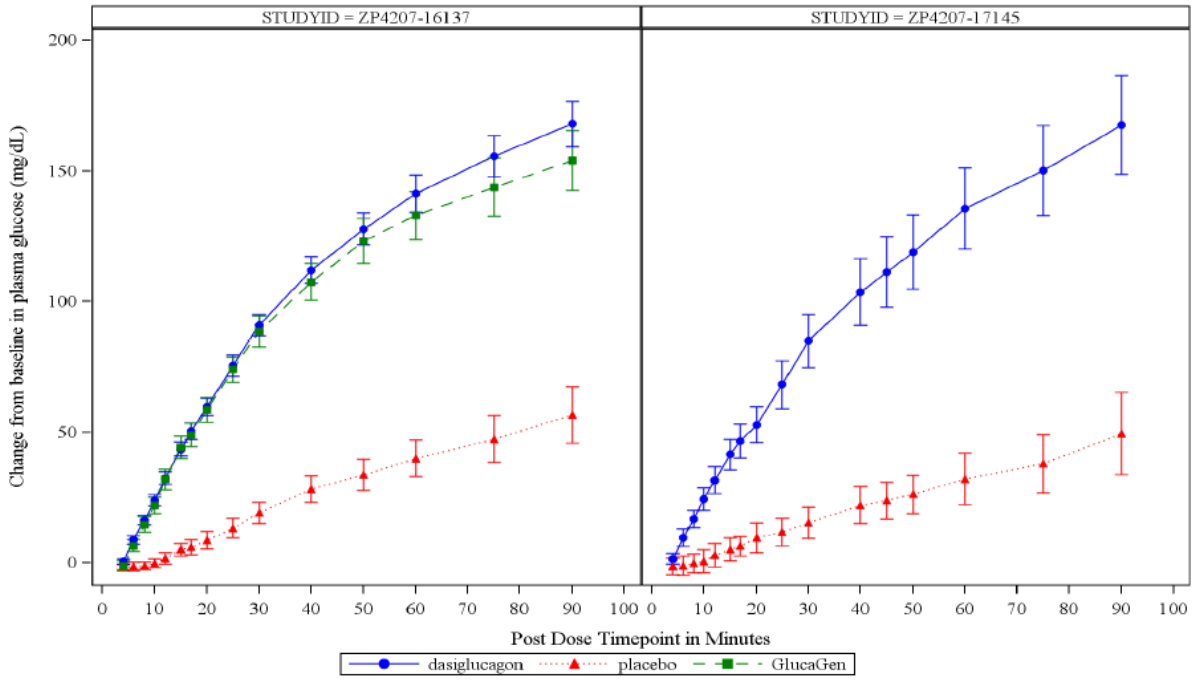
The phase 3 studies that are being used to support efficacy and safety conducted in adults (16137 and 17145) and pediatrics (17086) with T1DM incorporated PK/PD assessments at the following timepoints (see 6.1, 6.2, and 6.3 for additional information on trials 16137, 17145, and 17086, respectively):

- PD:
  - 16137 and 17145: pre-dose and 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 50, 60, 75, and 90 minutes post-dose
  - 17086: pre-dose and 4, 6, 8, 10, 12, 15, 17, 20, 30, 45, and 60 minutes post-dose
- PK:
  - 16137 and 17145: pre-dose and 15, 30, 35, 40, 50, 60, 90, and 120 minutes post-dose
  - 17086: pre-dose and 10, 20, 30, 40, 60, 90, 140, 220, and 300 minutes post-dose

PK data from adult trials were similar, with dasiglucagon demonstrating a C_{max} of 1280 pM and 1350 pM (geometric mean) and a t_{max} of 40 minutes and 35 minutes (median) in trials 16137 and 17145, respectively. $AUC_{0\text{-}90min}$ was also comparable between trials ($AUC_{0\text{-}90min}$ of 1430 and 1480 pmol*h/L (geometric mean) in 16137 and 17145, respectively). Various PK parameters were also comparable between adults and pediatrics, with trial 17086 demonstrating a C_{max} of 1160 pM (geometric mean) and a t_{max} of 21 minutes (median).

Regarding PD, the mean plasma glucose concentration is shown as change from baseline as a function of time for trials 16137 (Figure 4, left panel) and 17145 (Figure 4, right panel). Because these figures are derived using data from the controlled trials, the placebo data (in red) for both trials and the GlucaGen data (in green) for trial 16137 are also plotted with the dasiglucagon data in blue. The increase in plasma glucose due to dasiglucagon as compared to placebo is evident as early as five minutes post dose and maintained throughout the observation period of 90 minutes. The glucose excursion in the dasiglucagon group is similar to the glucose excursion in the GlucaGen group. These data are discussed in more detail in section 6 given the various secondary PD endpoints included in these trials (e.g., glucose change from baseline at certain time points).

Figure 4. Mean Plasma Glucose Change from Baseline (FAS) – Trials 16137 and 17145



Source: Applicant's ISE

Population PK Modeling

The Applicant performed population PK modeling to quantify the impact of specific covariates (renal function, weight, injection site, and age) on the PK of dasiglucagon in order to characterize between-subject variability. The covariate analysis was based on data from phase 2 and phase 3 trials (15126, 16136, 16137, 17145, 17084 and 17086). Population PK analysis and simulations showed that the AUC ratio 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. Body weight was observed to be the main covariate affecting dasiglucagon exposure (simulated estimated AUC ratios of 1.22 and 0.83 for a subject weighting 60 and 100 kg, respectively, compared to a typical male or female aged ≥ 24 years weighing 78 kg). Importantly however, the PK/PD and efficacy data from phase 3 clinical trials support that the proposed single 0.6 mg SC dose provides adequate efficacy for the broad body weight range in patients 6 years and above (for example, body weight in pediatric trial ranged from 21-117 kg in dasiglucagon-exposed subjects, with all subjects having achieved plasma glucose recovery within 20 minutes). Per Dr. Lau's memorandum, no dose adjustment is necessary for age, gender, body weight, race, organ impairment, injection site, or drug interaction.

Bridging Trial 17084 and Dual Storage Conditions

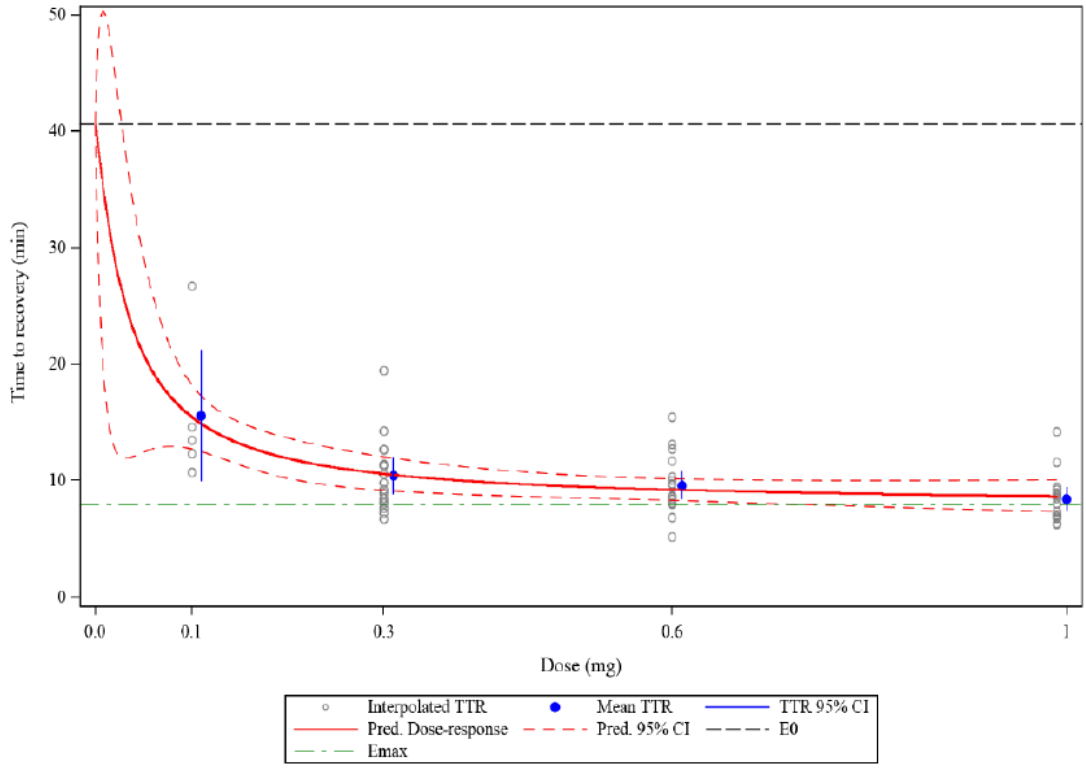
The Applicant developed dasiglucagon to be stored either under refrigeration (2°C to 8°C) or at room temperature (25°C), referred to in this review as 'dual storage conditions.' To support these storage conditions, the Applicant performed bridging trial 17084 (described below), which evaluated a batch of dasiglucagon stored under the proposed dual storage condition as compared to a batch stored solely under refrigeration. Additionally, (b) (4) the Applicant has proposed a shelf-life specification (b) (4) As the proposed dose of dasiglucagon is 0.6 mg, (b) (4)

Bridging trial 17084 was a phase 3, randomized, double-blind, crossover trial in patients with T1DM evaluating the efficacy and safety of single doses of two dasiglucagon batches. The trial compared a dasiglucagon batch reflecting storage under the intended dual storage conditions (Batch B) with a batch stored under refrigerated conditions (Batch A; representative of dasiglucagon tested in the rest of the clinical program). Compared to a drug content of 0.6 mg in Batch A, Batch B had a drug content of approximately (b) (4) mg dasiglucagon. Results for the primary per protocol analysis showed a difference in mean time to plasma glucose recovery for Batch B versus Batch A of 0.40 minutes (95% CI: -0.08 to 0.88), equivalent to a 24 second delay in plasma glucose recovery (See Dr. Yoonhee Kim's statistical review for additional information regarding the non-inferiority analysis for this trial).

Additionally, (b) (4) the applicant developed a model evaluating dasiglucagon dose and time to plasma glucose recovery per dose finding trial 15126 (Figure 5). Based on this modeling, a dose of 0.40 mg dasiglucagon delays time to glucose recovery by approximately 40.8 seconds [-0.76, 2.12 minutes]. Note, the 95% CI for the predicted recovery time includes zero indicating that this result is not statistically significant. As shown in Figure 5, doses >0.3 mg dasiglucagon near the E_{max} of dasiglucagon (green dotted line).

Reviewer comment: While any delay in the treatment of severe hypoglycemia is not desirable, the ability to store dasiglucagon under refrigeration and at room temperature (dual storage conditions) provides patients and caregivers portable and convenient access to dasiglucagon. The potential small increase (point estimates of 24-40 seconds with 95% CIs that include zero) in time to plasma glucose recovery associated with the proposed dual storage conditions seems acceptable in the context of enabling immediate access to this potentially life-saving treatment.

Figure 5. Model Prediction of Mean Time to Glucose Recovery as a Function of Dasiglucagon Dose - Trial 15126



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

4.6. Devices and Companion Diagnostic Issues

For details refer to the Center for Devices and Radiological Health (CDRH) review by Dr. David Wolloscheck and OPQ review by Dr. Muthukumar Ramaswamy dated November 27, 2020. Furthermore, see the Division of Medication Error Prevention and Analysis (DMEPA) reviews of labelling and human factors (HF) results by Dr. Colleen Little dated December 11, 2020.

Dasiglucagon is supplied in two presentations, a prefilled syringe and AI, and is therefore a combination product (Figure 6). Per CDRH's review, no approvability issues were identified regarding the device component of this combination product. Importantly however, the final commercial AI assembly has not been fully validated as two modifications were made to the assembly line after it was validated for the manufacturing of clinical batches of the AI. (b) (4)

As this is a high-risk, emergency use device, CDRH recommends a post-approval inspection to evaluate the final commercial AI assembly validation.

Figure 6. Prefilled Syringe (Top) and Autoinjector Devices (Bottom)

Source: M.2.3.P.7

Regarding the review of the results of the HF validation study, DMEPA identified use errors with some critical tasks. For example, in the HF validation for the AI device, there were three use errors related to administration into an incorrect injection site (e.g. forearm, lower back), two use errors where the user did not expose bare skin and injected through clothing, and five use errors related to removal of the AI prior to full dose delivery. Nonetheless, DMEPA notes that, taking into consideration the review of the subjective feedback, root cause analysis, and their independent review of similar currently approved products, they find residual risks associated with these use errors acceptable. Thus, DMEPA accepts the HF validation study results. Additionally, DMEPA has provided labeling recommendations (see Tables 5 and A in DMEPA's review memorandum) to address the findings observed in the HF validation and provide additional mitigations for potential use errors.

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Dasiglucagon for the treatment of severe hypoglycemia was evaluated in nine clinical trials (Table 2).

Table 2. Listing of Clinical Trials in the Dasiglucagon Clinical Development Program for Severe Hypoglycemia

Trial ID	Description	Design (Glycemic status at dosing)	Dosing (Randomization)	Trial Endpoints	No. of subjects completed	Trial Population
Trials to Support Safety and Efficacy						
16137	A phase 3, randomized, double-blind, trial to confirm the efficacy and safety of dasiglucagon for the treatment of hypoglycemia compared to placebo and with GlucaGen as a reference treatment arm.	Parallel (hypoglycemic clamp)	Single SC dose of 0.6 mg dasiglucagon, placebo, or 1 mg GlucaGen (2:1:1)	Time to plasma glucose recovery	168	Adults with T1DM
17145	A phase 3, randomized, double-blind trial to confirm the efficacy and safety of dasiglucagon vs. placebo.	Parallel (hypoglycemic clamp)	Single SC dose of 0.6 mg dasiglucagon or placebo (3:1)	Time to plasma glucose recovery	44	Adults with T1DM
17086	A phase 3, randomized, double-blind, trial to confirm the efficacy and safety of dasiglucagon for the treatment of hypoglycemia compared to placebo and with GlucaGen as a reference treatment arm.	Parallel (hypoglycemic clamp)	Single SC dose of 0.6 mg dasiglucagon, placebo, or 1 mg GlucaGen (2:1:1)	Time to plasma glucose recovery	41	Pediatrics with T1DM (≥6 to <18 years)
Supportive Trials to Support Safety and/or Efficacy						
16136	**Immunogenicity** - A phase 3, randomized, double-blind, safety trial to evaluate the immunogenicity of dasiglucagon and GlucaGen.	Parallel (euglycemic conditions)	Three single SC doses (given 7±1 days apart) of 0.6 mg dasiglucagon or 1 mg GlucaGen (1:1)	ADA Incidence	111	Adults with T1DM

17084	**Bridging** - A phase 3, randomized, double-blind trial evaluating the efficacy and safety of single doses of two dasiglucagon batches. The trial compared a dasiglucagon batch reflecting storage under the intended dual storage conditions (Batch B) with a batch stored under refrigerated conditions (Batch A; representative of dasiglucagon tested in the rest of the clinical program).	Crossover (hypoglycemic clamp)	Single SC dose of 0.6 mg dasiglucagon (Batch A) and 0.6 mg dasiglucagon (Batch B) (1:1)	Time to plasma glucose recovery	90	Adults with T1DM
15126	**Dose Finding** - A phase 2, randomized, double-blind trial of single doses of dasiglucagon to enable dose-finding and to describe the PK/PD of dasiglucagon vs. GlucaGen.	Parallel/crossover (hypoglycemic clamp)	Single SC dose of 0.1, 0.3, 0.6 or 1.0 mg dasiglucagon and 0.5 or 1.0 mg GlucaGen	PK/PD and Safety endpoints	58	Adults with T1DM
17144	**IV/QTc Trial** – A phase 1, randomized, double-blind, placebo-controlled, trial to evaluate the impact of dasiglucagon on cardiac repolarization.	Ascending dose (euglycemic conditions)	Single IV dose of 0.03, 0.1, 0.3, 0.6, or 1.5 mg dasiglucagon or placebo, or single SC dose of 0.6 mg dasiglucagon	Safety Endpoints	60	Healthy Subjects
15007	**Ascending Dose Trial** - A phase 2b, randomized, placebo-controlled, double-blind trial of multiple ascending doses of dasiglucagon to evaluate the safety, tolerability, PK, and PD of dasiglucagon.	Ascending dose (euglycemic conditions)	5 consecutive SC daily doses of 0.1, 0.3 or 1.0 mg dasiglucagon or placebo (3:1)	PK/PD and Safety endpoints	24	Healthy Subjects
14013	**First in Human** – A phase 1, randomized, double-blind trial of single ascending doses of dasiglucagon administered SC or IM (Part 1) and a single dose of dasiglucagon administered IM (Part 2) to evaluate the safety, tolerability, PK and PD of dasiglucagon as compared to GlucaGen.	Part 1: Ascending dose (euglycemic conditions) Part 2: Crossover (hypoglycemic clamp)	Part 1: Single SC doses of 0.01, 0.1, 0.3, 1.0, or 2.0 mg dasiglucagon or 1.0 mg GlucaGen (3:1). Single IM doses of 0.3, 1.0 or 2.0 mg dasiglucagon or 1.0 mg GlucaGen (3:1) Part 2: Single IM dose of 0.7 mg dasiglucagon and 1.0 mg GlucaGen	PK/PD and Safety endpoints	Part 1: 48 Part 2: 20	Part 1: Healthy Subjects Part 2: Adults with T1DM

5.2. Review Strategy

Three adequate and well-controlled trials conducted in subjects with T1DM provide substantial evidence of effectiveness for the pursued hypoglycemia indication: two trials in adults (16137 and 17145) and one trial in pediatrics (17086). Supportive trials include a dose-finding trial (15126) to support dose selection and a bridging trial (17084) to support efficacy and safety of dasiglucagon when stored under 'dual storage conditions' (see section 4.2 of this memo) as compared to dasiglucagon when stored under refrigerated conditions (of note, the dasiglucagon used in the trials 16137, 17145, and 17086 was stored under refrigerated conditions). Additional information for trials 15126 and 17084 can be found in section 4.5 of this memo, as well as Dr. Johnny Lau's clinical pharmacology review and Dr. Yoonhee Kim's statistical review.

Other trials completed in the clinical development program for dasiglucagon for the treatment of severe hypoglycemia were not utilized to support efficacy because they were either not conducted in the intended patient population, did not use the to-be-marketed formulation of dasiglucagon, and/or did not incorporate frequent post-dose blood sampling to allow for an evaluation of efficacy.

The primary safety analysis presented in this review is based on an analysis of a pooled dataset comprised of the placebo-controlled, adult phase 3 trials (16137 and 17145) that were also used to support efficacy, referred to herein as the 'placebo-controlled pool.' The pediatric safety evaluation derived from trial 17086 is assessed and presented separately.

To further assess safety, a secondary pool, referred to as the 'broad pool,' was created with all available data from studies conducted in adult subjects with T1DM exposed to dasiglucagon at doses ≥0.6 mg. While trials included in the broad pool enrolled a similar patient population (adults with T1DM), individual studies differed significantly (see Table 2 and Figure 14 for additional information on trials included in the broad pool). Additionally, there were no additional placebo-controlled data in the broad pool as compared to the placebo-controlled pool. Therefore, safety analyses conducted with the broad pool were used mainly for supportive and exploratory purposes.

Additional supportive safety data are presented from trials enrolling healthy subjects in the development program of dasiglucagon for the treatment of severe hypoglycemia and from trials completed for other indications (b) (4) where appropriate. See section 8.1 for additional details regarding the safety review approach.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial 16137

Overview and Objectives

Trial 16137 was a phase 3 efficacy and safety trial designed to evaluate dasiglucagon for treatment of severe hypoglycemia in patients with T1DM. The primary objective was to demonstrate superiority of 0.6 mg dasiglucagon compared to placebo on time to plasma glucose recovery in subjects with T1DM with insulin-induced hypoglycemia. The secondary objective of this trial was to compare the glycemic response observed after dasiglucagon with that of GlucaGen.

Trial Design Overview

Trial 16137 was a global, multicenter, randomized, parallel, blinded (specified below) clinical trial. Subjects were randomized 2:1:1 to receive dasiglucagon, placebo, or GlucaGen, respectively, by prefilled syringe. Subjects underwent a screening visit, a dosing visit, and a follow-up safety visit approximately 28 days post-dosing. The trial was conducted at five trial sites; two in Germany and one each in Austria, Canada, and the US. Randomization was stratified by injection site (abdomen, buttock, or thigh).

Dosing Regimen

Randomized subjects received one of the following investigational medical products (IMPs):

- Dasiglucagon, liquid formulation, 0.6 mg in 0.6 mL
- Placebo, liquid formulation, 0.6 mL
- GlucaGen (Novo Nordisk), 1 mg in 1 mL sterile water

Study Visits

Trial 16137 included three study visits (screening, dosing, and follow-up) as summarized below and displayed in Figure 7.

1. Screening Visit: A screening visit occurred between 30 and 3 days prior to the dosing visit. Subjects were assessed for inclusion/exclusion criteria and completed informed consent. Safety assessments (physical examination, routine chemistry and hematology labs, urinalysis, vital signs, ECGs, etc.) were completed. The subject's demography and medical history (concomitant illness/medications, diabetes history, etc.) were recorded. The investigator provided information to subjects regarding washout of his/her current insulin therapy, which was required leading up to the scheduled dosing day.

2. Dosing Visit: After an overnight stay in a study center intended to target a morning blood glucose level of 90-110 mg/dL, subjects were assessed for dosing-day exclusion criteria. A hypoglycemic clamp was initiated with an IV infusion of insulin glulisine (Apidra) to achieve a controlled decline in plasma glucose, targeting a plasma glucose level of 55 mg/dL. Once the glucose concentration declined to <60 mg/dL, the insulin infusion was stopped, and a baseline assessment of plasma glucose occurred approximately 5 minutes later. If plasma glucose was ≥45 mg/dL and <60 mg/dL, the IMP (i.e., dasiglucagon, GlucaGen, or placebo) was administered, defining time t=0 minutes. If plasma glucose was <45 mg/dL, IV glucose could be administered to raise plasma glucose to within the ≥45 to <60 mg/dL target range, and the run-in period was extended at least 30 minutes until the target glucose was achieved (glucose infusion was stopped at least 10 minutes prior to IMP administration). If a plasma glucose between ≥45 mg/dL and <60 mg/dL could not be achieved on the second attempt, the subject was rescheduled for a new treatment visit within 7 days (+ 2 days).

   The IMP was delivered in the abdomen, buttock, or thigh (according to stratification) via SC injection. The trial was double-blind (blinded to subject and to the analysis personnel) to increase trial validity and to reduce bias during evaluation of the treatments. Since the trial medications were not identical in appearance, the handling, preparation, and administration of trial medication was done by unblinded trial personnel who were not involved in any other trial procedures or assessments.

   Plasma glucose samples for efficacy evaluation were collected pre-dose, and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 50, 60, 75 and 90 minutes after dosing. The actual time of blood sampling for evaluation of plasma glucose was to not deviate from the nominal time by more than ± 30 seconds until the 20-minute collection time point and by more than ±1 minute for the subsequent collection time points. Pre-dose was defined as within 2 minutes prior to dosing. PK was assessed from samples collected pre-dose, and at 15, 30, 35, 40, 50, 60, 90, and 120 minutes post-dose.

   During insulin-induced hypoglycemia, plasma glucose levels were monitored closely, and subjects were to receive post-treatment rescue glucose IV infusion to ameliorate persistent hypoglycemia if one of the following criteria were met: if a subject experienced severe alarming escalation of symptoms of hypoglycemia (e.g., symptoms suggesting a change in consciousness), if plasma glucose was <45 mg/dL between t=8 and t=44 minutes, or if plasma glucose was <70 mg/dL at t=45 minutes.

3. Follow up Safety Visit: Subjects completed a follow up visit 28 ± 5 days post dosing day. Safety assessments (physical examination, routine chemistry and hematology labs, urinalysis, vital signs, ECGs, etc.) were completed. Blood was collected for the assessment of anti-drug antibodies (ADAs).

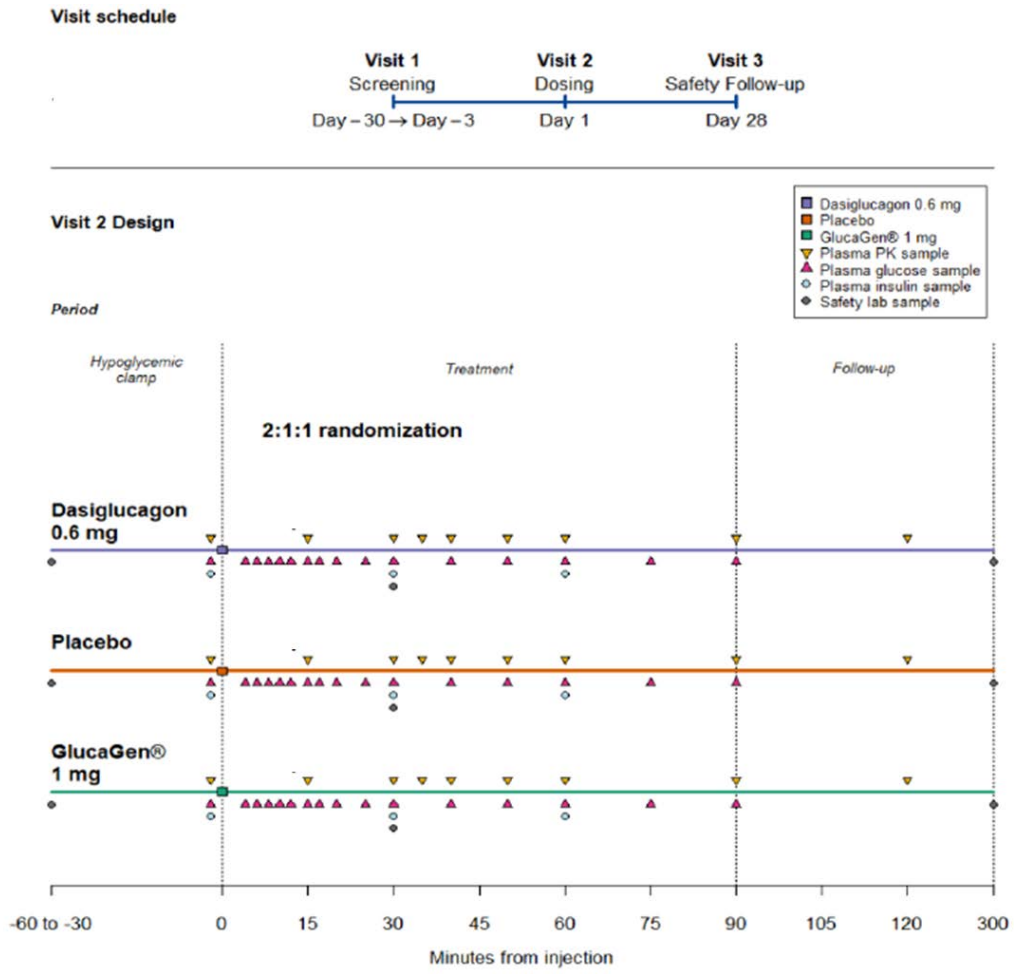


Figure 7. Overview of 16137 Trial Design
Source: Modified from ZP4207-16137 Study Report Body

Inclusion Criteria (summarized):

1. Informed consent was obtained
2. Female or male subject with T1DM for at least one year
3. Treated with insulin for T1DM for at least one year and with stable insulin treatment (defined as no more than a 10-unit daily variation in total daily insulin dose) 30 days prior to screening
4. HbA1c <10%
5. Aged between 18 and 75 years (inclusive)
6. Female and male subjects on appropriate contraception

Exclusion Criteria (summarized)

1. Previously treated with dasiglucagon
2. Known or suspected allergy to trial product(s) or related products
3. History of anaphylaxis or symptoms of severe systemic allergy (such as angioedema)
4. Previous participation (randomization) in this trial
5. Females who were pregnant, actively attempting to get pregnant, or were lactating
6. History of hypoglycemic events associated with seizures 12 months prior to screening
7. History of severe hypoglycemia (defined as plasma glucose <54 mg/dL) 30 days prior to screening
8. Receipt of any investigational drug within 3 months prior to screening
9. Active malignancy within the last 5 years
10. Congestive heart failure, New York Heart Association Class II-IV
11. Inadequately treated blood pressure, defined as systolic pressure ≥160 mmHg or diastolic pressure (DBP) ≥90 mmHg, at screening
12. Current bleeding disorder, including anti-coagulant treatment
13. Known presence or history of pheochromocytoma or insulinoma
14. Use of a daily systemic beta-blocker drug, indomethacin, warfarin or anticholinergic drugs in the previous 28 days before Day 1 of this trial
15. AST or ALT >2.5 × the upper limit of the normal range (ULN), bilirubin >1.5 × ULN, eGFR <30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease study definition, or altered electrolyte values of clinical relevance for cardiac conduction, as judged by the investigator
16. Clinically significant abnormal ECG at screening as judged by the investigator
17. Clinically significant illness within 4 weeks before screening, as judged by the investigator
18. Donation of blood or plasma in the past month, or in excess of 500 mL within 12 weeks prior to screening
19. Surgery or trauma with significant blood loss within the last 2 months prior to screening
20. A positive result in the alcohol and/or urine drug screen at the screening visit. Significant history of alcoholism or drug abuse
21. Subjects with mental incapacity or language barriers which preclude adequate understanding or cooperation, who are unwilling to participate in the trial, or who in the opinion of the investigator, should not participate in the trial
22. Any condition interfering with trial participation or evaluation or that could be hazardous to the subject
23. The use of prescription or non-prescription medications known to cause QT prolongation

Reviewer comment: The Applicant implemented several exclusion criteria that were likely

unnecessary such as excluding subjects with a history of malignancy (#9), subjects with congestive heart failure (#10), or subjects with inadequately treated high blood pressure (#11). While this reviewer does not agree with some of the exclusion criteria implemented by the Applicant when designing/conducting their phase 3 trials, the implementation of these criteria is not expected to have an impact on the ability of dasiglucagon to effectively raise blood glucose given that the mechanism of action of dasiglucagon is via activation of hepatic glucagon receptors. Regarding criteria that could affect the labeling, presence or history of pheochromocytoma or insulinoma (criterium #13) will be included as contraindications in the labeling. Use of a daily systemic beta-blocker drug, indomethacin, warfarin or anticholinergic drugs (criterium #14) will be listed in the drug interactions section of the labeling.

Dosing Day Exclusion Criteria (summarized):

Additional dosing day exclusion criteria were employed. Subjects who met one or more of the following criteria were allowed to be rescheduled up to one week later. The dosing visit could only be rescheduled once.

1. Atypically strenuous exercise within 4 days prior to dosing
2. Clinically significant illness within 4 weeks before dosing
3. Consumption of alcohol within 24 hours prior to dosing visit
4. Not fasting from 22:00 hours the evening prior to dosing, apart from water (small amounts of carbohydrates (up to 20 g) to prevent hypoglycemia were allowed)
5. The use of any non-prescribed systemic or topical medication, except routine vitamins and occasional use (as judged by the investigator) of acetylsalicylic acid and paracetamol within 2 weeks prior to dosing
6. Use of insulin degludec or insulin glargine U300 within 48 hours prior to dosing; or use of other long-acting insulins (e.g., insulin glargine U100 or insulin detemir) within 24 hours prior to dosing; or use of insulin NPH within 16 hours prior to dosing
7. Use of any short acting (bolus) insulin within 6 hours prior to dosing, except insulin glulisine (Apidra)
8. Changes in medical history or concomitant medication resulting in fulfillment of clinical exclusion criteria, as judged by the investigator
9. Plasma glucose value <50 mg/dL within the last 24 hours or plasma glucose value <60 mg/dL within the last 5 hours prior to initiation of the hypoglycemic procedure

Reviewer comment: Dosing day exclusion criteria 1-4 and 6-7 (regarding insulin washout, strenuous exercise, illness, and alcohol use leading up to the clamp procedure) were employed to enable the reliable estimation of the primary endpoint during the clamp procedure. It is unclear to this reviewer why the Applicant employed criterion 5 regarding the use of any non-prescribed systemic or topical medication; however, this could also be due to concern about supplements with unknown ingredients and their effect on glucose homeostasis. Criteria 8 and 9

were presumably employed as additional measures to protect subject safety in the trial and do not have labeling implications. Overall, these criteria are typical for clamp studies intending to obtain reliable plasma glucose data, and do not have further labeling implications.

Trial Endpoints

Primary Efficacy Endpoint:

- Time to plasma glucose recovery, defined as the first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose

Key Secondary Efficacy Endpoints:

- Plasma glucose recovery within 30, 20, 15 and 10 minutes after IMP administration without administration of rescue IV glucose
- Plasma glucose change from baseline at 30, 20, 15 and 10 minutes after IMP administration or at the time of rescue

Other Efficacy Endpoints:

- Clinical efficacy (PD) endpoints:
    - Time to first plasma glucose concentration 70 mg/dL without administration of rescue IV glucose
    - Plasma glucose response as area under the effect curve above baseline from time zero to 30 minutes ($AUE_{0\text{-}30min}$)
- Exposure (PK) endpoints:
    - Area under the drug concentration curve from time zero to 90 minutes ($AUC_{0\text{-}90min}$)
    - Area under the drug concentration curve from time zero to 120 minutes ($AUC_{0\text{-}120min}$); post hoc endpoint
    - Maximum plasma drug concentration (C_{max})
    - Time to maximum plasma drug concentration (t_{max})

Immunogenicity endpoint:

- Occurrence of ADAs

Safety Endpoints:

- AEs, clinical laboratory assessments (biochemistry, hematology, urinalysis), vital signs, physical examination, ECG and local tolerability
- Administration of rescue infusion of IV glucose during the hypoglycemic clamp procedure
- Time to first rescue infusion of IV glucose during the post-treatment procedure

Exploratory Endpoints:

- Plasma glucose concentration ≥70 mg/dL or increase of ≥20 mg/dL within 30 minutes after IMP administration without administration of rescue IV glucose
- Plasma insulin response as area under the curve above baseline from time zero to 60 minutes ($AUE_{0\text{-}60min}$)

Sample Size

The Applicant intended for a total of 156 subjects to complete trial 16137. Sample size calculations incorporated findings from the phase 2 dose-finding trial 15126, where the median time to an increase of 20 mg/dL of the 0.6 mg dasiglucagon dose was approximately 10 minutes. With a 2:1:1 randomization ratio (dasiglucagon to placebo to GlucaGen) and assuming exponential time-to-recovery distributions with median times of 10 and at least 20 minutes for dasiglucagon and placebo, respectively, a two-sided log-rank test would be able to detect a difference between dasiglucagon and placebo with 90% power at a 5% significance level with 78 subjects treated with dasiglucagon and 39 subjects with placebo and a follow-up time of 45 minutes.

Statistical Analysis Plan

The Applicant summarized the primary endpoint using Kaplan-Meier (KM) estimates for median time to glucose recovery. The treatment group difference between dasiglucagon and placebo was evaluated inferentially using a pairwise two-sided log rank test to show superiority of dasiglucagon. Subjects who received IV glucose were to be censored (i.e., set to not recovered) at 45 minutes post-dose. If recovery had not occurred at 45 minutes after investigational product injection, censoring was applied irrespective of the use of rescue IV glucose. The primary endpoint was additionally analyzed using a Cox proportional hazards time to event statistical model. Linear interpolation (between the two time points before and after recovery was observed) was carried out to estimate the subject's actual time of recovery.

Reviewer comment: In addition to replicating the analysis performed by the Applicant, Dr. Yoonhee Kim, the FDA statistical reviewer, also employed a recovery (survival) time ratio analysis. Because the primary endpoint (i.e., time to recovery) is a beneficial outcome rather than hazardous outcome, Dr. Kim applied the concept of a survival time ratio from the parametric survival model with log-normal distribution for a comparison of time to plasma glucose recovery in two groups. With time to recovery in the placebo group as a reference, the survival time ratio will be the ratio of time to recovery in the dasiglucagon group over the placebo group. In this review, the "recovery" time ratio is used in lieu of the survival time ratio. If the recovery time ratio is less than 1, then the results are interpreted as favorable to dasiglucagon because the recovery time becomes shorter with the group change from placebo.

The key secondary endpoints of plasma glucose recovery within 30, 20, 15 and 10 minutes were compared between treatment groups using Fisher's exact test. Plasma glucose change from baseline at 30, 20, 15 and 10 minutes were analyzed using an Analysis of Covariance (ANCOVA) model with treatment group modelled as a fixed effect and with the baseline plasma glucose modelled as a covariate.

An *a priori* defined hierarchical inferential test order was applied for the control of the type 1 error rate across the planned multiple comparisons. The primary endpoint and key secondary endpoints were inferentially evaluated in the following order, where inference proceeded at the two-sided 0.05 criterion significance level until the first failure to reject the null hypothesis for a dasiglucagon versus placebo comparison:

- Time to plasma glucose recovery (primary endpoint #1)
- Plasma glucose recovery within 30, 20, 15, and 10 minutes (secondary endpoints #1-4) after IMP administration without administration of rescue IV glucose (four separate endpoints in the stated hierarchical order)
- Plasma glucose change from baseline at 30, 20, 15, and 10 minutes (secondary endpoints #5-8) after IMP administration or at the time of rescue (four separate endpoints in the stated hierarchical order).

The following analysis sets were pre-specified in the trial protocol:

- Safety analysis set (SAS) and full analysis set (FAS): All randomized subjects who received at least one dose of trial medication.
- Per protocol (PP) set: All subjects of the FAS for whom no relevant protocol deviations were documented.

Analyses of the primary and secondary endpoints were based on the FAS. The Applicant completed a secondary analysis of the primary endpoint based on the PP set.

Protocol Amendments

There were four protocol amendments. Two protocol amendments were implemented before trial initiation. Two amendments were implemented when the trial was ongoing: January 26, 2018 (protocol version 4.0) and April 4, 2018 (protocol version 5.0). Key changes to version 4.0 were related to the investigational use of Apidra in Germany. Key changes in protocol version 5.0 included minor changes to the collection of lab parameters (coagulation was removed as a laboratory safety endpoint; addition of C-peptide and coagulation at screening), removal of the inclusion criteria requiring subjects to use additional contraception when already using systemic contraceptives, and additional local German requirements related to the use of Apidra.

6.1.1. Study Results

Compliance with Good Clinical Practices

The Applicant provided a statement that this trial was conducted in accordance with International Council for Harmonization (ICH) of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki as well as other applicable local ethical and legal requirements.

Financial Disclosure

See section 13.2 for details.

Subject Disposition

In total, 235 subjects were screened, of whom 170 were randomized (Table 3). Two subjects randomized to the dasiglucagon group discontinued prior to being treated and were therefore not included in any analysis set. The reason for subject discontinuation prior to treatment was 'subject withdrawal of consent' for one subject (subject (b) (6)) and an adverse event (AE) for another subject which occurred prior to dosing (subject (b) (6) had an AE of ventricular extrasystoles; this subject also withdrew consent). Of the remaining 168 subjects, there were no dropouts, and all subjects completed the trial up to the safety follow-up visit (Table 3). The analyses completed by the Applicant and in this review are based on the FAS population.

Table 3. Subject Disposition - Trial 16137

		Randomized	***Treated (FAS)***	***Completed***
Trial 16137	*Dasiglucagon*	84*	82	82
	Placebo	43	43	43
	GlucaGen	43	43	43

**Two subjects withdrew consent after randomization but before administration of the investigational product.*
Source: Modified from statistical reviewer analysis

Protocol Violations/Deviations

Four protocol deviations were recorded for three different subjects as summarized below:

- Subject (b) (6): The subject was included into the trial despite meeting the exclusion criterion of diastolic blood pressure ≥90 mmHg. Screening BP was 138/90 mmHg in the right arm and 143/89 in the left arm, but only the left arm BP was used for assessment of eligibility. In addition, the pre-dose plasma glucose and glucagon lab samples were not collected for this subject.
- Subject (b) (6): The subject's glucose (using a blood glucose meter) of 50 mg/dL was not confirmed at the site using the YSI 2300 analyzer. If the blood glucose value had been confirmed as <50 mg/dL, dosing day exclusion criterion #9 would have been met.

- Subject (b) (6): The subject was included into the trial despite meeting the exclusion criterion of diastolic blood pressure ≥90 mmHg. Screening BP was 138/96 mmHg in the right arm and 129/85 mmHg in the left arm, but only the left arm BP was used for assessment of eligibility.

The decision regarding whether a protocol deviation was relevant or not for exclusion of subjects in the PP analysis set was made on a case-by-case blinded review prior to treatment unmasking and database lock. Subjects (b) (6) were excluded from the PP data set. As noted above, the main analysis in this review is based on the FAS. Analyses completed by the Applicant with the PP set did not alter the conclusions of the trial.

Subject Demographics and Baseline Disease Characteristics

The mean age of the trial participants was 39.1 years and the mean HbA1c was 7.4% (Table 4). More subjects were male (63%), and the majority were White (92%) and non-Hispanic/Latino (96%). Prior medical history/concomitant illnesses at screening were consistent with conditions expected in an adult T1DM population (data not shown). Demographics and baseline disease characteristics were generally balanced between treatment arms. Fourteen percent of subjects were from the US.

Table 4. Subject Demographics and Baseline Characteristics – Trial 16137

	0.6 mg Dasiglucagon n=82	1.0 mg GlucaGen n=43	Placebo n=43	Totals n=168
Age - years				
Age - mean (std.dev.)	39.2 (12.1)	40.2 (11.5)	38.0 (13.1)	39.1 (12.2)
Age - range	18-71	23-66	18-65	18-71
<65 - count (%)	79 (96%)	41 (95%)	42 (98%)	162 (96%)
≥65 - count (%)	3 (4%)	2 (5%)	1 (2%)	6 (4%)
Sex - count subjects (%)				
Male	50 (61%)	28 (65%)	27 (63%)	105 (63%)
Female	32 (39%)	15 (35%)	16 (37%)	63 (38%)
Race - count subjects (%)				
White	76 (93%)	39 (91%)	39 (91%)	154 (92%)
Asian	3 (4%)	0 (0%)	2 (5%)	5 (3%)
Black/African American	1 (1%)	2 (5%)	1 (2%)	4 (2%)
Multiple	1 (1%)	1 (2%)	0 (0%)	2 (1%)
Other	1 (1%)	0 (0%)	1 (2%)	2 (1%)
Native Hawaiian/Pacific Islander	0 (0%)	1 (2%)	0 (0%)	1 (0.6%)
Ethnicity - count subjects (%)				
Not Hispanic/Latino	80 (98%)	40 (93%)	41 (95%)	161 (96%)
Hispanic/Latino	2 (2%)	3 (7%)	2 (5%)	7 (4%)
Region – count subjects (%)				
US	12 (15%)	6 (14%)	6 (14%)	24 (14%)
Outside of US	70 (85%)	37 (86%)	37 (86%)	144 (86%)
Screening BMI – kg/m^2				
Mean (std.dev.)	26.1 (4.1)	25.9 (3.4)	26.1 (3.3)	26.1 (3.8)
Range	18.6-38.4	19.4-35.0	19.7-34.2	18.6-38.4
Duration of diabetes - years				
Mean (std.dev.)	22.6 (12.3)	19.8 (11.2)	19.4 (11.0)	21.0 (11.7)
Range	2.5-56.1	2.6-57.2	2.6-41.8	2.5-57.2
Screening HbA1c - %				
Mean (std.dev.)	7.5 (0.95)	7.4 (0.97)	7.2 (0.74)	7.4 (0.91)
Range	5.2-9.7	5.4-8.9	6.0-9.2	5.2-9.7
Baseline plasma glucose - mg/dL				
Mean (std.dev.)	58.9 (5.6)	58.5 (5.1)	58.8 (4.4)	58.8 (5.2)

Source: Generated by Reviewer in JReview with ADSL, ADLB, and ADEFF datasets
Std.dev: standard deviation, BMI: body mass index

Efficacy Results – Primary Endpoint

Trial 16137 demonstrated superiority of dasiglucagon compared to placebo on median time to

plasma glucose recovery, defined as first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose (Table 5 and Figure 8). The median time to plasma glucose recovery was statistically significantly less in the dasiglucagon group (10 minutes [95% CI: 10, 10]) than in the placebo group (40 minutes [95% CI: 30, 40]; log-rank test 2-sided p-value <0.001). All subjects who received dasiglucagon met the primary endpoint within 45 minutes. Thirty-one (72%) subjects who received placebo recovered within 45 minutes, but 12 subjects (28%) were censored either because they required rescue glucose or because they had not achieved recovery by 45 minutes post-dose.

Reviewer comment: As explained by Dr. Kim in her statistical review, since the primary endpoint is time to recovery, a hazard ratio (HR) >1 favors the dasiglucagon group over the placebo group. The HR from a discrete-time Cox proportional hazard model was 111 (38; 330) consistent with a statistically significantly shorter time to recovery for dasiglucagon (Table 5). Dr. Kim points out, however, that the HR is not intuitively understood, and she calculated a recovery time ratio to interpret the data. A recovery time ratio <1 favors dasiglucagon. The recovery time ratio from a parametric survival model was 0.29 which indicates that, versus placebo, recovery time for dasiglucagon is decreased by more than two-thirds. The confidence interval is narrow suggesting the estimate is reliable.

Table 5. Time to Plasma Glucose Recovery (FAS) – Trial 16137

	Trial 16137 *N=82 (dasiglucagon)* *N=43 (placebo)*
Dasiglucagon	
Number of subjects rescued[*]	0
Number of subjects censored[†]	0
Median time (95% CI)	10 minutes (10, 10)
Min, Max	4, 25 minutes
Placebo	
Number of subjects rescued[*]	0
Number of subjects censored[†]	12
Median time (95% CI)	40 minutes (30, 40)
Min, Max	15, 45 minutes
Hazard Ratio (95%CI)[‡]	111 (38, 330)
Recovery Time Ratio (95%CI) [‡‡]	0.29 (0.26, 0.33)

[*]Rescued: Number of subjects who received IV glucose within 45 minutes after dosing; [†]Censored: Number of subjects who were censored at 45 minutes after dosing due to no recovery or having rescue IV glucose within 45 minutes after dosing; [‡]By Applicant using a discrete Cox Proportional Hazard model [‡‡] By statistical reviewer using the survival time ratio from Parametric Survival Model.
Source: Statistical reviewer analysis (with modified formatting)

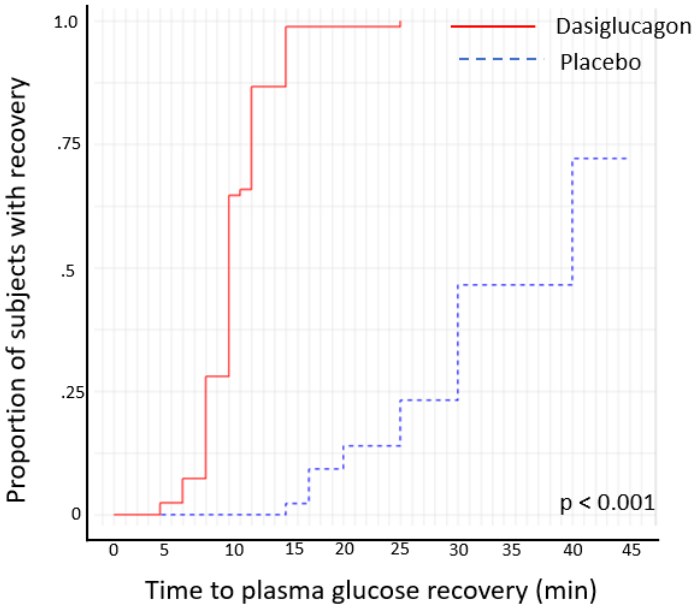


Figure 8. Cumulative Proportions of Subjects with Recovery (FAS) – Trial 16137
Source: Statistical reviewer analysis (with modified formatting)

While no formal statistical comparison was carried out between dasiglucagon and GlucaGen, the median time to plasma glucose recovery was similar between dasiglucagon (10 minutes [95% CI: 10, 10]) and GlucaGen (12 minutes [95% CI: 10, 12]).

The Applicant performed sensitivity analyses for the primary endpoint using 1) linearly interpolated time between assessed time points, 2) without censoring for subjects who required rescue IV glucose and 3) with censoring at the time of administration of rescue IV glucose. The FDA statistical reviewer confirmed that the sensitivity analyses were consistent with the primary analysis and do not alter the trial results.

Blood samples for the assessment of the primary endpoint were drawn at discrete time points (i.e., recovery was met at the discrete timepoint at which the first increase in plasma glucose of ≥20 mg/dL from baseline was observed). The Applicant performed linear interpolation between the two time points before and after plasma glucose recovery had occurred with the FAS dataset (i.e. including subjects who were censored) to obtain an estimate of the actual recovery time. This method estimated that the median time to plasma glucose recovery was 9.0 minutes (95% CI: 8.4, 9.7) in the dasiglucagon group and 33.7 minutes (95% CI: 26.1, 36.1) in the placebo group (Applicant's analysis). In the GlucaGen group, the median time to plasma glucose recovery as derived by linear interpolation was 10 minutes (95% CI: 9.0, 10.6).

Data Quality and Integrity

I did not identify any issues regarding data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Plasma Glucose Recovery within 30, 20, 15 and 10 minutes:

The percentages of subjects in the FAS who achieved plasma glucose recovery within 30, 20, 15 and 10 minutes were significantly higher in the dasiglucagon group than in the placebo group ($p<0.01$ at each time point, Fisher's exact test; Table 6). The single dasiglucagon-exposed subject who was considered to have not achieved plasma glucose recovery within 20 minutes had a plasma glucose increase at 20 minutes of 19.98 mg/dL, nearly at the threshold of ≥20 mg/dL defining plasma glucose recovery.

Table 6. Number of Subjects (Percent) with Time to Plasma Glucose Recovery Within Defined Time Points (FAS) – Trial 16137

Plasma Glucose Recovery (min)	***Dasiglucagon N=82***	***Placebo N=43***
Recovery within ≤30 mins	82 (100%)	20 (47%)
Recovery within ≤20 mins	81 (99%)	6 (14%)
Recovery within ≤15 mins	81 (99%)	1 (2%)
Recovery within ≤10 mins	53 (65%)	0 (0%)

Source: Statistical reviewer analysis (with modified formatting)

Plasma Glucose Change from Baseline at 30, 20, 15 and 10 minutes:

Least squared (LS) mean changes in plasma glucose from the ANCOVA model from baseline to 30, 20, 15 and 10 minutes are summarized in Table 7. The mean plasma glucose changes are consistently greater for dasiglucagon compared to placebo. All p-values of ANCOVA tests for treatment differences were significant (p-value <0.001).

Table 7. Plasma Glucose Change from Baseline at Defined Timepoints (FAS) – Trial 16137

Δ Glucose mg/dL	***Dasiglucagon*** *LS mean (SE)*	***Placebo*** *LS mean (SE)*
at 30 minutes	91.1 (1.9)	19.1 (2.5)
at 20 minutes	59.7 (1.5)	8.7 (2.1)
at 15 minutes	43.6 (1.2)	5.1 (1.7)
at 10 minutes	24.0 (0.9)	-0.14 (1.3)

Source: Statistical reviewer analysis (with modified formatting)
LS: Least squared; SE: standard error

6.2. Trial 17145

Overview and Objectives

The primary objective of this study was to demonstrate superiority of dasiglucagon compared to placebo on time to plasma glucose recovery following a single 0.6 mg dasiglucagon dose administered SC to subjects with T1DM with insulin-induced hypoglycemia. Secondary objectives were to evaluate the safety, immunogenicity, and PK of dasiglucagon.

Trial Design

Trial 17145 was a multi-center, randomized, parallel-group, blinded clinical trial. Subjects were randomized 3:1 to receive dasiglucagon or placebo, respectively, via an AI device. Subjects underwent a screening visit, a dosing visit, and a follow-up safety visit approximately 28 days post-dosing. The study was conducted at three trial sites within the US. Randomization was stratified by injection site (buttock or deltoid).

Reviewer comment: Trials 17145 and 16137 employed a similar design, mainly differing with respect to randomization ratio, injection site, the inclusion of a GlucaGen treatment arm in trial 16137, and the use of an AI in trial 17145 (versus a prefilled syringe in trial 16137). Therefore, relevant sections in section 6.1 will be referenced, where appropriate, to avoid duplication of information.

Dosing Regimen

Randomized subjects received one of the following IMPs:

- Dasiglucagon, 0.6 mg/0.6 mL delivered in an AI device
- Placebo, 0.6 mL delivered in an AI device

Study Visits

Trial 17145 included three study visits (screening, dosing, and follow-up) (Figure 9). The study visits and assessments previously described in section 6.1 are relevant to trial 17145. Serial blood samples to assess plasma glucose were collected at the same timepoints as collected in trial 16137, which included pre-dose and at t=0, 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 45, 50, 60, 75, and 90 minutes post-dosing.

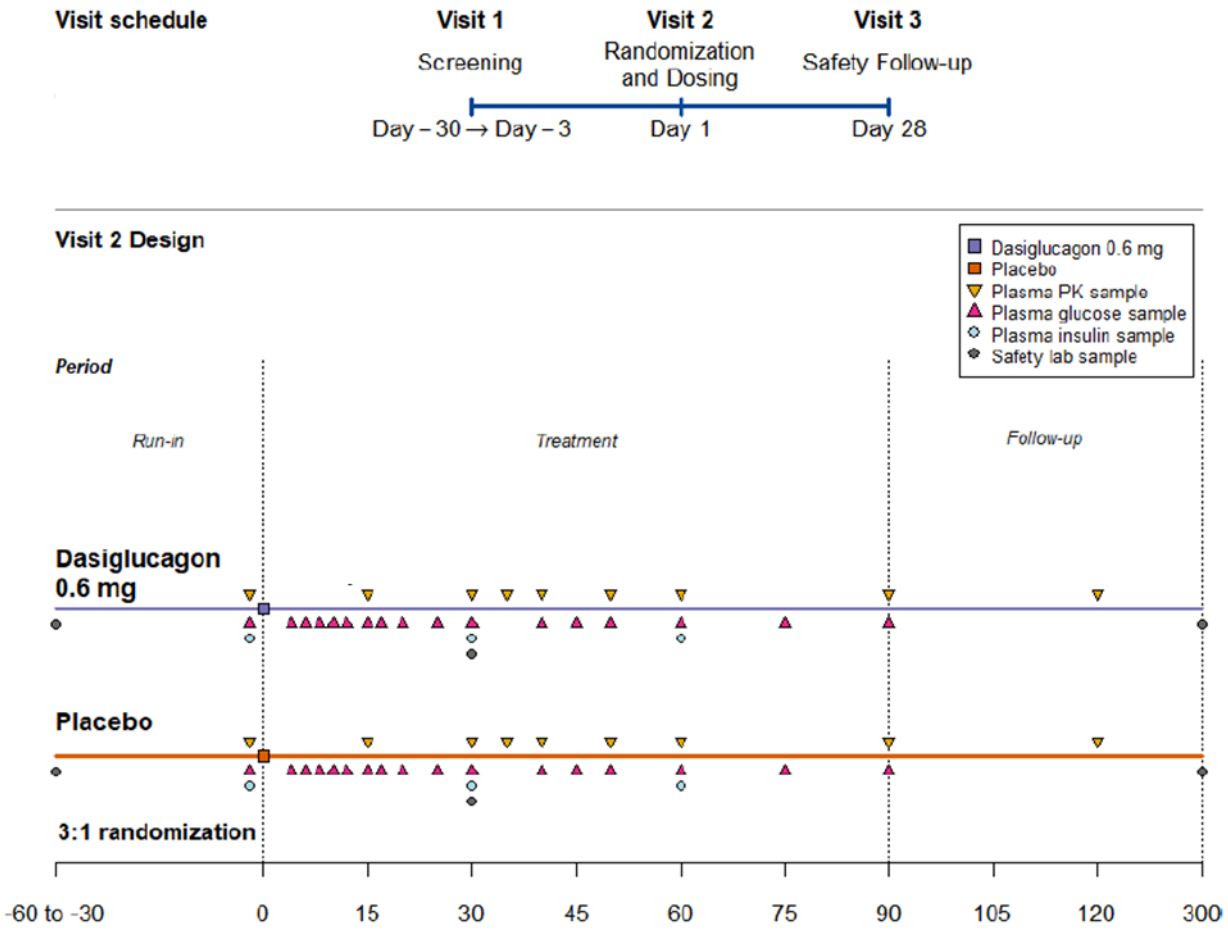


Figure 9. Overview of 17145 Study Design
Modified from ZP4207-17145 Study Report Body

Inclusion Criteria and Exclusion Criteria

Inclusion and exclusion criteria for trial 17145 were the same as inclusion and exclusion criteria

for trial 16137 as detailed in section 6.1.

Study Endpoints

Study endpoints for trial 17145 were the same as endpoints for trial 16137 as detailed in section 6.1.

Sample Size:

In the phase 2, dose-finding trial 15126, the median time to an increase in plasma glucose of 20 mg/dL with 0.6 mg dasiglucagon was approximately 10 minutes. For subjects in the placebo group, it was assumed that the median time to recovery would be more than 50 minutes. Assuming an exponential time-to-recovery distribution with median times of 10 and 50 minutes, a two-sided log-rank test would be able to detect a difference between dasiglucagon and placebo with 92% power at a 5% significance level with 40 subjects randomized 3 to 1 between dasiglucagon and placebo and a follow-up time of 45 minutes.

Statistical Analysis Plan

The statistical analysis plan for trial 17145 did not differ meaningfully from trial 16137, and the Applicant utilized the same statistical methods to characterize the primary and secondary endpoints. The SAS, FAS, and PP analysis sets were also defined as described in section 6.1. Additionally, the statistical reviewer utilized the same methodology for the analyses for all phase 3 trials used to support efficacy (i.e. 16137, 17145, and 17086). See section 6.1 for additional information.

Protocol Amendments

There were no amendments to the protocol for trial 17145.

6.2.1. Study Results

Compliance with Good Clinical Practices

The Applicant provided a statement that trial 17145 was performed in accordance with the ethical principles stated in the latest version of the Declaration of Helsinki and the applicable guidelines of Good Clinical Practice.

Financial Disclosure

See section 13.2 for details.

Subject Disposition

In total, 68 subjects were screened, of whom 45 were randomized (Table 8). One subject (subject (b) (6)) randomized to placebo did not wish to continue with the study and withdrew consent prior to IMP administration. Of the remaining 44 subjects, all completed the study up to the safety follow-up visit. The efficacy analyses completed by the Applicant and in this review use the full analysis set (FAS).

Table 8. Subject Disposition - Trial 17145

		Randomized	***Treated (FAS)***	***Completed***
Trial 17145	*Dasiglucagon*	34	34	34
	Placebo	11*	10	10

**Subject withdrew consent after randomization but before administration of the investigational product.*
Source: Modified from statistical reviewer analysis

Protocol Violations/Deviations

Protocol deviations were judged by the investigator or sub-investigator as either important or non-important. Seventeen protocol deviations were assessed by the investigator as non-important. Of these 17, 13 occurred in subjects randomized to dasiglucagon and four in subjects randomized to placebo. Non-important protocol deviations were mainly deviations from time of sampling, which the Applicant states do not have any major impact on the data usability, or not initiating the hypoglycemia clamp procedure in early morning as specified in the protocol. There were six deviations in five subjects judged as important by the investigator, all of which occurred in subjects who received dasiglucagon as described below:

- Subject (b) (6) was randomized and treated with dasiglucagon even though the subject experienced a hypoglycemia event within the 24 hours prior to randomization. Hence, the dosing day exclusion criterion #9 was violated for this subject. This subject was excluded from the Applicant's PP analysis.
- Three subjects (b) (6) had a single dosing day plasma glucose sampling out of window. All were included in the Applicant's PP analysis; however, the records collected out of window were excluded from the PP analysis according to pre-specified rules.
- Subject (b) (6) had a severe post-treatment hypoglycemic event that prompted rescue glucose treatment. The SAE describing hypoglycemia was not documented contemporaneously in source documents. This subject was included in the Applicant's PP analysis. A detailed narrative of this event is provided below.

Subject Demographic and Baseline Disease Characteristics

Subject demographics and baseline disease characteristics are presented in Table 9. The mean age of the study participants was 41 years and the mean HbA1c was 7.2%. The majority of subjects in this trial were white (93%) and non-Hispanic/Latino (84%). Baseline characteristics were generally balanced between treatment arms except that there were more male subjects in the placebo treatment assignment (90%) as compared to the dasiglucagon treatment assignment (47%). Prior medical history/concomitant illnesses at screening were consistent with conditions expected in an adult T1DM population (data not shown).

Table 9. Subject Demographics and Baseline Disease Characteristics – Trial 17145

	0.6 mg Dasiglucagon n=34	Placebo n=10	Totals n=44
Age - years			
Age - mean (std.dev.)	42.4 (13.5)	36.5 (12.8)	41.0 (13.4)
Age - range	24-69	18-55	18-69
<65 - count (%)	32 (94%)	10 (100%)	42 (95%)
≥65 - count (%)	2 (6%)	0 (0%)	2 (45%)
Sex - count subjects (%)			
Male	16 (47%)	9 (90%)	25 (57%)
Female	18 (53%)	1 (10%)	19 (43%)
Race - count subjects (%)			
White	34 (100%)	7 (70%)	41 (93%)
Multiple	0 (0%)	1 (10%)	1 (2%)
Native Hawaiian/Pacific Islander	0 (0%)	1 (10%)	1 (2%)
Black/African American	0 (0%)	1 (10%)	1 (2%)
Ethnicity - count subjects (%)			
Not Hispanic/Latino	30 (88%)	7 (70%)	37 (84%)
Hispanic/Latino	4 (12%)	3 (30%)	7 (16%)
Region – count subjects (%)			
US	34 (100%)	10 (100%)	44 (100%)
Outside of US	0 (0%)	0 (0%)	0 (0%)
Screening BMI – kg/m^2			
Mean (std.dev.)	28.4 (5.8)	27.9 (4.0)	28.3 (5.4)
Range	21.3-47.8	22.6-37.9	21.3-47.8
Duration of diabetes - years			
Mean (std.dev.)	22.5 (13.8)	21.2 (13.4)	22.2 (13.6)
Range	2-54	3-49	2-54
Screening HbA1c - %			
Mean (std.dev.)	7.2 (0.90)	7.2 (0.88)	7.2 (0.88)
Range	5.8-9.6	6.1-8.8	5.8-9.6
Baseline plasma glucose - mg/dL			
Mean (std.dev.)	54.8 (5.6)	54.1 (4.1)	54.7 (5.3)

Source: Generated in JReview by Reviewer using ADSL, ADLB and ADEFF datasets

Reviewer comment: The imbalance in male subjects is likely due to the small sample size of the trial. The FDA statistical reviewer confirmed that there was no sex-by-treatment interaction (see Dr. Kim's review for details).

Efficacy Results – Primary Endpoint

Trial 17145 demonstrated superiority of dasiglucagon compared to placebo on median time to plasma glucose recovery, defined as first increase in plasma glucose of ≥20 mg/dL from baseline

without administration of rescue IV glucose (Table 10 and Figure 10). The median time to plasma glucose recovery within 45 minutes was statistically significantly less in the dasiglucagon group (10 minutes [95% CI: 8, 12]) than in the placebo group (35 minutes [95% CI: 20, upper limit not estimable]; log-rank test 2-sided p-values < 0.001). Thirty-three subjects (97%) who received dasiglucagon met the primary endpoint within 45 minutes. One subject (105017) administered dasiglucagon received IV rescue glucose and was therefore censored (see below for additional discussion of this subject). Seven (70%) subjects who received placebo also recovered within 45 minutes. Of the three placebo subjects who did not meet the primary endpoint, two of the subjects were rescued with IV glucose 30 minutes after injection and one failed to recover by 45 minutes.

Table 10. Time to Plasma Glucose Recovery (FAS) – Trial 17145

	Trial 17145 *N=34 (dasiglucagon)* *N=10 (placebo)*
Dasiglucagon	
Number of subjects rescued[*]	1
Number of subjects censored[†]	1
Median time (95% CI)	10 minutes (8, 12)
Min, Max	4, 45 minutes
Placebo	
Number of subjects rescued[*]	2
Number of subjects censored[†]	3
Median time (95% CI)	35 minutes (20, NE**)
Min, Max	20, 45 minutes
Hazard Ratio (95%CI)[‡]	10 (4, 34)
Recovery Time Ratio (95%CI) [‡‡]	0.29 (0.21, 0.4)

[*]Rescued: Number of subjects who received IV glucose within 45 minutes after dosing; [†]Censored: Number of subjects who were censored at 45 minutes after dosing due to no recovery or having rescue IV glucose within 45 minutes after dosing; [**]NE: Not estimable [‡]By Applicant using a discrete Cox Proportional Hazard model [‡‡] By statistical reviewer using the survival time ratio from Parametric Survival Model.
Source: Statistical reviewer's analysis

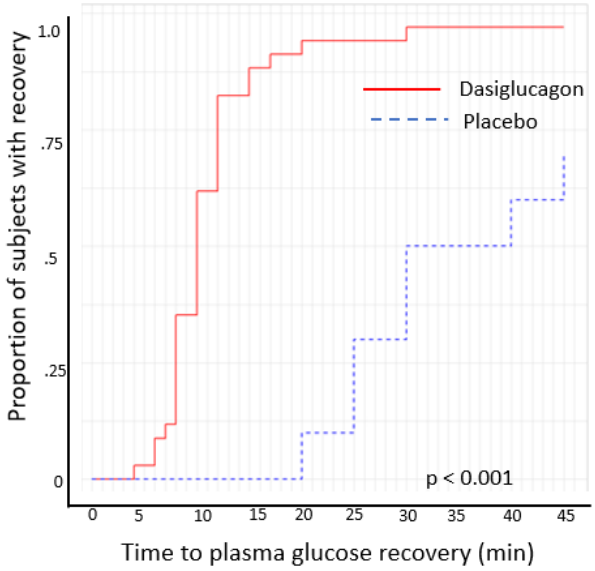


Figure 10. Cumulative Proportions of Subjects with Recovery (FAS) – Trial 17145
Source: Statistical reviewer's analysis (with modified format)

Reviewer comment: The results of trial 17145 independently demonstrate efficacy of dasiglucagon and are consistent with the results of trial 16137 with a median time to recovery of 10 minutes (versus 35 minutes with placebo). The point estimate of the recovery time ratio is the same as in trial 16137, albeit with a wider confidence interval. Additionally, Figure 10 shows that the dasiglucagon and placebo curves separate as early as 5 minutes continue to separate throughout the trial.

The Applicant performed the following sensitivity analyses that were prespecified in the SAP: assessment of time to plasma glucose recovery 1) without censoring for subjects who required rescue IV glucose before 45 minutes and 2) with censoring at the time of administration of rescue IV glucose before 45 minutes. Sensitivity analysis also was performed with the PP set. These analyses did not importantly alter the results of the trial, with dasiglucagon consistently demonstrating a shorter time to plasma glucose recovery as compared to placebo.

Blood samples for the assessment of the primary endpoint were drawn at discrete time points (i.e., recovery was met at the discrete timepoint at which the first increase in plasma glucose of ≥20 mg/dL from baseline was observed). Therefore, the Applicant performed linear interpolation with the FAS dataset (i.e. including censored subjects) between the two time points before and after plasma glucose recovery had occurred to obtain an estimate of the true recovery time. This method estimated that the median time to plasma glucose recovery was 9.3 minutes (95% CI: 7.8, 10.3) minutes in the dasiglucagon group and 25.8 minutes (95% CI: 19.2,

34.8) in the placebo group (Applicant's analysis).

Subject (b) (6):

A single subject (b) (6) randomized to dasiglucagon received IV rescue glucose treatment, which was given at 10 minutes after IMP administration. The rescue treatment was administered simultaneously with the 10-minute plasma glucose sample being drawn from the other arm. The decision to provide rescue treatment was prompted by the presence of post-dose hypoglycemia symptoms combined with a locally measured blood glucose level of 39.6 mg/dL at 5 minutes post-dose. The subsequently obtained plasma glucose results from the central laboratory showed an adequate glycemic response to dasiglucagon treatment up until the rescue treatment was given: the baseline value was 43.1 mg/dL, which declined to 37.1 mg/dL 4 minutes post-dose and then increased to 49.0 mg/dL at 6 minutes, 58.0 mg/dL at 8 minutes, and 63.1 mg/dL at 10 minutes. The latter value corresponds to an increase from baseline of 20 mg/dL at 10 minutes. Nonetheless, as rescue treatment and plasma glucose sampling at 10 minutes were performed simultaneously, this subject was disqualified from having achieved recovery.

Reviewer comment: I do not consider this subject to be a treatment failure. It is likely that the locally measured glucose level was falsely low.

Data Quality and Integrity

I did not identify any issues regarding data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Plasma Glucose Recovery within 30, 20, 15 and 10 minutes

The percentages of subjects in the FAS who achieved plasma glucose recovery within 30, 20, 15 and 10 minutes were significantly higher in the dasiglucagon group than in the placebo group ($p<0.01$ at each time point, Fisher's exact test; Table 11).

Table 11. Subjects (Percent) with Plasma Glucose Recovery Within Defined Time Points (FAS) – Trial 17145

Plasma Glucose Recovery (min)	***Dasiglucagon N=34***	***Placebo N=10***
Recovery within ≤30 mins	33 (97%)	5 (50%)
Recovery within ≤20 mins	32 (94%)	1 (10%)
Recovery within ≤15 mins	30 (88%)	0 (0%)
Recovery within ≤10 mins	20 (59%)	0 (0%)

Source: Statistical reviewer analysis (with modified formatting)

Plasma Glucose Change from Baseline at 30, 20, 15 and 10 minutes

Plasma glucose change in LS mean from an ANCOVA model from baseline to 30, 20, 15 and 10 minutes is summarized in Table 12. The mean plasma glucose change is greater than 20 mg/dL by 10 minutes post-dose in the dasiglucagon treatment group, while mean plasma glucose change is less than 20 mg/dL at all timepoints in the placebo treatment group. All p-values of ANCOVA tests for the treatment difference were significant (p-value < 0.001).

Table 12. Plasma Glucose Change from Baseline at Defined Timepoints (FAS) – Trial 17145

Δ Glucose mg/dL	***Dasiglucagon*** *LS mean (SE)*	***Placebo*** *LS mean (SE)*
at 30 minutes	85.4 (4.4)	15.6 (8.1)
at 20 minutes	53.0 (3.0)	10.0 (5.6)
at 15 minutes	41.7 (2.6)	5.3 (4.8)
at 10 minutes	24.6 (1.9)	0.7 (3.6)

Source: Statistical reviewer analysis (with modified formatting)
LS: least squares; SE: standard error

6.3. Study 17086

6.3.1. Study Design

Overview and Objectives

The primary objective was to demonstrate that dasiglucagon is superior to placebo following a single injection of 0.6 mg dasiglucagon on time to plasma glucose recovery in pediatric subjects with T1DM. The secondary objectives were to assess descriptively that a single dose of 0.6 mg dasiglucagon is comparable to a single dose of GlucaGen, and to assess the safety and PK profile of dasiglucagon in pediatrics with T1DM.

Trial Design

Trial 17086 was a global, multicenter, randomized, parallel, and blinded clinical trial. Subjects were randomized 2:1:1 to receive dasiglucagon, placebo, or GlucaGen, respectively, by prefilled syringe. Subjects underwent a screening visit, a dosing visit, and a follow-up safety visit approximately 28 days post-dosing. The trial was conducted at five trial sites; three in the US, one in each Slovenia and Germany. Randomization was stratified by age category (≥6 years to <12 years, and ≥12 years to <18 years) and by injection site (abdomen or thigh).

Dosing Regimen

Randomized subjects received one of the following IMPs:

- Dasiglucagon, liquid formulation, 0.6 mg/0.6 mL delivered in a prefilled syringe
- Placebo, liquid formulation, 0.6 mL delivered in a prefilled syringe
- Recombinant glucagon hydrochloride (GlucaGen, Novo Nordisk)
    - 1 mg for subjects ≥25 kg or 0.5 mg for subjects <25 kg per the USPI for GlucaGen

Study Visits

Similar to the adult phase 3 trials detailed in 6.1 and 6.2, pediatric trial 17086 included three study visits (screening, dosing, and follow-up) as displayed in Figure 11. Procedures completed at the screening and follow up visit for the pediatric trial did not differ importantly from the adult trials (see section 6.1 for additional information). Procedures on the dosing day were also similar to adult trials, although a more conservative approach was taken regarding the plasma glucose levels targeted during hypoglycemic clamp procedure for the pediatric population. The dosing day visit for pediatric trial 17086 is summarized below:

> Dosing Visit: An overnight stay in a study center was intended to target a morning blood glucose level of 90-160 mg/dL. A hypoglycemic clamp was initiated with insulin glulisine (Apidra) IV infusion to achieve a target a plasma glucose level of 80 mg/dL. Once the glucose concentration declined to <80 mg/dL, the insulin infusion was stopped, and baseline plasma glucose was assessed approximately 5 minutes later. If plasma glucose was ≥54 mg/dL and <80 mg/dL the IMP (i.e., dasiglucagon, GlucaGen, or placebo) was administered, defining time t=0. Plasma glucose samples for efficacy evaluation were collected pre-dose, and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 45, and 60 minutes after dosing. The actual time of blood sampling for evaluation of plasma glucose was not to have deviated from the nominal time by more than ± 30 seconds until the 20-minute collection time point and by more than ±1 minute for the subsequent collection time points. After 60 minutes, subjects were allowed to eat and drink moderately (with a maximum of 50 g carbohydrates) to decrease the potential for nausea.

The IMP was delivered in the abdomen or thigh (according to stratification) via SC injection. The trial was double-blind (blinded to subject and to the analysis personnel) to increase trial validity and to reduce bias during evaluation of the treatments. Because the trial medications were not identical in appearance, the handling, preparation and administration of trial medication was performed by unblinded trial personnel who were not involved in any other trial procedures or assessments.

During insulin-induced hypoglycemia, plasma glucose levels were monitored closely, and subjects were to receive a post-treatment rescue glucose IV infusion to ameliorate persistent hypoglycemia if one of the following criteria was met: if a subject experienced escalating symptoms of hypoglycemia, if plasma glucose was <54 mg/dL between t=8 and t=44 minutes, or if plasma glucose was <70 mg/dL at t=45 minutes.

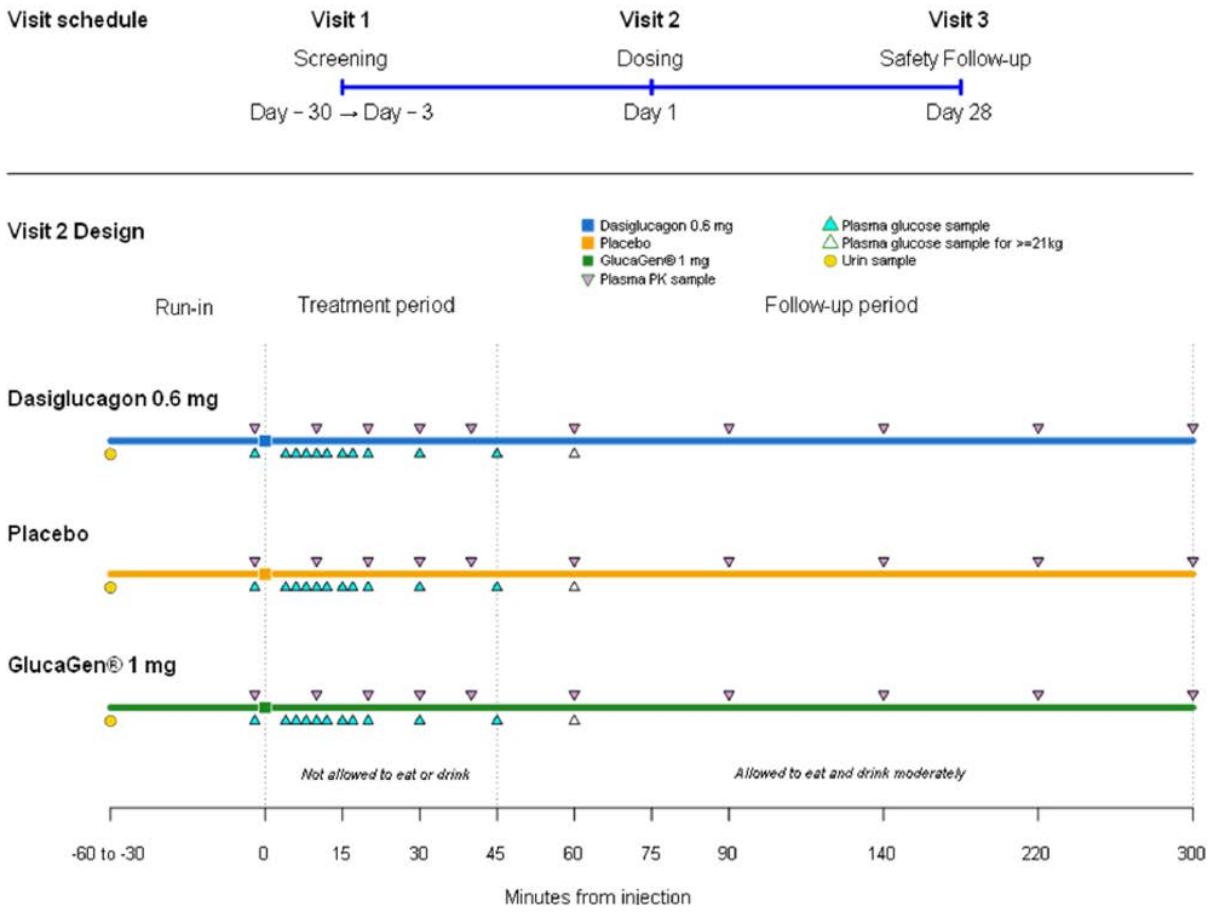


Figure 11. Overview of 17086 Study Design
Source: 17086 Study Report

Inclusion Criteria (summarized)

1. Informed consent obtained
2. Female or male patient with T1DM for at least 1 year and receiving daily insulin
3. ≥6 to <18 years of age
4. Body weight ≥20 kg
5. Appropriate contraception requirements (if applicable)

Exclusion Criteria (summarized)

1. Females who were pregnant, actively attempting to get pregnant, or were lactating
2. Known or suspected allergy to IMP(s) or related products

3. History of anaphylaxis or symptoms of severe systemic allergy (such as angioedema)
4. Previous randomization in this trial
5. History of an episode of severe hypoglycemia that required a third-party assistance within a month before screening visit
6. History of hypoglycemic events associated with seizures or hypoglycemia unawareness in the last year before screening
7. History of epilepsy or seizure disorder
8. Receipt of any investigational drug within 3 months before screening
9. Active malignancy within the last 5 years
10. Congestive heart failure, New York Heart Association class II-IV
11. Current bleeding disorder, including anti-coagulant treatment
12. Known presence or history of pheochromocytoma or insulinoma
13. Use of a daily systemic beta-blocker drug, indomethacin, warfarin or anticholinergic drugs in the previous 28 days before Day 1 of this trial
14. AST or ALT >2.5 × the upper limit of the normal range, bilirubin >1.5 × the upper limit of the normal range, eGFR <30 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease study definition, or altered electrolyte values of clinical relevance for cardiac conduction, as judged by the investigator
15. Clinically significant abnormal ECG at screening, as judged by the investigator
16. Clinically significant illness within 4 weeks before screening, as judged by the investigator
17. Surgery or trauma with significant blood loss within the last 2 months before screening
18. Subjects with mental incapacity or language barriers which preclude adequate understanding or cooperation, who were unwilling to participate in the trial, or who in the opinion of the investigator should not participate in the trial
19. Any condition interfering with trial participation or evaluation or that could be hazardous to the subject
20. The use of prescription or non-prescription medications known to cause QT prolongation

Additional dosing day exclusion criteria were also prespecified, which did not differ significantly from the dosing day exclusion criteria applied to adult trials (see section 6.1 for criteria).

Reviewer Comment: As discussed in in 6.1 (see the 'reviewer comment' associated with the inclusion/exclusion criteria), the Applicant implemented several exclusion criteria that were likely unnecessary. However, the implementation of these criteria is not expected to have an impact on the ability of dasiglucagon to effectively raise blood glucose. As noted previously, additional dosing day criteria were employed to enable the reliable estimation of the primary endpoint during the clamp procedure, and do not have further labeling implications.

Reviewer comment: Only subjects with body weight ≥20 kg were eligible for enrollment in this trial. See sections 7.2.1 and 8.4.5 for additional discussion on efficacy and safety considerations regarding this exclusion criterion.

Study Endpoints

The primary and secondary endpoints were the same for pediatric trial 17086 as for adult trials 16137 and 17145. Endpoints related to PK/PD differed between adult and pediatric trials.

Primary Efficacy Endpoint:

- Time to plasma glucose recovery, defined as the first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose

Key Secondary Efficacy Endpoints:

- Plasma glucose recovery within 30, 20, 15 and 10 minutes after IMP administration without administration of rescue IV glucose
- Plasma glucose change from baseline at 30, 20, 15 and 10 minutes after IMP administration or at the time of rescue

Safety Endpoints:

- AEs, clinical laboratory assessments (biochemistry, hematology, coagulation, and urinalysis), vital signs, physical examination, clinically significant changes in ECGs, local tolerability, administration of rescue IV glucose infusion after IMP injection, time to first IV glucose infusion
- Immunogenicity endpoint: occurrence of antidrug antibodies (ADAs)

Pharmacokinetic endpoints:

- Area under the plasma dasiglucagon or GlucaGen concentration versus time curve from 0 to 30 minutes post-dose ($AUC_{0\text{-}30min}$)
- Area under the plasma dasiglucagon or GlucaGen concentration versus time curve from 0 to 300 minutes post-dose ($AUC_{0\text{-}300min}$)
- Area under the plasma dasiglucagon or GlucaGen concentration versus time curve from 0 to infinitely post-dose ($AUC_{0\text{-}inf}$)
- Maximum of all valid plasma dasiglucagon or GlucaGen concentration measurements from 0 to 300 minutes post-dose (C_{max})
- Time to maximum of plasma dasiglucagon or GlucaGen concentration measurements (t_{max})
- Terminal elimination rate constant of plasma dasiglucagon or GlucaGen (λz)
- Terminal plasma elimination half-life of dasiglucagon or GlucaGen (t½)
- Total body clearance of plasma dasiglucagon or GlucaGen (CL/f)
- Volume of distribution of plasma dasiglucagon or GlucaGen (Vz/f)
- Mean residence time of plasma dasiglucagon or GlucaGen (MRT)

Pharmacodynamic endpoints:

- Plasma glucose response as area under the effect curve above baseline from time 0 to 30 minutes, $AUE_{0\text{-}30min}$

Sample Size

The primary comparison was between dasiglucagon and placebo treatment arms. From dose-finding trial 15126, the median time to an increase of 20 mg/dL of the 0.6 mg dasiglucagon was approximately 10 minutes. For subjects in the placebo group, the median time to recovery was assumed to be more than 50 minutes. Assuming an exponential time-to-recovery distribution with median times of 10 and 50 minutes, a 2-sided log-rank test would be able to detect a difference between dasiglucagon 0.6 mg and placebo with 90% power at a 5% significance level with 20 subjects randomized to the dasiglucagon arm and 10 subjects to placebo and with a follow-up time of 45 minutes. GlucaGen was included as a reference to compare the responses and AE profile of dasiglucagon with those of a marketed product. It was considered that 10 subjects in the GlucaGen group would suffice for the comparison.

Statistical Analysis Plan

The statistical analysis plan for trial 17086 was similar to the plans for the adult trials. Additionally, the statistical reviewer utilized the same methodology for her analysis for all phase 3 trials used to support efficacy (i.e. 16137, 17145, and 17086). See Section 6.1 and Dr. Yoonhee Kim's statistical review for additional information.

Protocol Amendments

The trial protocol version used in the US and Slovenia was protocol version 1.0 dated June 8, 2018. The protocol version used in Germany was protocol version 3.0 dated January 8, 2019. Version 3.0 differs from version 1.0 in the following aspects: the inclusion of a "staggered approach" whereby a positive safety assessment needed to be available for at least 10 subjects in the age group of ≥12 years to <18 years before younger subjects were allowed to be enrolled, additional inclusion criteria stating that subjects had to be in good and stable medical condition, and minor edits to the assessment of anticipated benefits/risks.

6.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided a statement that trial 17086 was performed in compliance with International Council for Harmonization guideline on Good Clinical Practice.

Financial Disclosure

See section 13.2 for details.

Subject Disposition

A total of 59 subjects were screened of whom 42 were randomized (Table 13). One subject who was randomized to receive dasiglucagon did not agree to rescheduling the dosing visit after having failed to reach the required pre-dose plasma glucose range at the initial dosing visit. This subject was not included in any analysis set. Of the remaining 41 subjects who received an IMP, there were no dropouts and all subjects completed the study to the safety follow-up visit. The analyses completed by the Applicant and in this review are based on the FAS population.

Table 13. Subject Disposition - Trial 17086

		Randomized	***Treated (FAS)***	***Completed***
Trial 17086	*Dasiglucagon*	21*	20	20
	Placebo	11	11	11
	GlucaGen	10	10	10

**Subject withdrew consent after randomization but before administration of the investigational product.*
Source: Statistical reviewer's analysis (modified format)

Protocol Violations/Deviations

Protocol deviations were recorded by the investigator and, prior to data release for statistical analysis, a treatment-masked review of all data took place to identify protocol deviations that may have potentially affected the results. Protocol deviations were classified as either major or minor. Three subjects, one from each treatment group, were not included in the PP analysis due to irregularities with plasma glucose sampling at the dosing visit, such that it was either not possible to reliably calculate the primary endpoint, or the estimate of the primary endpoint was likely to be biased. Deviations for these subjects are summarized as follows:

- Subject (b) (6) (dasiglucagon group): Blood sampling was out of window by 4 minutes at pre-dose, and by 2 minutes each at 15, 17, and 20 minutes after dosing.
- Subject (b) (6) (placebo group): No blood samples were collected at 8, 10, and 12 minutes due to problems with the IV access.
- (b) (6) (GlucaGen group): Blood sampling was out of window by 5 minutes at pre-dose.

The decision whether a protocol deviation was relevant or not for the exclusion of subjects from the PP analysis set was made case-by-case in a data review meeting before breaking the

blind.

Subject Demographic and Baseline Disease Characteristics

Subject demographics and baseline characteristics are presented in Table 14. Forty-one subjects with T1DM with a mean age in younger pediatrics (≥6 to <12 years) of 9 years and a mean age in adolescents (≥12 to <18) of 15 years were enrolled. Approximately half of the subjects were male in the dasiglucagon (50%) and placebo (56%) treatment groups. In all age cohorts and treatment groups, the population was predominantly White (95%) and non-Hispanic/Latino (81%). Body weight ranged from 21.2 to 117 kg in the dasiglucagon group. There were some imbalances in treatment groups and subgroups by age because of the small sample size. Prior medical history/concomitant illnesses at screening were also similar among treatment groups (data not shown). Seventy-one percent of subjects were from the US.

Table 14. Demographics and Baseline Characteristics – Trial 17086

	0.6 mg Dasiglucagon n=20		1.0 mg GlucaGen n=10		Placebo n=11		Totals n=41
	12-17 years n=12	6-11 years n=8	12-17 years n=6	6-11 years n=4	12-17 years n=7	6-11 years n=4	
Age - years							
Mean	14.7	8.8	14.7	9.0	15.0	9.0	12.5
Range	12-17	7-11	12-17	7-11	13-17	7-10	7-17
Sex - count subjects (%)							
Male	7 (35%)	3 (15%)	6 (60%)	2 (20%)	5 (45%)	0 (0%)	23 (56%)
Female	5 (25%)	5 (25%)	0 (0%)	2 (20%)	2 (18%)	4 (36%)	18 (44%)
Race - count subjects (%)							
White	11 (55%)	8 (40%)	6 (60%)	4 (40%)	7 (64%)	3 (27%)	39 (95%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	1 (2%)
Multiple	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Ethnicity - count subjects (%)							
Not Hispanic/Latino	9 (45%)	7 (35%)	5 (50%)	4 (40%)	6 (55%)	2 (18%)	33 (81%)
Hispanic/Latino	3 (15%)	1 (5%)	1 (10%)	0 (0%)	1 (9%)	1 (9%)	7 (17%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (9%)	1 (2%)
Region							
US	10 (50%)	3 (15%)	5 (50%)	2 (20%)	6 (55%)	3 (27%)	29 (71%)
Outside of US	2 (10%)	5 (25%)	1 (10%)	2 (20%)	1 (9%)	1 (9%)	12 (29%)
Screening weight – kg							

Mean (std.dev.)	62.8 (19.6)	34.7 (13.9)	59.4 (5.3)	32.9	66.1 (16.6)	35.4 (13.2)	51.8(20.1)
Range	38.8-117	21.2-60.4	53.2-67.1	25.0-39.9	45.0-91.7	23.0-53.7	21.2-117
Screening HbA1C - %							
Mean (std.dev.)	7.9 (1.4)	7.2 (0.4)	8.1 (1.4)	7.4 (0.6)	7.9 (1.4)	7.6 (0.86)	7.7 (1.1)
Range	6-11.2	6.7-7.8	6.9-10.7	6.9-8.1	5.3-9.9	6.7-8.7	5.3-11.2
Baseline glucose - mg/dL							
Mean (std.dev.)	73.2 (6.2)	72.3 (3.9)	70.3 (7.2)	72.4 (2.7)	69.2 (7.5)	75.1 (1.6)	72.0 (5.9)

Source: Generated in JReview by Reviewer using ADSL, ADLB, and ADVS datasets
Std.dev.: standard deviation

Reviewer comment: The observed imbalances between treatment groups, which are likely attributable to the small size of the study, are not expected to have an impact on the efficacy results.

Reviewer Comment: Although the protocol specified enrollment of subjects ≥6 years of age, the youngest subjects enrolled in trial 17086 were 7 years old. See sections 7.2.1 and 8.4.5 for efficacy and safety considerations to support extrapolation of data from the younger pediatric subgroup to support approval in pediatrics down to 6 years of age.

Efficacy Results – Primary Endpoint

Trial 17086 demonstrated superiority of dasiglucagon compared to placebo on median time to plasma glucose recovery, defined as first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose (Table 15 and Figure 12). The median time to plasma glucose recovery within 45 minutes was statistically significantly less in the dasiglucagon group (10 minutes [95% CI: 8, 12]) than in the placebo group (30 minutes [95% CI: 20, upper limit not estimable]; log-rank test 2-sided p-values < 0.001). All subjects who received dasiglucagon met the primary endpoint within 45 minutes and therefore no censoring occurred in this treatment arm. Seven (64%) subjects who received placebo also recovered within 45 minutes. One subject who received placebo was administered rescue glucose 12 minutes after dosing but did not recover within 45 minutes despite this intervention, and an additional three subjects also failed to recover within 45 minutes of dosing. Thus, four subjects who received placebo were censored (i.e., set to 'not recovered') in the analysis.

Table 15. Time to Plasma Glucose Recovery (FAS) – Trial 17086

	Trial 17086 *N=20 (dasiglucagon)* *N=11 (placebo)*
Dasiglucagon	
Number of subjects rescued[*]	0
Number of subjects censored[†]	0
Median time (95% CI)	10 minutes (8, 12)
Min, Max	8, 17 minutes
Placebo	
Number of subjects rescued[*]	1
Number of subjects censored[†]	4
Median time (95% CI)	30 minutes (20, NE)
Min, Max	17, 45 minutes
Hazard Ratio (95%CI)[‡]	51 (6, 424)**
Recovery Time Ratio (95%CI) [‡‡]	0.29 (0.23, 0.36)

*[*]Rescued: Number of subjects who received IV glucose within 45 minutes after dosing; [†]Censored: Number of subjects who were censored at 45 minute after dosing due to no recovery or having rescue IV glucose within 45 minutes after dosing; ** only for a reference due to violation of assumption of proportional hazards [‡]By Applicant using a discrete Cox Proportional Hazard model [‡‡] By statistical reviewer using the survival time ratio from Parametric Survival Model.*
Source: Statistical reviewer's analysis

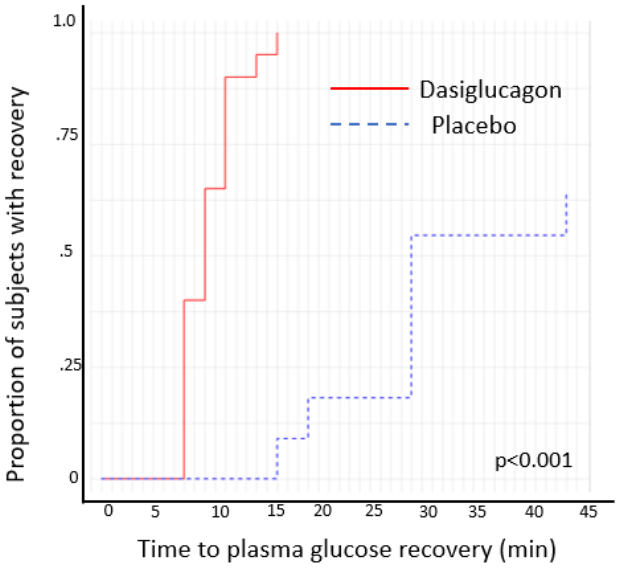


Figure 12. Cumulative Proportions of Subjects with Recovery (FAS) – Trial 17086
Source: Statistical reviewer's analysis (modified format)

An analysis by age group was also performed (Table 16), which did not reveal any significant differences in time to recovery between younger pediatric subjects and adolescents.

Table 16. Time to Plasma Glucose Recovery by Age Group - Trial 17086

	6-11 years *N=8 (dasiglucagon) N=4 (placebo)*	***12-17 years*** *N= 12 (dasiglucagon) N=7 (placebo)*
Dasiglucagon		
Median time (95% CI)	9 minutes (8, 12)	10 minutes (8,12)
Number of subjects rescued*	0	0
Number of subjects censored†	0	0
Placebo		
Median time (95% CI)	25 minutes (17, NE)	45 minutes (30, NE)
Number of subjects rescued*	0	1
Number of subjects censored†	1	3

**Rescued: Number of subjects who received IV glucose within 45 minutes after dosing; †Censored: Number of subjects who were censored at 45 minutes after dosing due to no recovery or having rescue IV glucose within 45 minutes after dosing; NE: Not estimable*
Source: Statistical reviewer's analysis

Reviewer comment: Efficacy results from trial 17086 are similar to the results from the adult trials. No important differences in efficacy between adult and pediatric populations are evident from these data.

While no formal statistical comparison was carried out between dasiglucagon and GlucaGen, the median time to recovery was similar between dasiglucagon (10 minutes [95% CI: 8, 12]) and GlucaGen (10 minutes [95% CI: 8, 12]) (Applicant's analysis).

The Applicant performed the following sensitivity analyses that were prespecified in the SAP: assessment of time to plasma glucose recovery 1) without censoring for subjects who required rescue IV glucose before 45 minutes and 2) with censoring at the time of administration of rescue IV glucose before 45 minutes. Sensitivity analysis also was performed with the PP set. These analyses did not importantly alter the results of the trial, with dasiglucagon consistently demonstrating a shorter time to plasma glucose recovery than placebo. The Applicant utilized linear interpolation with the FAS dataset (i.e. including censored subjects) between the two time points before and after recovery had occurred to obtain an estimate of the true recovery time. This method estimated a median time to plasma glucose recovery of 8.7 minutes (95% CI: 6.9 to 10.6) in the dasiglucagon group, 29.3 minutes (95% CI: 18.5, upper limit not estimable) in the placebo group, and 9.8 minutes (95% CI: 7.4 to 10.6) in the GlucaGen group (Applicant's analysis).

Data Quality and Integrity

I did not identify any issues regarding data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Plasma glucose recovery within 30, 20, 15, and 10 minutes post-dose

The numbers and percentages of subjects with plasma glucose recovery within 30, 20, 15 and 10 minutes are shown in Table 17. At all timepoints, a greater proportion of dasiglucagon-exposed subjects had recovered compared with the placebo group; all differences were statistically significant with Fisher's exact p-values < 0.01.

Table 17. Number of Subjects (Percent) with Plasma Glucose Recovery Within Defined Time Points (FAS) – Trial 17086

Plasma Glucose Recovery (min)	***Dasiglucagon N=20***	***Placebo N=11***
Recovery within ≤30 mins	20 (100%)	6 (55%)
Recovery within ≤20 mins	20 (100%)	2 (18%)
Recovery within ≤15 mins	19 (95%)	0 (0%)
Recovery within ≤10 mins	13 (65%)	0 (0%)

Source: Statistical reviewer analysis (with modified formatting)

Plasma Glucose Change from Baseline at 30, 20, 15 and 10 minutes:

Plasma glucose changes in LS mean from an ANCOVA model from baseline to 30, 20, 15 and 10 minutes are summarized in Table 18. The mean plasma glucose increase is greater than 20 mg/dL by 10 minutes post-dose in the dasiglucagon group, whereas the increase is less than 20 mg/dL at all timepoints in the placebo group. All treatment differences are statistically significant (ANCOVA).

Table 18. Plasma Glucose Change from Baseline at Defined Timepoints (FAS) – Trial 17086

Δ Glucose mg/dL	***Dasiglucagon*** *LS mean (SE)*	***Placebo*** *LS mean (SE)*
at 30 minutes	98.2 (4.4)	17.3 (4.7)
at 20 minutes	65.4 (3.5)	7.3 (4.0)
at 15 minutes	45.3 (3.4)	0.8 (3.4)
at 10 minutes	27.2 (3.1)	-3.4 (2.4)

Source: Statistical reviewer analysis (with modified formatting)
LS: Least squared; SE: Standard error

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The efficacy evaluation is derived from three placebo-controlled trials in subjects with T1DM; two trials in adults (16137 and 17145) and one trial in pediatrics (17086), as detailed in sections 6.1, 6.2 and 6.3. These were the only placebo-control studies in the clinical development program of dasiglucagon for the treatment of severe hypoglycemia, and therefore the

integrated assessment of efficacy will be limited to these trials.

7.1.1. Primary Endpoint

The primary endpoint in all three placebo-controlled trials was time to plasma glucose recovery, defined as the first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose. This endpoint was agreed upon with the Agency during EOP2 discussions as a clinically meaningful endpoint for which substantial evidence of effectiveness can be established.

Results from trials 16137, 17145, and 17086 are summarized in Table 19. All results were significant to demonstrate the superiority of dasiglucagon compared to placebo (all log-rank test 2-sided p-values <0.001). The results are also remarkably similar across the three trials.

Table 19. Summary of Time to Plasma Glucose Recovery – 16137, 17145, 17086

	Trial 16137 *N=82 (dasiglucagon) N=43 (placebo)*	***Trial 17145*** *N=34 (dasiglucagon) N=10 (placebo)*	***Trial 17086*** *N=20 (dasiglucagon) N=11 (placebo)*
Dasiglucagon			
Number of subjects rescued*	0	1	0
Number of subjects censored†	0	1	0
Median time (95% CI)	10 minutes (10, 10)	10 minutes (8,12)	10 minutes (8,12)
Min, Max	4, 25 minutes	4, 45 minutes	8, 17 minutes
Placebo			
Number of subjects rescued*	0	2	1
Number of subjects censored†	12	3	4
Median time (95% CI)	40 minutes (30, 40)	35 minutes (20, NE)	30 minutes (20, NE)
Min, Max	15, 45 minutes	20, 45 minutes	17, 45 minutes
Hazard Ratio (95%CI)‡	111 (38, 330)	10 (4, 34)	51 (6, 425)**
Recovery Time Ratio (95%CI) ‡‡	0.29 (0.26, 0.33)	0.29 (0.21, 0.4)	0.29 (0.23, 0.36)

**Rescued: Number of subjects who received IV glucose within 45 minutes after dosing; †Censored: Number of subjects who were censored at 45 minutes after dosing due to no recovery or having rescue IV glucose within 45 minutes after dosing; ** only for a reference due to violation of assumption of proportional hazards ‡By Applicant using a discrete Cox Proportional Hazard model ‡‡ By statistical reviewer using the survival time ratio from Parametric Survival Model*
Source: Statistical reviewer's analysis

7.1.2. Secondary and Other Endpoints

Dasiglucagon demonstrated superiority to placebo for all secondary endpoints, which were the proportion of subjects obtaining plasma glucose recovery within 30, 20, 15, and 10 minutes after investigational product injection without administration of rescue IV glucose (four separate endpoints; all Fisher's exact p-values <0.01), and plasma glucose change from baseline at 30, 20, 15, and 10 minutes after investigational product injection or at the time of rescue (four separate endpoints; all ANCOVA p-values <0.001). See sections 6.1, 6.2, and 6.3 for additional information. These results support the primary endpoint.

7.1.3. Subpopulations

A subgroup analysis comprised of pooled data from adult placebo-controlled trials 16137 and 17145 was performed by the FDA statistical reviewer, Dr. Kim, to investigate the impact of selected intrinsic and extrinsic factors on efficacy. Note, this review included only adult, placebo-controlled studies in the subgroup evaluation, as the main evaluation of dasiglucagon efficacy is against placebo. In contrast, the Applicant pooled the data from trial 15126 and 17086 with the data from 16137 and 17145 to generate a larger pool for analysis. Per Dr. Kim's review, no significant information is added to the small sample sized subgroups (e.g. non-White, ≥65 years of age, etc.) with inclusion of 15126 and 17086, and therefore subgroup analysis should be limited to the pooled dataset of placebo-controlled adult studies. Subpopulation analysis for the pediatric trial was performed separately.

Subgroup analyses using the primary efficacy analysis (i.e., Kaplan-Meier estimates for median time to recovery and 95% CI, log-rank test) were performed. Subgroups investigated included the following:

- Sex (Female vs. Male)
- Age categories (≥65 vs. <65 years) and quartiles
- Race (White, African American, and Others)
- Ethnicity (Hispanic/Latino, Non-Hispanic/Latino)
- Geographic region (US vs. outside of US)
- Injection site (Abdominal, Buttock, Deltoid, and Thigh)
- BMI quartiles
- Weight (20-40 kg vs. ≥40 kg; pediatrics only)

Consistent superiority of dasiglucagon compared to placebo was demonstrated in all demographic subgroups utilizing the adult placebo-controlled pool (Table 20). Likewise, consistent superiority of dasiglucagon compared to placebo was also demonstrated for pediatric trial 17086 (Table 21). Note, a subgroup analysis based on race was not performed in pediatrics because all but two subjects in the study were White.

Table 20. Time to Plasma Glucose Recovery by Subgroups – Placebo-Controlled Pool

Demographic parameters	0.6 mg Dasiglucagon		Placebo	
	N* (n**)	Median Time to Plasma Glucose Recovery (95% CI)	N* (n**)	Median Time to Plasma Glucose Recovery (95% CI)
Overall				
	116 (115)	10 minutes (10, 10)	53 (38)	40 minutes (30, 40)
Sex				
Male	66 (66)	10 minutes (10, 12)	36 (23)	40 minutes (30, NE)
Female	50 (49)	10 minutes (8, 10)	17 (15)	30 minutes (20, 40)
Age				
<65 years	111 (110)	10 minutes (10, 10)	52 (37)	40 minutes (30, 40)
≥65 years	5 (5)	15 minutes (15, NE)	1 (1)	30 minutes (NE, NE)
Q1: <30 years	26 (26)	8 minutes (8, 10)	16 (15)	25 minutes (25, 30)
Q2: ≥30 to <37 years	26 (26)	10 minutes (10, 10)	13 (7)	45 minutes (30, NE)
Q3: ≥37 to <48 years	30 (30)	10 minutes (8, 12)	10 (9)	40 minutes (20, 40)
Q4: ≥48 years	34 (33)	12 minutes (10,12)	14 (7)	40 minutes (30, NE)
Race				
White	110 (109)	10 minutes (10, 10)	46 (35)	35 minutes (30, 40)
African American	1 (1)	12 minutes (NE, NE)	2 (2)	37.5 minutes (30, NE)
Others	5 (5)	10 minutes (8, NE)	5 (1)	20 minutes (NE, NE)
Geographic Region				
US	34 (33)	10 minutes (8, 12)	10 (7)	35 minutes (20, NE)
Outside of US	82 (82)	10 minutes (10, 10)	43 (31)	40 minutes (30, 40)
Ethnicity				
Hispanic or Latino	6 (6)	10 minutes (8, NE)	5(4)	30 minutes (25, NE)
Not Hispanic or Latino	116 (115)	10 minutes (10, 10)	53 (38)	40 minutes (30, 40)
BMI Quartile				
Q1: <23 kg/m^2	31 (31)	10 minutes (10, 12)	8 (5)	42.5 minutes (17, NE)
Q2: ≥23 to <26 kg/m^2	30 (30)	10 minutes (10 ,12)	18 (13)	40 minutes (30, 40)
Q3: ≥26 to <29 kg/m^2	22 (22)	10 minutes (8, 10)	18 (14)	35 minutes (25, 40)
Q4: ≥29 kg/m^2	33 (32)	10 minutes (10, 12)	9 (6)	30 minutes (20, NE)

**N: number of subjects in the subgroup; **n: number of subjects who recovered within 45 minutes after dosing without a rescue IV glucose administration, NE: Not estimable*
Source: statistical reviewer's analysis

Table 21. Time to Plasma Glucose Recovery by Subgroups – Pediatric Trial 17086

Demographic parameters	0.6 mg Dasiglucagon		Placebo	
	N* (n**)	Median Time to Plasma Glucose Recovery (95% CI)	N* (n**)	Median Time to Plasma Glucose Recovery (95% CI)
Overall				
	20 (20)	10 minutes (8, 12)	11 (7)	30 minutes (20, NE)
Sex				
Male	10 (10)	10 minutes (8, 12)	5 (3)	45 minutes (30, NE)
Female	10 (10)	9 minutes (8, 12)	6 (4)	30 minutes (17, NE)
Age				
6-11 years	8 (8)	9 minutes (8, 12)	4 (3)	25 minutes (17, NE)
12-17 years	12 (12)	10 minutes (8,12)	7 (4)	45 minutes (30, NE)
Geographic Region				
US	13 (13)	10 minutes (8, 12)	9 (7)	30 minutes (17, NE)
Outside of US	7 (7)	8 minutes (8, 12)	2 (0)	NE
Ethnicity				
Hispanic or Latino	4 (4)	12 minutes (8, 17)	2 (1)	30 minutes (30, NE)
Not Hispanic or Latino	16 (16)	10 minutes (8, 10)	8 (5)	37.5 minutes (20, NE)
Weight				
≥20 to <40 kg	6 (6)	9 minutes (8, NE)	3 (2)	30 minutes (20, NE)
≥40 kg	14 (14)	10 minutes (8,12)	8(5)	37.5 minutes (17, NE)

**N: number of subjects in the subgroup; **n: number of subjects who recovered within 45 minutes after dosing without a rescue IV glucose administration, NE: Not estimable*
Source: Statistical reviewer's analysis

Figure 13 illustrates a forest plot with recovery time ratios to compare overall efficacy results across subgroups in the placebo-controlled pool. As described in 6.1 (Statistical Analysis Plan), with time to recovery in the placebo group as a reference, the survival time ratio is the ratio of recovery time in the dasiglucagon group to recovery time in the placebo group. Recovery time ratios <1 favor dasiglucagon.

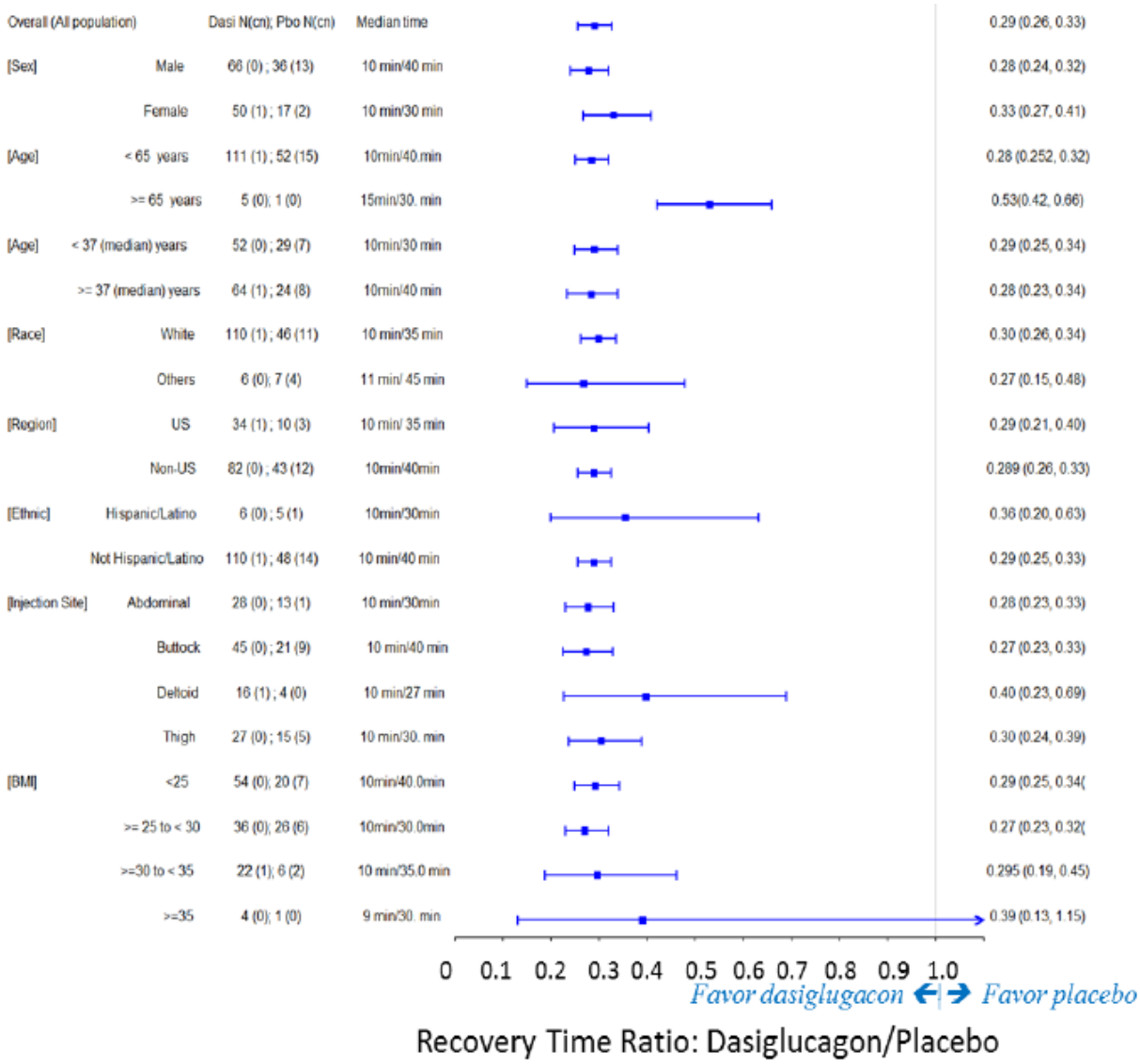


Figure 13. Forest Plot of Recovery Time Ratio by Subgroups - Pooled 16137 and 17145
** N(cn): sample size (censored subjects); The rightmost column is survival time ratio (95% CI) in each subgroup.*
Source: statistical reviewer's analysis

The recovery time ratio for overall population from the pooled placebo-controlled adult trials was 0.29 (0.26, 0.33). The recovery time ratio of each subgroup was within the range of 0.27 to 0.53, and consistently less than 1 (grey vertical line in Figure 13).

Reviewer comment: Although the data suggest a trend towards increasing response time with older age and increasing BMI these data are inconclusive, and based on the available data, recovery is adequate regardless of age or BMI. Section 8.5 of the PI should note that clinical

studies of dasiglucagon did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adults.

7.1.4. Dose and Dose-Response

All subjects in the adult and pediatric phase 3 trials received the intended dose of 0.6 mg dasiglucagon. Dose-response is acceptable for all subpopulations.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Since this is an emergency use product for treatment of severe hypoglycemia, patients are instructed to administer oral glucose/carbohydrates after initial recovery; therefore, duration and persistence of efficacy are not applicable for this product.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the postmarket setting, dasiglucagon is anticipated to have a similar treatment effect as was observed within the context of the clinical development program once the injection is administered. In the post-market setting, dasiglucagon will be administered by a caregiver, as opposed to in phase 3 trials where dasiglucagon was administered by unblinded trial personnel. As discussed in section 4.6, human factors studies were conducted to support this application, and potential use errors can be mitigated by product labeling (see Dr. Colleen Little's review dated December 11, 2020 for additional information).

Due to the potential confounding effect of endogenous insulin production in patients with T2DM, the enrolled trial population was limited to patients with T1DM. The mechanism of action of dasiglucagon is through the activation of hepatic breakdown of glycogen, which is not expected to importantly differ between populations. Furthermore, guidelines for treatment of severe hypoglycemia do not distinguish between treatment of patients with T1DM and T2DM, and the efficacy outcome of the development program is considered applicable to both populations

As discussed in sections 6.1 and 6.3, the Applicant implemented various exclusion criteria that were likely unnecessary such as excluding subjects with a history of malignancy, subjects with congestive heart failure, and/or subjects with inadequately treated elevated blood pressure. However, the implementation of these criteria is not expected to have an impact on the ability of dasiglucagon to effectively raise blood glucose given the mechanism of action of dasiglucagon. Exclusion criteria that have clinically meaningful implications are recommended

for the labeling.

Regarding pediatric trial 17086, the Applicant limited enrollment to subjects weighing ≥20 kg, which is approximately 50th percentile for pediatrics 6 years of age. Therefore, dasiglucagon may be administered to pediatric patients <20 kg in real-world use. While this is not expected to impact the efficacy of dasiglucagon for the treatment of severe hypoglycemia, it is theoretically possible that post-dose glycemic excursions (i.e., excess hyperglycemia) could be observed in young children weighing <20 kg. However, as dasiglucagon is a potentially life-saving drug, this does not impact the risk-benefit assessment. Lastly, the youngest pediatric subject enrolled in 17086 was 7 years old. There is no concern that efficacy would differ between a patient 6 versus 7 years of age in the post-market setting.

7.2.2. Other Relevant Benefits

As dasiglucagon will be available in prefilled syringe/AI devices, there is potential for faster time to recovery from hypoglycemia and fewer medication errors as compared to older glucagon rescue products that require reconstitution. Note, however, that the clinical development program did not assess these potential benefits. Additionally, dasiglucagon can be stored either under refrigeration or at room temperature allowing for flexibility regarding storage options.

7.3. Integrated Assessment of Effectiveness

Dasiglucagon in comparison to placebo was evaluated in two phase 3 trials (16137 and 17145) conducted in adults with T1DM, and one trial (17086) conducted in pediatrics with T1DM. Dasiglucagon demonstrated superiority to placebo in all three trials for the clinically relevant endpoint of time to plasma glucose recovery, defined as the first increase in plasma glucose of ≥20 mg/dL from baseline without administration of rescue IV glucose. The median time to glucose recovery was 10 minutes (95% CI: 10, 10) and 10 minutes (95% CI: 8,12) with dasiglucagon in trials 16137 and 17145 compared to 40 minutes (95% CI 30, 40) and 35 minutes (20, upper limit not estimable) with placebo, respectively. The median time to recovery in pediatric trial 17086 was 10 minutes (95% CI: 8, 12) with dasiglucagon versus 30 minutes (20, not estimable) with placebo. All results were highly statistically significant. Dasiglucagon also demonstrated superiority to placebo for all secondary endpoints, although the secondary endpoints were also based on plasma glucose recovery.

Although no formal statistical comparison between dasiglucagon and GlucaGen was carried out, the inclusion of GlucaGen in trials 16137 and 17086 allows for the informal comparison of dasiglucagon to another glucagon product available for the treatment of severe hypoglycemia. Subjects who were administered GlucaGen demonstrated a median time to glucose recovery of 12 minutes (95% CI: 10, 12) and 10 minutes (95% CI: 8, 12) in trials 16137 and 17086,

respectively. Therefore, dasiglucagon appears similar to GlucaGen with respect to time to plasma glucose recovery from hypoglycemia.

No data quality issues were identified. Key analyses were reproducible. Dr. Kim performed an assessment of derived variables from STDM to ADAM datasets and no issues that would impact data analysis or quality were identified. OSI inspections were requested for selected adult and pediatric trial sites, and the inspectional findings support validity of data as reported by the Applicant under this NDA (see 4.1 for additional information). Additionally, because there were no missing data for the three studies, there were no concerns with respect to the handling of missing data in the evaluation of efficacy.

Overall, the data presented in this review from trials 16137, 17145, and 17086 provide robust evidence for superiority of dasiglucagon compared to placebo with two adequate and well-controlled trials in adults and one adequate and well-controlled trial in pediatric subjects aged ≥6 to <18 years. Secondary endpoints support the primary endpoint. Sensitivity analyses performed by the Applicant confirmed the robustness of the primary efficacy analyses. There were no important efficacy-by-subpopulation interactions. Descriptive analyses suggest that dasiglucagon is as effective as GlucaGen, a widely used native glucagon product approved for the treatment of severe hypoglycemia. The efficacy evidence presented herein supports approval of dasiglucagon for the treatment of severe hypoglycemia in adults and pediatrics with diabetes aged 6 years and older.

8. Review of Safety

8.1. Safety Review Approach

The pooling strategy shown in Figure 14 was agreed upon during a pre-NDA meeting. For this safety review, I confirmed the Applicant's key safety analyses using the FDA reviewer tool JReview and performed additional safety analyses where appropriate as described in relevant subsections.

Placebo-controlled pool

The primary safety analysis presented in this review is based on a pooled dataset comprised of two, phase 3, placebo-controlled trials (16137 and 17145), which were also used to support efficacy, referred herein as the 'placebo-controlled pool' (Figure 14, left panel). These trials were of similar design, employed the same inclusion/exclusion criteria, and used the to-be-marketed formulation and dose of dasiglucagon. The trials differ with respect to the comparators (i.e., inclusion of an active comparator treatment arm (GlucaGen) in trial 16137), randomization ratios, anatomic injection sites, and device used (i.e., the use of an AI instead of

a prefilled syringe in trial 17145). These two trials both had a parallel design and, therefore, data from these trials were pooled without any further data handling considerations aside from Cochran Mantel Haenszel (CMH) weighting. CMH weighting was applied to analyses of the placebo-controlled pool and broad pool to account for potential bias that may occur when combining data from studies with different randomization ratios (Simpson's paradox). The CMH weighting method and individual weights applied to each trial was confirmed by the statistical reviewer (Dr. Yoonhee Kim) as an appropriate method to account for pooling studies of different designs. The CMH weighting presented in this review was performed by the Applicant and randomly assessed for accuracy.

Broad pool

A secondary pool, referred to as the 'broad pool,' consisted of all available data from studies conducted in adult subjects with T1DM exposed to dasiglucagon ≥0.6 mg (Figure 14, middle panel). Individual studies differed significantly, utilizing various study designs (crossover and parallel), dasiglucagon doses (0.6 to 1.0 mg), routes of administrations (IM and SC), and baseline glycemic status (euglycemic vs. insulin-induced hypoglycemia via a hypoglycemic clamp). Safety analyses conducted using the broad pool are considered supportive (see Table 2 for additional details regarding the study designs for each trial included in the broad pool).

For crossover trials (14013 Part 2 and 15126), where subjects received a dose of dasiglucagon and a dose of GlucaGen, subject data from each single dose crossover period were considered to be independent outcomes, and the subject is counted twice, i.e. counted once in the denominator of each treatment arm. In crossover trials, it is assumed that there are no carry-over effects of each treatment due to the 7 ± 3-day washout period between treatments, which is reasonable given the 30- and 45- minute half-life of dasiglucagon and GlucaGen, respectively.

For trials with repeated single doses (bridging trial 17084 and immunogenicity trial 16136), subjects count once in the denominator but count as having an AE if the event was experienced at least once after any of the single doses. It is assumed that there is not an accumulated effect (either of dasiglucagon or GlucaGen) across the doses, which is reasonable given the short half-life of each drug.

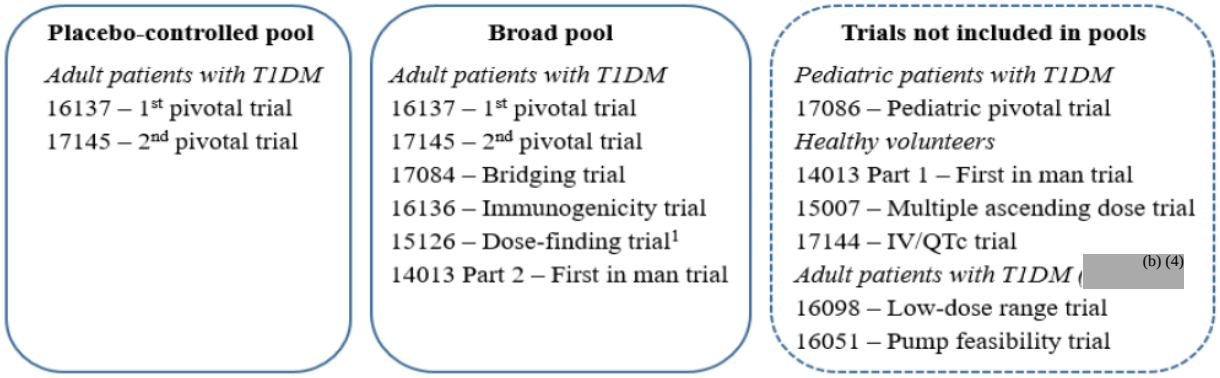
Note that GlucaGen was used as an active comparator in several trials in the clinical development program and therefore is included as a treatment arm in both the placebo-controlled and broad pools. Safety data from GlucaGen were used in this review to place the dasiglucagon safety data into context with respect to another therapeutic option for the treatment of severe hypoglycemia.

Trials not included in pools

The pediatric safety evaluation derived from trial 17086 is presented independently to support safety in this population.

Where relevant, additional supportive safety data is presented from trials enrolling healthy subjects in the development program of dasiglucagon for the treatment of severe hypoglycemia (trials 14013 (Part 1), 15007, and 17144), and from trials with dasiglucagon completed for other indications (b) (4)

Figure 14. Pooling Strategy for Safety Review



[1]Subjects exposed to dasiglucagon doses <0.6 mg (n=22) and GlucaGen doses of 0.5 mg (n=17) in dose-finding trial 15126 are not included in the broad pool
Source: ISS

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Overview

Across the dasiglucagon clinical development program for the treatment of severe hypoglycemia, 466 subjects were exposed to dasiglucagon at doses ranging from 0.01 to 2.0 mg (Table 22). Of the 466 people exposed to dasiglucagon, 358 had T1DM (338 adult and 20 pediatric subjects), and 108 were healthy subjects (HS). A total of 390 subjects were exposed to at least 0.6 mg (the proposed to-be-marketed dose). No subjects had T2DM.

The higher number of 'doses given' than 'subjects exposed' in Table 22 is attributable to trials in which repeat doses of dasiglucagon were administered. Studies that employed crossover designs such that subjects are represented in multiple treatment arms are indicated where appropriate.

Table 22. Number of Subjects Exposed to Dasiglucagon in the Clinical Development Program for Severe Hypoglycemia

Trial	Population	Route of Administration	<0.6 mg n (doses)	≥0.6 mg n (doses)	Placebo n (doses)	1 mg GlucaGen n (doses)
16137	T1DM	SC	-	82 (82)	43 (43)	43 (43)
17145	T1DM	SC	-	34 (34)	10 (10)	-
17084	T1DM	SC	-	90 (174)	-	-
16136	T1DM	SC	-	57 (163)	-	54 (155)
15126*	T1DM	SC	22 (22)	33 (33)	-	51 (51)**
17144	HS	IV/SC	18 (18)	24 (24)	18 (18)	-
15007	HS	SC	12 (60)	6 (30)	6 (30)	-
14013 - Part 1 - Part 2*	 HS T1DM	 - SC/IM - IM	 24 (24) -	 24 (24) 20 (20)	 - -	 16 (16) 20 (20)
17086	T1DM	SC	-	20 (20)	11 (11)	10 (10)
Total exposed - <0.6 mg - ≥ 0.6 mg			466 o 76 o 390		88	194

n: subjects exposed; doses: number of total doses given, including multiple dose trials.
**Crossover studies where subjects are counted in both dasiglucagon and GlucaGen treatment arms*
***Trial 15126 administered 0.5 mg (17 subjects) and 1.0 mg (34 subjects) doses of GlucaGen*
Source: Adapted from Table 1-6 in ISS with data confirmed by reviewer using ADEX dataset in JReview

Overall Exposure

Placebo-Controlled Pool

In the placebo-controlled pool, subjects were exposed to a single dose of 0.6 mg dasiglucagon (116 subjects), placebo (53 subjects), or 1 mg GlucaGen (43 subjects) and were in-study until the follow-up visit, a period of approximately four weeks. As the half-life of dasiglucagon is approximately 30 minutes the follow up period is acceptable. Due to different randomization ratios (3:1 dasiglucagon to placebo in 17145 and 2:1:1 dasiglucagon to GlucaGen to placebo in 16137), the absolute number of patient days of observation (PDO) differed among treatment arms (3,651 PDO for dasiglucagon, 1,689 PDO for placebo, and 1,246 PDO for GlucaGen); however, there were no withdrawals and all subjects completed the study to follow up and therefore the exposure among treatment arms is proportionally balanced.

Broad Pool

In the broad pool, 316 subjects were exposed to ≥0.6 mg dasiglucagon (506 doses), 53 to placebo (53 doses), and 151 to 1 mg GlucaGen (252 doses). As study designs differed between trials in the broad pool, PDOs differed significantly among treatment arms (15,115 PDOs for dasiglucagon, 1,689 PDO for placebo, and 7,538 PDO for GlucaGen). The percentage of subjects

in each treatment arm remained proportionally similar with respect to the duration of the observation period for approximately five weeks, after which there was more PDO with dasiglucagon and GlucaGen as compared to placebo. This imbalance was mainly driven by the inclusion of immunogenicity trial 16136 in the broad pool, in which subjects were dosed three times with either dasiglucagon or GlucaGen and attended three follow-up visits for the assessment of ADAs. While exposure is imbalanced between dasiglucagon/GlucaGen and placebo in the broad pool, key analyses in this review that utilize the broad pool were either limited to a 12-hour post-dose evaluation time frame (e.g., hemodynamics events) or were analyses that did not identify any events (e.g., renal and hepatic events). Therefore, this imbalance is of limited relevance for this review and exposure-adjusted safety analyses were not needed to assess the data.

Pediatric Trial

Twenty pediatric subjects were exposed to dasiglucagon (8 subjects in the 6-11 year-old subgroup, 12 subjects in the 12-17 year-old subgroup), 11 subjects to placebo (4 subjects in the 6-11 year-old subgroup, 7 subjects in the 12-17 year-old subgroup), and 10 subjects to GlucaGen (4 subjects in the 6-11 year-old subgroup, 6 subjects in the 12-17 year-old subgroup). As with the adult placebo-controlled trials, pediatric subjects were in-study for approximately four weeks after dasiglucagon exposure. There were no withdrawals, and all subjects completed the study. Therefore, the exposure between treatment arms is balanced.

8.2.2. Relevant Characteristics of the Safety Population:

Baseline characteristics of subjects from trials that comprise the placebo-controlled safety pool (16137 and 17145) are the same as in the Full Analysis Sets used for efficacy assessment and are provided individually in sections 6.1.2 and 6.2.2. The placebo-controlled pool consisted of 212 adult subjects with T1DM with a mean age of 39.5 years (18-71) years, a mean diabetes duration of 20.5 years (1.5-56.2 years), and a baseline mean HbA1c of 7.4% (5.2-9.7%). The majority of subjects were male (61%), White (92%), and non-Hispanic/Latino (93%). Relevant characteristics in the broad pool are similar to the placebo-controlled pool.

Relevant characteristics of the pediatric safety population (all from trial 17086) are provided in section 6.2.3. To re-summarize, 41 subjects with T1DM were enrolled with a mean age of 9 years in the younger pediatric cohort (6-11 year-old subgroup) and a mean age of 15 years in adolescents (12-17 year-old subgroup). Approximately half of the subjects were male in the dasiglucagon (50%) and placebo (46%) treatment assignments, with more males (80%) in the GlucaGen treatment assignment. In all age cohorts and treatment assignments, the population was predominantly White (95%) and non-Hispanic/Latino (81%).

8.2.3. Adequacy of the Safety Database:

The safety database (i.e. the placebo-controlled pool) appears adequate for evaluation of common adverse events associated with the administration of dasiglucagon. The broad pool allows for additional analyses and provides supportive safety information. Pediatric trial 17086 supports safety in the claimed pediatric population. Although subjects were predominantly white and non-Hispanic/Latino, race/ethnicity is not expected to impact the safety of dasiglucagon, and the safety database is sufficient to establish safety and efficacy in the intended use population in the US. Given that this product is intended for single-dose emergency use, the safety database is considered adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the submission appears adequate. The key safety findings presented in this NDA were reproducible and confirmed using the submitted datasets. In addition, the findings from OSI inspections of three clinical sites supports the validity of the clinical data (see 4.1 for additional information).

8.3.2. Categorization of Adverse Events

All adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) using the current MedDRA version at the time of trial reporting. For pooling purposes, the Applicant mapped AEs presented in the placebo-controlled and broad pool datasets to MedDRA version 22.0. MedDRA version 22.0 was also used for all queries.

The Applicant defined an AE as any untoward medical occurrence in a clinical trial subject administered a medicinal (investigational or non-investigational) product that did not necessarily have a causal relationship with the treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of the product, whether related to the product or not. A serious AE (SAE) was defined as any untoward medical experience that resulted in any of the following: death, a life-threatening experience, in-patient hospitalization or prolongation of existing hospitalization, or a congenital anomaly. Important medical events would also be considered an SAE when (based on appropriate medical judgement) the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE.

Investigators provided their assessment of whether there may be a causal relationship between the investigational product and each AE, and events were graded by the investigator as mild,

moderate, or severe.

Hypoglycemia was defined as a plasma glucose of <45 mg/dL in the time period from initiation of the hypoglycemic clamp procedure until 45 minutes after dosing. For the remainder of the trial, hypoglycemia was defined as a plasma glucose of <70 mg/dL.

See 8.5.1 for definitions of pre-defined AESIs (i.e., hemodynamic events).

8.3.3. Routine Clinical Tests

Routine clinical tests included clinical chemistry and hematology laboratory tests (8.4.6), vital signs (8.4.5), ECGs (8.4.6), and physical examinations at screening, dosing, and follow-up visits.

8.4. Safety Results

8.4.1. Deaths

To date, no deaths have been reported in dasiglucagon-exposed subjects in clinical studies for any proposed indication.

8.4.2. Serious Adverse Events

One SAE was reported in the clinical development program of dasiglucagon for the treatment of severe hypoglycemia. The SAE occurred in the immunogenicity trial 16136 and is summarized below.

- Subject ID (b) (6): A 64-year-old male subject experienced an SAE of hypoglycemia approximately 26 hours after the first dose of dasiglucagon. On the morning of the SAE, the subject took his regular seven units of insulin with breakfast but consumed a lighter meal than usual. While driving, the subject developed symptoms of hypoglycemia (shaking and slurred speech) at approximately 11 am and pulled the car over to take some glucose tablets. However, before this was possible, a police officer arrived at the scene and, assuming the subject to be intoxicated, asked that he stepped out of the car to be searched. As a consequence, the subject was unable to take his glucose tablets and lost consciousness. An ambulance was called, and the subject regained consciousness following treatment at the scene with IV glucose. The subject recalled being informed that his blood glucose was below 36 mg/dL prior to IV treatment. The subject recovered and was not taken to a hospital. The investigator concluded that hypoglycemia was caused by a temporary mismatch between insulin administered and required, with the inability of the subject to take glucose tablets in due time

contributing to the severity of the hypoglycemia.

Reviewer Comment: This event occurring in an insulin-treated T1DM subject appears to be due to an excess of insulin administered versus carbohydrates ingested and unrelated to treatment with dasiglucagon.

No other SAEs were reported in the development program of dasiglucagon for severe hypoglycemia including in the pediatric trial. (b) (4) (b) (4) (b) (4). Two SAEs likely related to dasiglucagon were hyperglycemia (Subject ID (b) (6)) and necrolytic migratory erythema (Subject ID (b) (6)). Necrolytic migratory erythema is a skin rash associated with extended high exposure to glucagon described in patients with glucagonomas.

Reviewer comment: (b) (4) (b) (4) (b) (4) *Although these AEs are likely drug related, they are not relevant for single-dose administration of dasiglucagon for the proposed rescue indication. Temporary hyperglycemia after rescue from severe hypoglycemia is not a clinical concern.*

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No AEs leading to withdrawal occurred in the placebo-controlled pool or the pediatric trial.

Seven subjects in the broad pool (dasiglucagon: 6/316, GlucaGen: 1/151, placebo: 0/53) withdrew from additional treatment with study drug after the first dose in multiple dose trials. Of these subjects, all remained in the trial to the safety follow-up visit except for Subject (b) (6) in trial 16136. See Supplementary Table 1 in section 13.3 of this review for summary narratives for each event. In general, withdrawals seemed to be related to tolerability issues, such as vomiting and headache, and do not raise concerns about the safety of dasiglucagon for the intended use in the emergency setting.

8.4.4. Significant Adverse Events

See section 8.5.1 for the review of hemodynamics events, which were AESIs in all phase 3 trials.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The following section focuses on AEs that occurred in the placebo-controlled pool and in the pediatric trial. As dasiglucagon has a half-life of approximately 30 minutes, a 12-hour post-dose data flag was used in the analysis to enrich for events that may be more likely related to dasiglucagon as compared to events that may have occurred during the study observation period (a time frame of approximately four weeks) but may be unrelated to dasiglucagon treatment. There is precedent for following this approach; see Section 6 of Gvoke PI (glucagon injection, NDA 212097). Analysis of submission-specific safety issues (e.g., hemodynamic events, injection site reactions, renal/hepatic events) are reviewed in section 8.5.

Placebo-Controlled Pool

A similar proportion of subjects experienced at least one AE in the dasiglucagon and GlucaGen treatment arms (65.6% and 67.4% of subjects, respectively) with a lower proportion of subjects experiencing at least one AE in the placebo arm (15.9%) (Table 23). Events by severity category were similar between dasiglucagon and GlucaGen treatment arms, with over half of all events being categorized as mild in severity by the investigator (data not shown). Of the subjects who experienced an AE, subjects administered dasiglucagon and GlucaGen experienced a similar number of events per person (1.9 vs 1.7 events/person for dasiglucagon and GlucaGen, respectively).

The most frequent AEs (occurring in ≥2% of subjects) were nausea, vomiting, headache, diarrhea, and injection site pain. Nausea was reported for 56.5% and 53.5% of subjects receiving dasiglucagon and GlucaGen, respectively, compared to 4.1% receiving placebo. Vomiting was less frequently observed (24.6% of subjects receiving dasiglucagon, 20.9% of subjects receiving GlucaGen, and 1.8% of subjects receiving placebo). Events of nausea and vomiting generally occurred one to three hours after treatment with dasiglucagon or GlucaGen. Approximately one-third of subjects with nausea also experienced vomiting (dasiglucagon: 23/66 subjects; GlucaGen: 7/23 subjects; placebo: 1/2 subjects).

Reviewer comment: The observed AEs occurring in in ≥2% of adult subjects and greater than with placebo are consistent with AEs that would be anticipated with glucagon receptor agonism or with use of an injectable product; they are also expected pharmacodynamic effects based on nonclinical data (see the nonclinical review in section 4.4). With the exception of diarrhea, AEs observed with dasiglucagon and greater than with placebo are also observed with marketed native glucagon products. Additionally, the number of subjects experiencing an event, the severity of events, and the average number of events per subject were comparable between dasiglucagon and GlucaGen. While diarrhea is not listed in the labeling for other approved glucagon products, these events do not alter the benefit-risk assessment for this potentially life-saving drug. I recommend that the following events be included in the labeling as AEs occurring in ≥2% of adult subjects: nausea, vomiting, headache, diarrhea and injection site pain.

AEs that occurred in <2% of dasiglucagon-exposed subjects within 12 hours of dosing included hypoglycemia, hyperglycemia, and ketosis.

Reviewer's comment: These AEs could possibly be related to dasiglucagon treatment (either directly or indirectly) based on the mechanism of action of dasiglucagon. Importantly however, these events were non-serious, occurred at a low frequency (1 subject experienced hyperglycemia and 1 subject experienced ketosis in the dasiglucagon group versus none in placebo), or were higher in the placebo group (e.g., hypoglycemia) compared to the dasiglucagon group, and therefore do not present a concern. All other AEs occurred in one subject and generally appear to be unrelated to the mechanism of action of the dasiglucagon.

Hemodynamic events of interest (presyncope and bradycardia) and injection site reactions are reviewed in additional detail in 8.5.

Table 23. AEs by SOC/PT within 12 Hours Post-Dose – Placebo-Controlled Pool

	0.6 mg Dasiglucagon n=116	1 mg GlucaGen n=43	Placebo n=53
Subjects with at least 1 AE – subject count (%)	**76 (65.6%)**	**29 (67.4%)**	**8 (15.9%)**
Gastrointestinal disorders	**73 (63.0%)**	**25 (58.1%)**	**2 (4.1%)**
Nausea	66 (56.5%)	23 (53.5%)	2 (4.1%)
Vomiting	29 (24.6%)	9 (20.9%)	1 (1.8%)
Diarrhea	6 (5.1%)	1 (2.3%)	0 (0.0%)
Dyspepsia	0 (0.0%)	0 (0.0%)	1 (2.3%)
Hypoesthesia oral	0 (0.0%)	0 (0.0%)	1 (1.8%)
Nervous system disorders	**15 (12.8%)**	**6 (14.0%)**	**2 (3.6%)**
Headache	13 (11.2%)	5 (11.6%)	2 (3.6%)
Burning sensation	1 (0.9%)	0 (0.0%)	0 (0.0%)
Dizziness	1 (0.7%)	1 (2.3%)	0 (0.0%)
Presyncope	1 (0.9%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	**7 (5.8%)**	**3 (7.0%)**	**2 (3.6%)**
Injection site pain	3 (2.3%)	0 (0.0%)	0 (0.0%)
Injection site erythema	2 (1.6%)	2 (4.7%)	2 (3.6%)
Infusion site extravasation	1 (0.7%)	0 (0.0%)	0 (0.0%)
Infusion site rash	1 (0.9%)	0 (0.0%)	0 (0.0%)
Pyrexia	1 (0.9%)	0 (0.0%)	0 (0.0%)
Injection site edema	0 (0.0%)	1 (2.3%)	0 (0.0%)
Metabolism and nutrition disorders	**4 (3.5%)**	**2 (4.7%)**	**2 (4.6%)**
Hypoglycemia	2 (1.6%)	1 (2.3%)	2 (4.6%)
Hyperglycemia	1 (0.9%)	0 (0.0%)	0 (0.0%)
Ketosis	1 (0.9%)	1 (2.3%)	0 (0.0%)

Vascular disorders	**2 (1.6%)**	**1 (2.3%)**	**0 (0.0%)**
Phlebitis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Hot flush	1 (0.9%)	0 (0.0%)	0 (0.0%)
Orthostatic hypotension	0 (0.0%)	1 (2.3%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Cough	1 (0.9%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	**1 (0.7%)**	**0 (0.0%)**	**0 (0.0%)**
Hyperhidrosis	1 (0.7%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Dysmenorrhea	1 (0.9%)	0 (0.0%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	**1 (0.9%)**	**1 (2.3%)**	**1 (1.8%)**
Back pain	1 (0.9%)	0 (0.0%)	0 (0.0%)
Myalgia	0 (0.0%)	1 (2.3%)	0 (0.0%)
Pain in extremity	0 (0.0%)	0 (0.0%)	1 (1.8%)
Cardiac disorders	**1 (0.9%)**	**0 (0.0%)**	**0 (0.0%)**
Bradycardia	1 (0.9%)	0 (0.0%)	0 (0.0%)
Ear and labyrinth disorders	**0 (0.0%)**	**1 (2.3%)**	**0 (0.0%)**
Vertigo	0 (0.0%)	1 (2.3%)	0 (0.0%)
Infections and infestations	**0 (0.0%)**	**0 (0.0%)**	**1 (1.8%)**
Sinusitis	0 (0.0%)	0 (0.0%)	1 (1.8%)

Source: Generated by reviewer in JReview with ADSL and ADAE datasets; CMH weighing from Applicant's analysis

Subjects were observed for AEs after dosing for a period of approximately 4 weeks. The Applicant's rationale for the 4-week follow-up period was driven by the anticipated time needed to mount an antibody response to dasiglucagon for the assessment of ADAs and was not driven by anticipated AEs of delayed onset. In this reviewer's judgment, because ADA formation is more common with repeated dosing, this 4-week follow up period after a single dose is of limited utility for immunogenicity assessment. Table 24 displays AEs by SOC reported during the entire observation period in the placebo-controlled pool. This table also includes events that occurred in the initial 12-hour observation window.

Events in the SOC 'metabolism and nutrition disorders' account for the majority of AEs that occurred outside of the 12-hour post-dose time frame, which is driven by the PT of hypoglycemia (dasiglucagon: 25.6%, GlucaGen: 20.9%, placebo: 13.6%).

Reviewer comment: Narratives were not provided, but it is reasonable to surmise that these events are due to insulin therapy in these T1DM patients and unrelated to dasiglucagon use. This is also supported by additional events of hypoglycemia observed in the GlucaGen arm, and to a lesser extent, the placebo arm. Other events that occurred outside of the 12-hour post-dose timeframe occurred at low frequency, were not serious events, and/or appear to be unrelated to the mechanism of action of the drug.

Table 24. AEs by SOC Over Entire Observation Period – Placebo-Controlled Pool

	0.6 mg Dasiglucagon n=116	1 mg GlucaGen n=43	Placebo n=53
Subjects with at least 1 AE – subject count (%)	90 (78.2%)	32 (74.4%)	17 (32.0)
Gastrointestinal disorders	73 (63.0%)	25 (58.1%)	2 (4.1%)
Metabolism and nutrition disorders	31 (27.5%)	11 (25.6%)	7 (13.6%)
Nervous system disorders	16 (13.7%)	7 (16.3%)	2 (3.6%)
Infections and infestations	8 (7.5%)	0 (0.0%)	4 (7.7%)
General disorders and administration site conditions	7 (5.8%)	3 (7.0%)	2 (3.6%)
Musculoskeletal and connective tissue disorders	3 (2.8%)	1 (2.3%)	2 (3.6%)
Vascular disorders	3 (2.6%)	1 (2.3%)	0 (0.0%)
Respiratory, thoracic and mediastinal disorders	3 (2.6%)	0 (0.0%)	0 (0.0%)
Reproductive system and breast disorders	1 (0.9%)	0 (0.0%)	0 (0.0%)
Renal and urinary disorders	1 (0.9%)	0 (0.0%)	0 (0.0%)
Immune system disorders	1 (0.9%)	0 (0.0%)	0 (0.0%)
Eye disorders	1 (0.9%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	1 (0.9%)	0 (0.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	1 (0.7%)	0 (0.0%)	0 (0.0%)
Blood and lymphatic system disorders	0 (0.0%)	1 (2.3%)	1 (1.8%)
Ear and labyrinth disorders	0 (0.0%)	1 (2.3%)	0 (0.0%)

Source: Generated by reviewer in JReview with ADSL and ADAE datasets; CMH weighing from Applicant's analysis

To further assess the data, FDA Medical Queries (FMQs) were used to query for potentially meaningful safety signals (Table 25). No additional safety signals were identified when utilizing a ≥2% threshold aside from those previously discussed that will be presented in the labeling within 12 hours of dosing, or those which occurred outside of the 12-hour timeframe such as hypoglycemia (see above reviewer comment). Infections and injection site reactions were less frequently observed in the dasiglucagon group versus the placebo group. See Section 8.5.3 for additional information in how injection site reactions were evaluated and assessed in placebo-controlled studies.

Table 25. FMQs with Events in ≥2% of Dasiglucagon Treated Subjects Over Entire Observation Period – Placebo-Controlled Pool

FMQ	0.6 mg Dasiglucagon n=116	Placebo n=53	1 mg GlucaGen n=43	RR*	95% CI
Nausea	66 (56.9%)	2 (3.8%)	23 (53.5%)	15.1	(3.8, 59.3)

Hypoglycemia	29 (25%)	7 (13.2%)	9 (20.9%)	1.9	(0.9, 4)
Vomiting	29 (25%)	1 (1.9%)	9 (20.9%)	13.3	(1.9, 94.7)
Headache	14 (12.1%)	2 (3.8%)	5 (11.6%)	3.2	(0.8, 13.6)
Infections	8 (6.9%)	4 (7.5%)	0 (0%)	0.9	(0.3, 2.9)
Diarrhea	6 (5.2%)	(0%)	1 (2.3%)	N/A	N/A
Injection Site Reactions	4 (3.4%)	2 (3.8%)	3 (7%)	0.9	(0.2, 4.8)

**RR= risk ratio (dasiglucagon versus placebo)*
Source: Generated by reviewer in JMP with ADSL and ADAE datasets

Pediatrics

AEs by SOC/PT observed in pediatric trial 17086 by age group (6−11 years and 12−17 years) that occurred within 12 hours of dosing are displayed in Table 26. For both dasiglucagon and GlucaGen, the most frequently reported AEs were nausea and vomiting (no gastrointestinal events were reported for placebo). These events were reported for a greater proportion of subjects receiving dasiglucagon compared with those receiving GlucaGen. This imbalance is attributable to gastrointestinal events being more frequently reported for dasiglucagon than for GlucaGen in the age group of 12−17 years. Additionally, while diarrhea was observed in 5.1% of adult subjects, it was not observed in pediatrics.

Reviewer comment: Although the small sample size limits the interpretability of these data, I do not see evidence for meaningful differences in safety between the adult and pediatric populations, or between pediatric subjects given dasiglucagon vs. GlucaGen.

Table 26. AEs by SOC and Age Group within 12 Hours of Dosing by SOC/PT – Pediatric Trial

	0.6 mg Dasiglucagon	1.0 mg GlucaGen	Placebo
6-11 years at screening	**n=8**	**n=4**	**n=4**
Subjects with at least 1 TEAE count and %	**3 (37.5%)**	**4 (100.0%)**	**0 (0.0%)**
Gastrointestinal disorders	**3 (37.5%)**	**2 (50.0%)**	**0 (0.0%)**
Nausea	2 (25.0%)	2 (50.0%)	0 (0.0%)
Vomiting	2 (25.0%)	1 (25.0%)	0 (0.0%)
General disorders and administration site conditions	**0 (0.0%)**	**2 (50.0%)**	**0 (0.0%)**
Injection site erythema	0 (0.0%)	2 (50.0%)	0 (0.0%)
Injection site induration	0 (0.0%)	1 (25.0%)	0 (0.0%)
Injection site edema	0 (0.0%)	1 (25.0%)	0 (0.0%)
Nervous system disorders	**0 (0.0%)**	**1 (25.0%)**	**0 (0.0%)**
Headache	0 (0.0%)	1 (25.0%)	0 (0.0%)
12-17 years at screening	**n=12**	**n=6**	**n=7**
Subjects with at least 1 TEAE count and %	**11 (91.7%)**	**2 (33.3%)**	**3 (42.9%)**
Gastrointestinal disorders	**11 (91.7%)**	**1 (16.7%)**	**0 (0.0%)**

Nausea	11 (91.7%)	1 (16.7%)	0 (0.0%)
Vomiting	8 (66.7%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	**2 (16.7%)**	**0 (0.0%)**	**0 (0.0%)**
Headache	2 (16.7%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions	**1 (8.3%)**	**1 (16.7%)**	**1 (14.3%)**
Injection site pain	1 (8.3%)	0 (0.0%)	0 (0.0%)
Injection site erythema	0 (0.0%)	1 (16.7%)	0 (0.0%)
Infusion site bruising	0 (0.0%)	0 (0.0%)	1 (14.3%)
Vascular disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (14.3%)**
Hypertension	0 (0.0%)	0 (0.0%)	1 (14.3%)
Metabolism and nutrition disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (14.3%)**
Hypoglycemia	0 (0.0%)	0 (0.0%)	1 (14.3%)

Source: Generated by reviewer in JReview with ADSL and ADAEP datasets

Reviewer comment: As discussed in section 6.3.2, the Applicant limited enrollment in 17086 to subjects weighing ≥20 kg, which is approximately 50th percentile for pediatrics 6 years of age. Therefore, dasiglucagon may be administered to pediatric patients <20 kg in real-world use. No apparent relationship was observed between body weight and adverse events (Table 26). In other words, subjects with lower body weight appear to have a similar safety profile as the general pediatric pool. Therefore, the restriction on body weight in trial 17086 does not appear to present a safety concern based on available information.

Reviewer comment: The youngest pediatric subjects enrolled in 17086 were 7 years old, and therefore data in subjects 6 years of age were not obtained in this trial. As there is no apparent relationship between younger age group and adverse events this does not present a safety concern.

Adverse events that that occurred in dasiglucagon exposed subjects outside of the 12-hour post-dose timeframe included hypoglycemia (dasiglucagon: 10%, GlucaGen: 20%, placebo: 36.4%), leukopenia (dasiglucagon: 5% (i.e. one subject), GlucaGen: 0%, placebo: 0%), and AEs within the SOC 'infections and infestations' (dasiglucagon: 10%, GlucaGen: 0%, placebo: 18.2%). Events of hypoglycemia and events in the SOC 'infections and infestations' do not present a safety concern as the incidence of events was higher in the placebo group as compared to the dasiglucagon group. Regarding the one subject who experienced an event of 'leukopenia,' the WBC value was 1.7 x 10^9/L at the follow-up safety visit; however, the full CBC data were reviewed and there were no other out of range values that would suggest aplastic anemia. Additionally, this subject had a leukocyte count below the normal range at screening (4.3 x 10^9/L), and a concurrent upper tract respiratory infection at the follow up visit that confounds interpretation.

8.4.6. Laboratory Findings

Blood samples for hematology and biochemistry assessments were collected at screening, dosing, and follow-up visits in all adult trials. Collection times on the dosing day in adult trials occurred pre-dose (prior to hypoglycemic clamp) and at various pre-specified, post-dose timepoints that varied by the specific study (placebo-controlled studies collected blood samples at 30 and at 300 minutes post-dose).

To conserve blood sampling for PK/PD and efficacy measurements on the dosing day in pediatric trial 17086, blood samples for biochemistry and hematology assessments occurred only at screening and follow-up visits.

Hematology

Hematology parameters (erythrocytes, hematocrit, hemoglobin, leukocytes, and platelets) were assessed in the placebo-controlled pool for central tendencies and outliers (Figures 15-19). Transient increases in mean leukocyte count, up to or marginally above the ULN, were observed post-dosing with dasiglucagon, and to a lesser extent with GlucaGen and placebo; levels returned to baseline by the follow-up measurement (Figure 18). Transient increases in leukocyte count have been characterized in the literature following glucagon treatment, and do not appear clinically meaningful.[18] No other important central tendencies in hematology parameters were observed in the placebo-controlled pool.

Hematology parameter outliers, as identified by Box and Whisker plots, were low in frequency, generally similar between treatment arms, and lacked an apparent association with dasiglucagon dosing. One subject in the dasiglucagon group had a treatment emergent leukocyte level of ~18,500 cells/uL at 300-minutes post-dose (Figure 18); however, the leukocyte count at screening was similarly increased (~14,000 cells/uL). The transient increase in leukocytes post-dose appears similar to the increases observed in other subjects. The Applicant also performed an outlier analysis utilizing the broad pool for selected hematology parameters with the following thresholds derived according to NIH National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 criteria: hemoglobin: <7.9 g/dL, leukocytes: $<2 \times 10^9$/L, platelets: $<50 \times 10^3$/uL. This analysis did not identify any among dasiglucagon-exposed subjects.

Pediatric data as reviewed by Box and Whisker plots in JReview (data not shown) were consistent with the data obtained from adults, with no meaningful pre- to post-dose changes. As discussed in 8.4.5, one subject was leukopenic at the follow-up visit (see the 'pediatric' section of 8.4.5 for additional information).

Figure 15. Erythrocytes over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

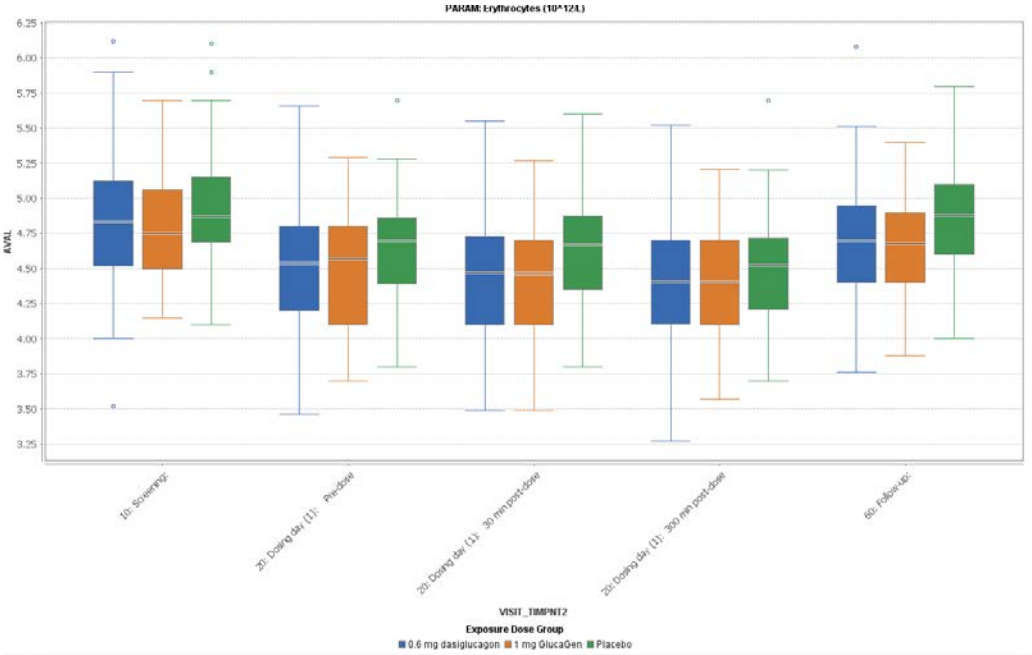


Figure 16. Hematocrit over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

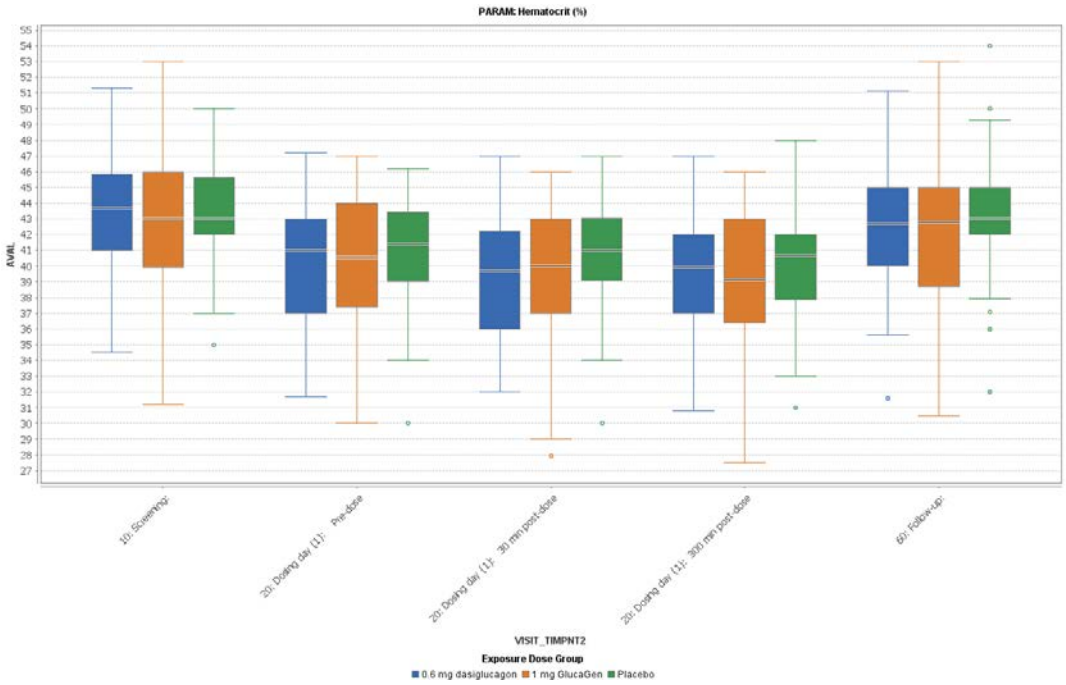


Figure 17. Hemoglobin over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

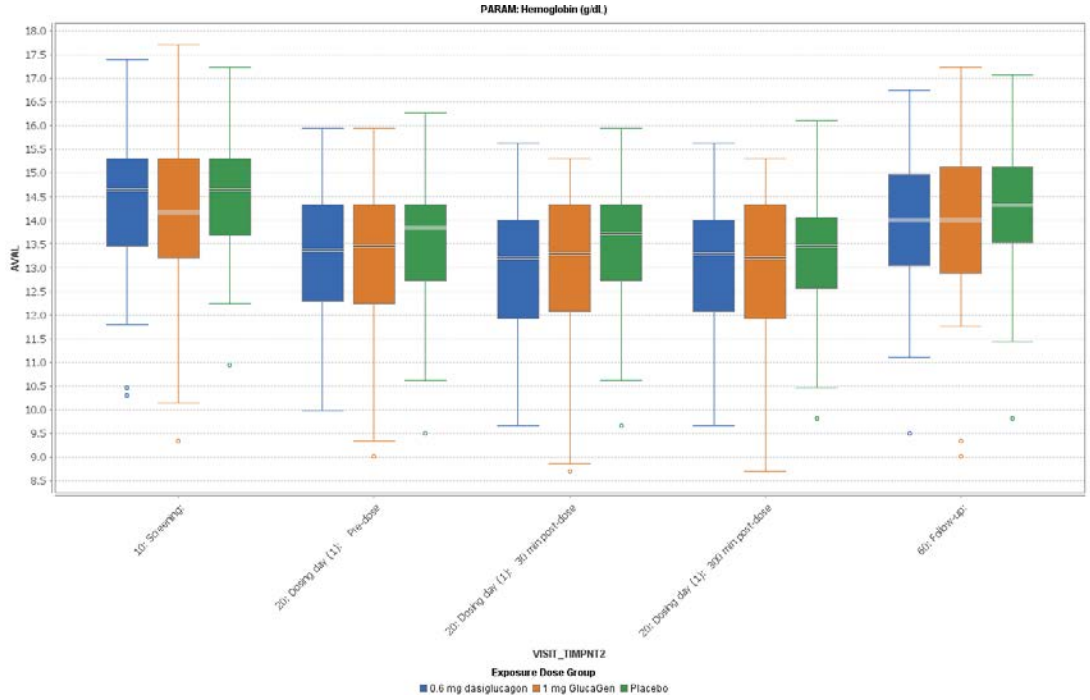


Figure 18. Leukocytes over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

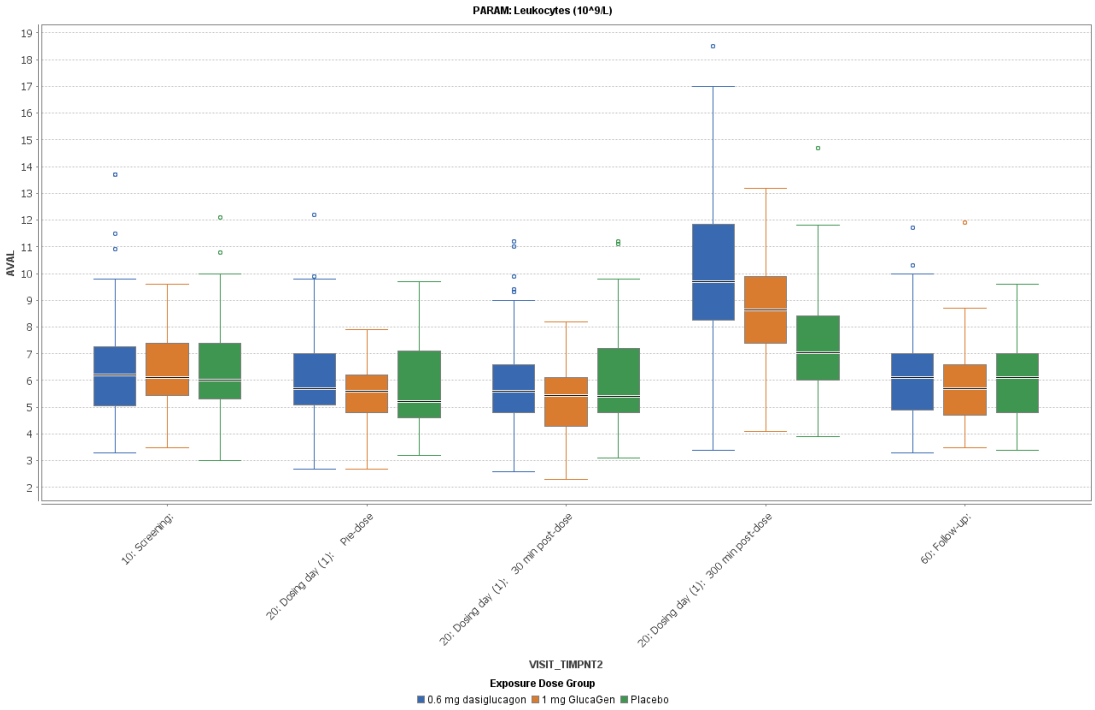
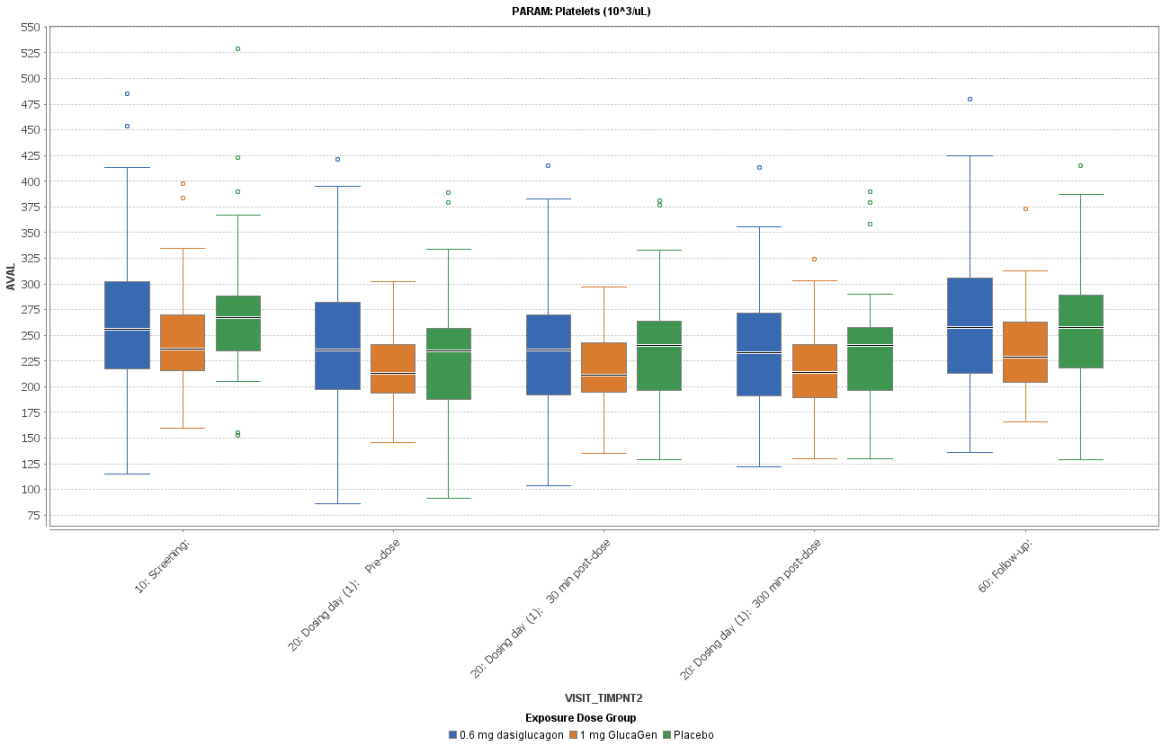


Figure 19. Platelets over Screening, Dosing, and Follow Up – Placebo-Controlled Pool



Chemistry

No apparent change in central tendencies from screening to follow up or over the course of the dosing day were observed among chemistry parameters assessed in the placebo-controlled pool, which included the assessment of electrolytes (sodium, potassium, and calcium), and markers of hepatic and renal function (Figures 20-27). Chemistry parameter outliers, as identified by Box and Whisker plots, in the placebo-controlled pool were low in frequency, generally similar between treatment arms, and lacked an apparent association with dasiglucagon dosing. The Applicant performed an analysis with the broad pool for outliers based on CTCAE Grade 3 criteria (potassium: <3 and >6 mEq/L, sodium: <130 mEq/L, calcium: <7 and >12.4 mg/dL), or based on thresholds of >3x ULN (creatinine, urea, AST, ALT) or 2x ULN (ALP, bilirubin). No treatment emergent outliers among dasiglucagon-exposed subjects were identified with the exception of one subject with ALT ~3.5x ULN. See 8.5.4 for additional information regarding this subject and for additional analyses of renal and hepatic events. Pediatric data were consistent with the data obtained from adults, with no apparent pre- to post-dose change in central tendencies and no noteworthy treatment-emergent outliers.

Figure 20. Calcium over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

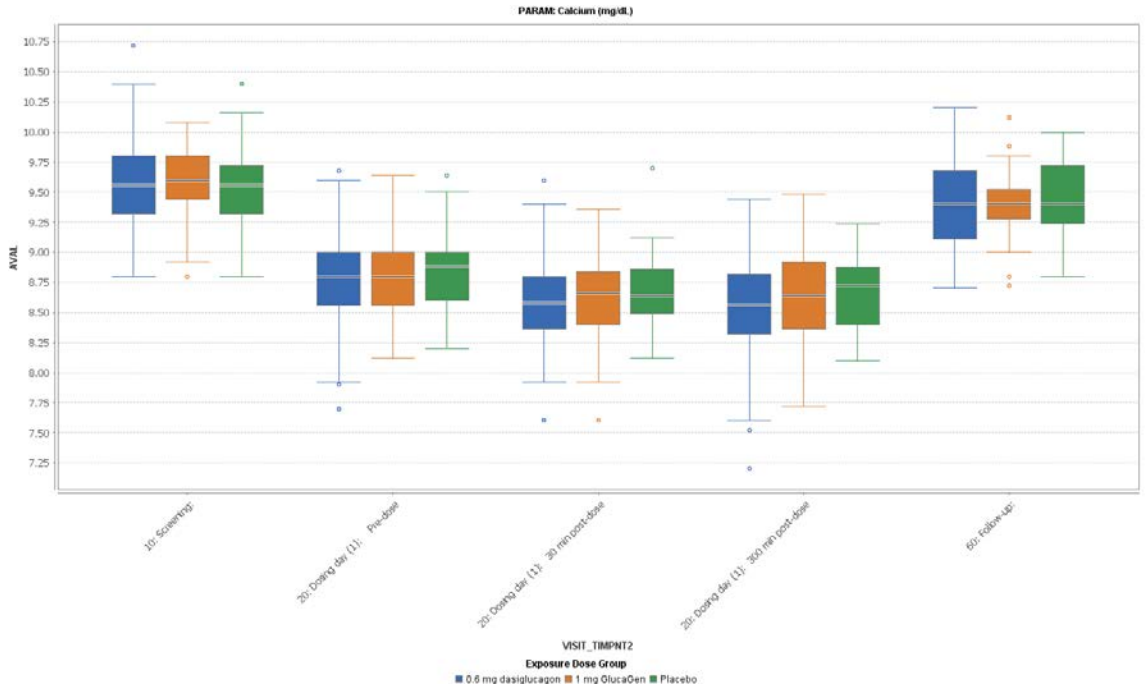


Figure 21. Potassium over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

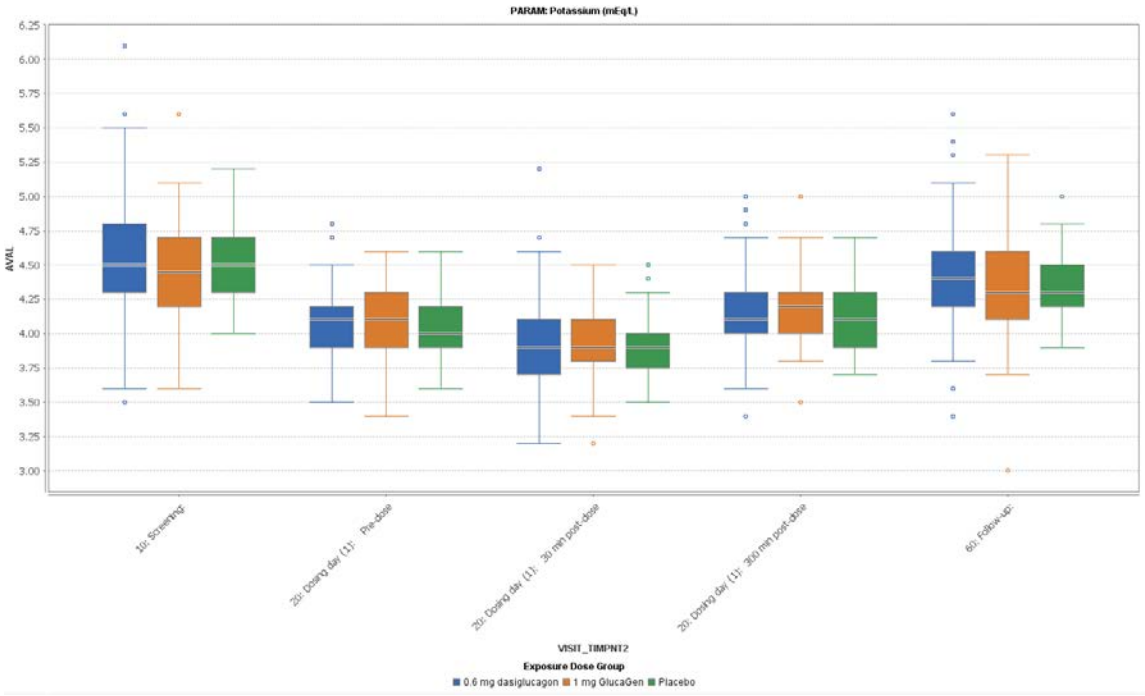


Figure 22. Sodium over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

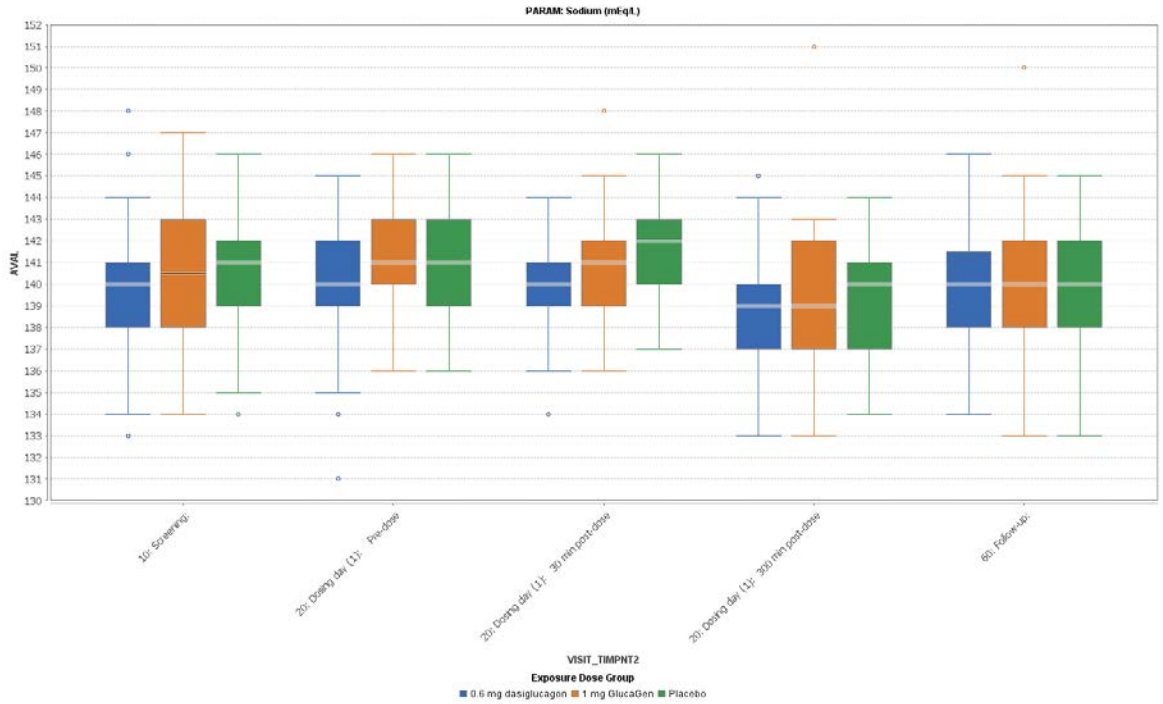


Figure 23. ALT over Screening, Dosing, and Follow Up– Placebo-Controlled Pool

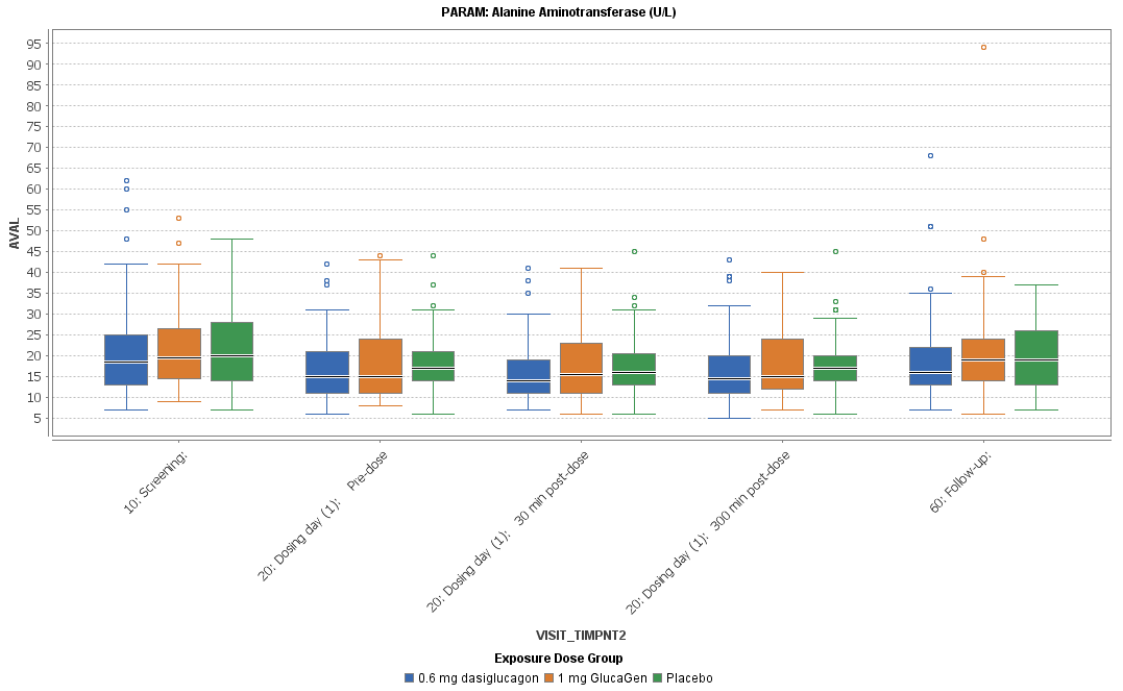


Figure 24. Alk Phos over Screening, Dosing, and Follow Up– Placebo-Controlled Pool

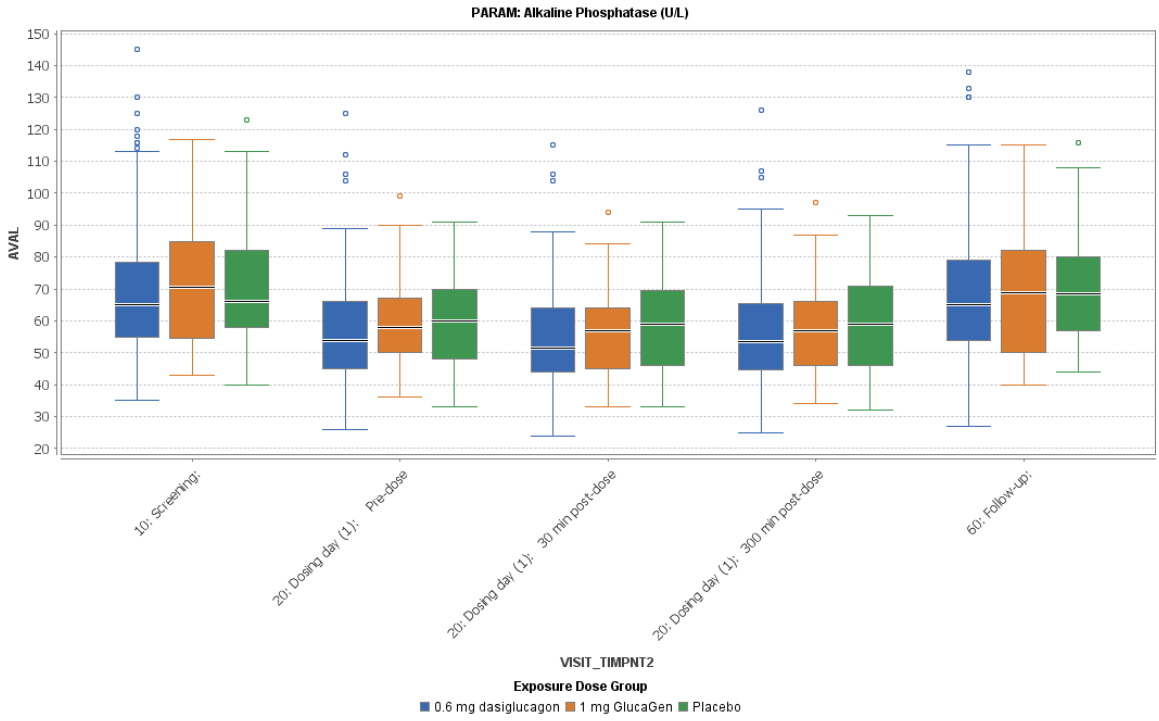


Figure 25. AST over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

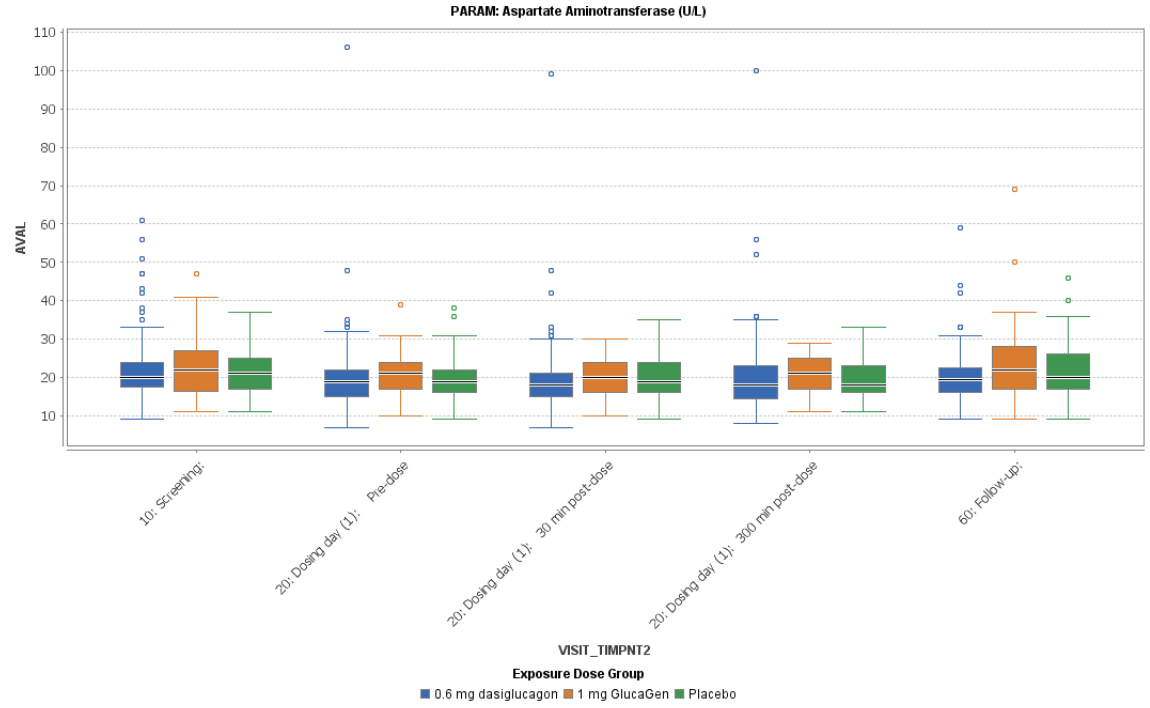


Figure 26. Bilirubin over Screening, Dosing, and Follow Up – Placebo-Controlled Pool

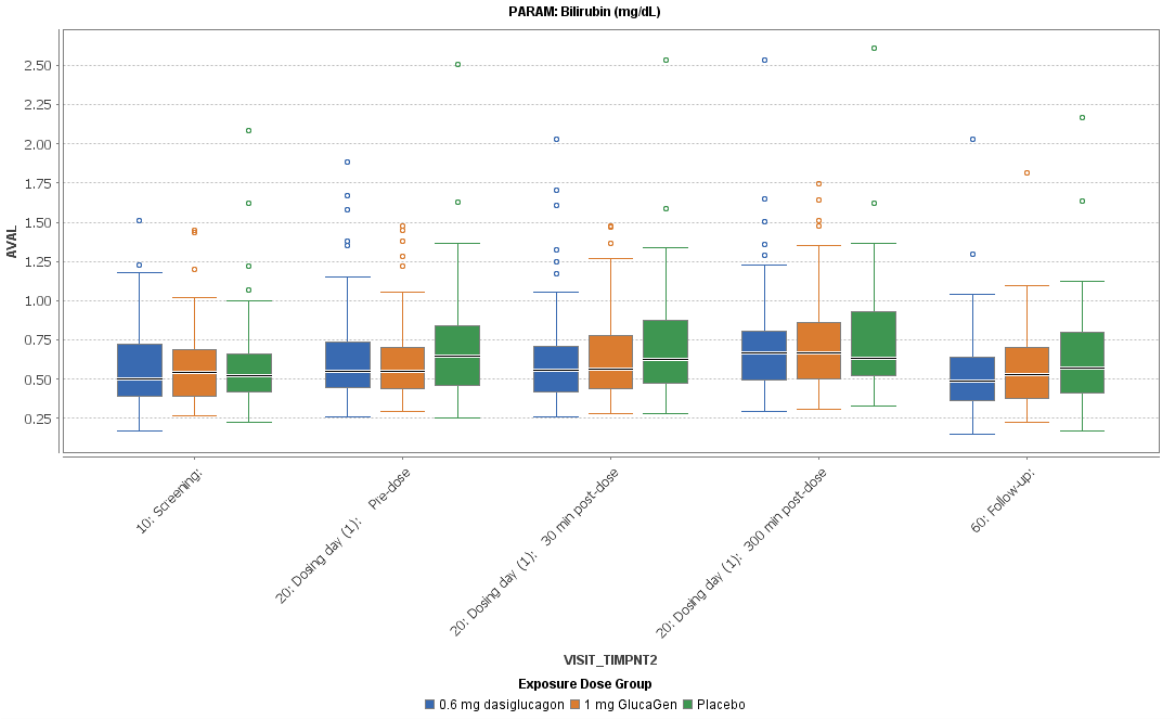
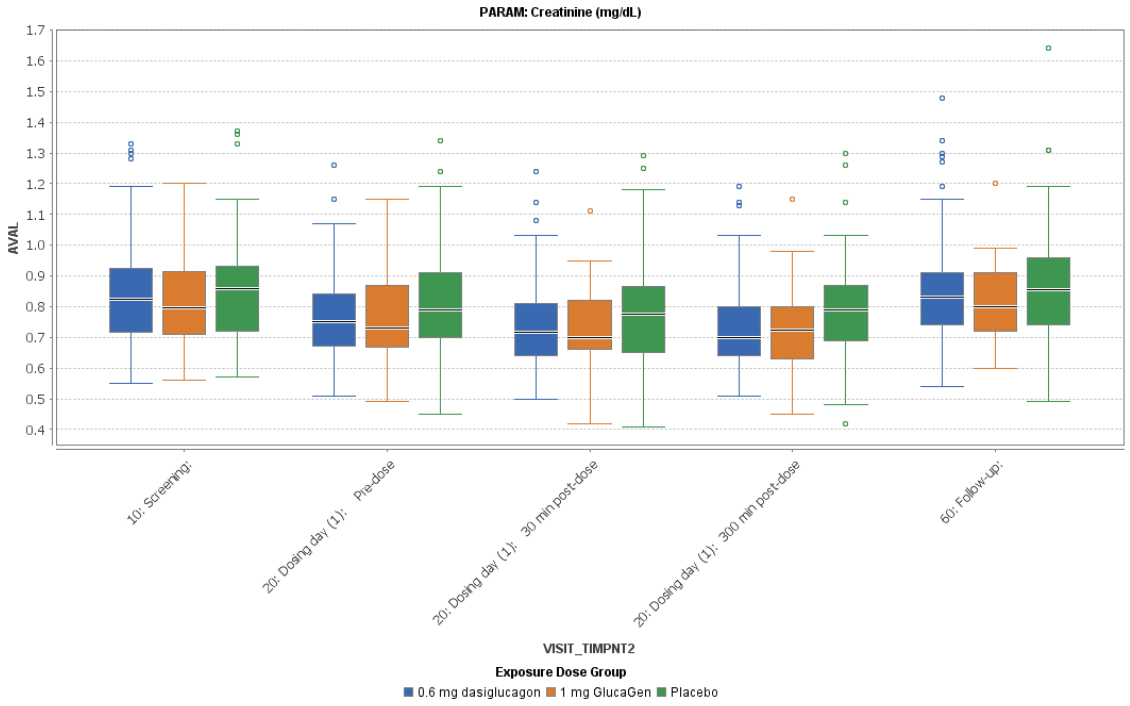


Figure 27. Creatinine over Screening, Dosing, and Follow Up – Placebo-Controlled Pool



8.4.7. Vital Signs

Vital signs (heart rate, blood pressure, and temperature) were measured at screening, dosing, and follow-up visits for all trials in the clinical development program. In the placebo-controlled pool on the dosing day, vital signs were measured pre-dose (i.e. prior to initiation of the hypoglycemic clamp) and at 30, 90, and 300 minutes post-dose. Adverse events related to clinically significant changes in pulse and blood pressure (hemodynamic events) are reviewed in Section 8.5.1.

Glucagon receptor agonism has been shown to exert inotropic and chronotropic effects on the heart, and therefore it would not be unexpected to observe transient changes in heart rate and/or blood pressure with dasiglucagon.

Blood Pressure

Mean changes in systolic or diastolic blood pressure from pre-dose to any post-dose timepoint were <5 mmHg in all treatment groups in the placebo-controlled pool (data not shown). Shift table analyses were performed to identify potential outliers of significance based on the systolic and diastolic blood pressure categories listed below. Additionally, analyses assessing change from pre-dose to the minimum- and maximum-post-dose values for systolic (Figures 28-29) and diastolic (Figure 30) blood pressure were used to evaluate all data in the placebo-controlled pool.

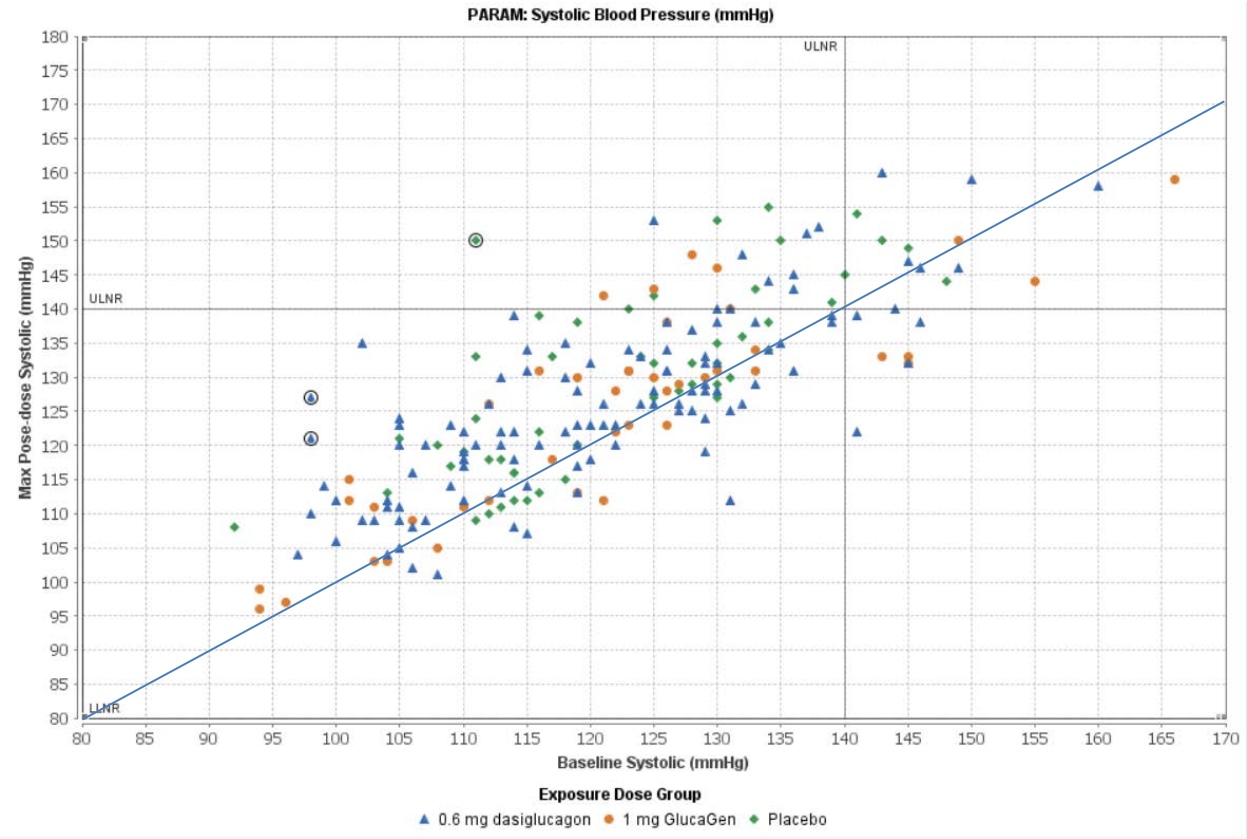
Categories for Shift Table Analysis:
- Systolic blood pressure: <80, ≥80 to <100, ≥100 to <120, ≥120 to <140 and ≥140 mmHg
- Diastolic blood pressure: <60, ≥60 to <80, ≥80 to <100 and ≥100 mmHg

Systolic blood pressure

Approximately 60−70% of the subjects across treatment groups remained in the same systolic blood pressure category on all assessments on the dosing day. Most of the remaining subjects had a shift up to the next category (in analyses based on maximum values) or down to the next category (in analyses based on minimum values), with no apparent trends among treatment groups. Six subjects had a shift spanning over two categories: two subjects (1.7%) in the dasiglucagon group and one subject (1.9%) in the placebo group had an upwards shift by two categories, and two subjects (1.7%) in the dasiglucagon group and one subject (2.3%) in the GlucaGen group had a downwards shift by 2 categories (these six subjects are indicated in Figures 28 and 29 with circled datapoints). Additionally, it appears that a similar number of subjects experienced both downward and upward changes in post-dose systolic blood pressure relative to baseline such that there is no evidence of bias in Figures 28 and 29. None of the six subjects with shifts greater than two categories had documented hemodynamic AEs.

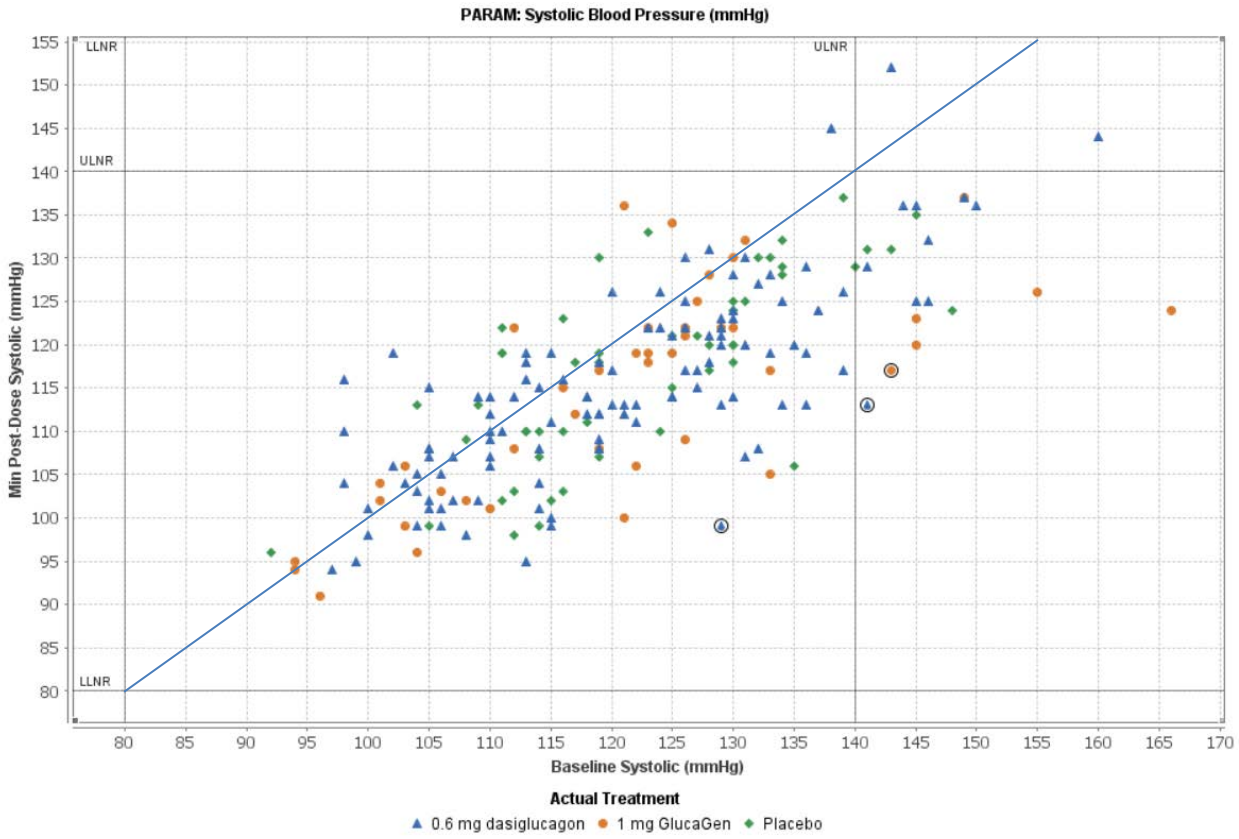
Additionally, none of the subjects administered dasiglucagon who shifted from normal (≤140 mmHg) to high (>140 mmHg) systolic pressure experienced a hemodynamic event. No subjects had a post-dose low (<90 mmHg) systolic blood pressure at pre-specified vital sign measurement timepoints.

Figure 28. Pre-Dose to Maximum Post-Dose Systolic Value (Pre-Specified Monitoring Timepoints; Dosing Day) - Placebo-Controlled Pool



Note, the diagonal line represents no change in systolic blood pressure
Source: Generated by reviewer with ADVS dataset in JReview

Figure 29. Pre-Dose to Minimum Post-Dose Systolic Value (Pre-Specified Monitoring Timepoints; Dosing Day) - Placebo-Controlled Pool

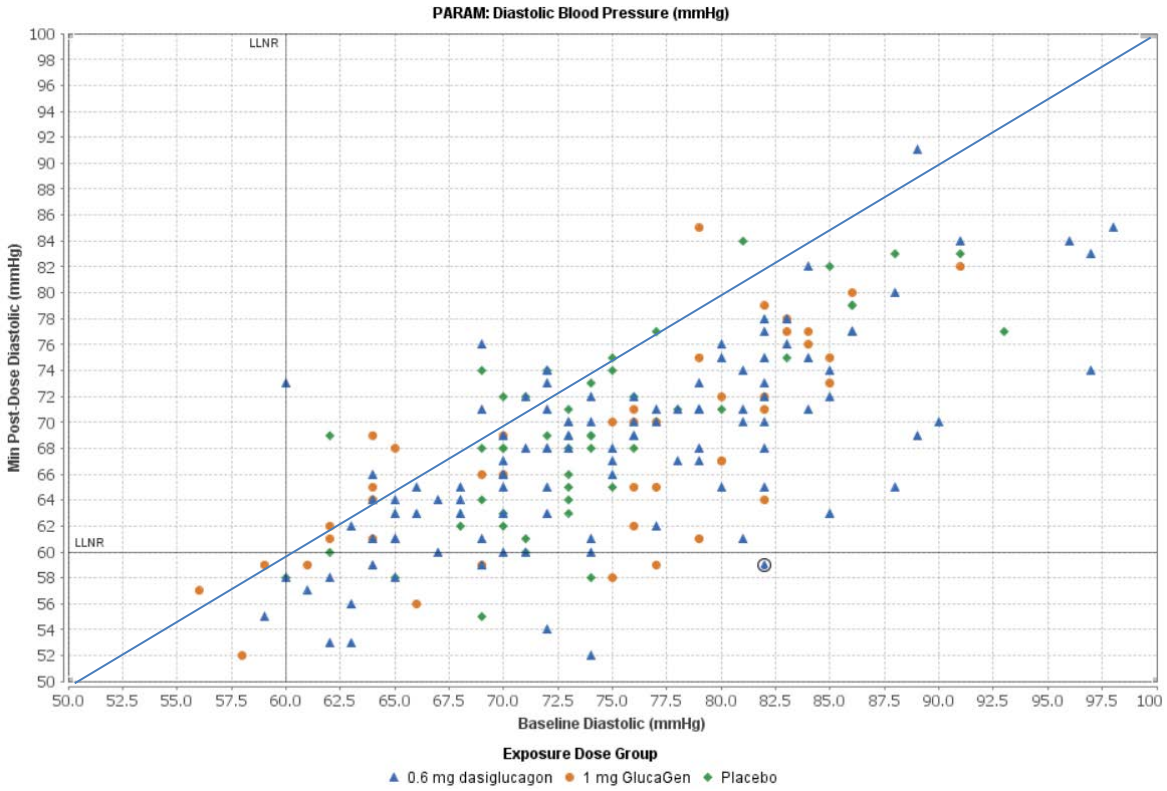


Note, the diagonal line represents no change in systolic blood pressure
Source: Generated by reviewer from ADVS dataset in JReview

Diastolic blood pressure

More than half of the subjects across treatment groups remained in the same diastolic blood pressure category on all assessments on the dosing day. Most of the remaining subjects had a shift down to the next category, which is in accordance with an analysis of central tendencies (data not shown) that demonstrated a mean decrease in diastolic blood pressure of -2.7, -2.8, and -3.1 mmHg for dasiglucagon, GlucaGen, and placebo, respectively, at 30 minutes post-dose. One subject (0.9%) in the dasiglucagon group had a shift spanning over 2 categories (from ≥80 to <100 mmHg pre-dose to <60 mmHg post-dose), which was not associated with a reported hemodynamic AE (circled datapoint in Figure 30). None of the dasiglucagon exposed subjects who shifted from normal (≥60 mmHg) to low (<60 mmHg) diastolic pressure at the pre-specified monitoring timepoints experienced a hemodynamic AE.

Figure 30. Pre-dose to Minimum Post-Dose Diastolic Value (Pre-Specified Monitoring Timepoints; Dosing Day) - Placebo-Controlled Pool



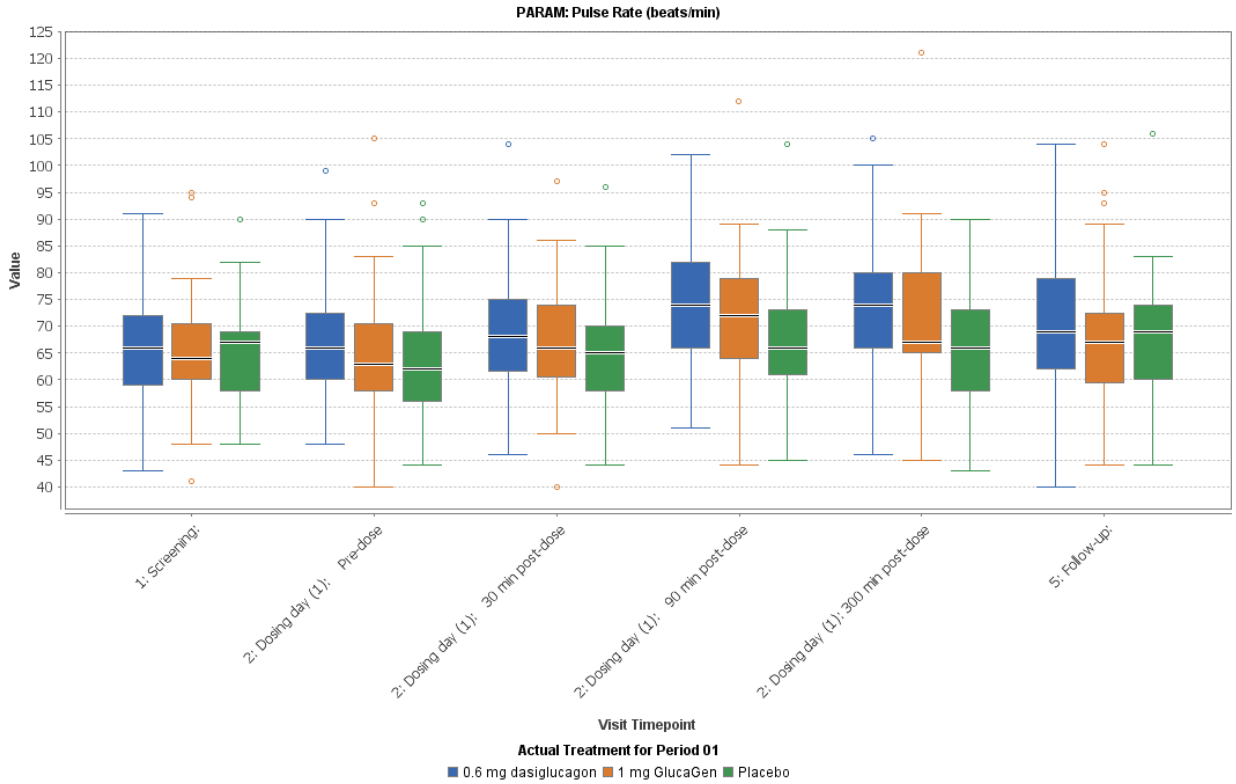
Note, the diagonal line represents no change in diastolic blood pressure
Source: Generated by reviewer from ADVS dataset in JReview

Heart Rate

In the placebo-controlled pool, modest increases in mean post-dose heart rate were observed in all treatment groups with numerically higher increases in the active treatment groups versus placebo (maximum mean increase of 7, 6, and 4 bpm observed at 90 minutes post-dose for dasiglucagon, GlucaGen, and placebo, respectively; Figure 31). An analysis utilizing pre-dose to maximum/minimum post-dose heart rate values from pre-specified monitoring timepoints was used to identify subjects who may have had potentially meaningful changes in heart rate (Figures 32 and 33). There were three subjects treated with dasiglucagon who shifted from normal (50-100 bpm) to low (<50 bpm) heart rate (dasiglucagon: 2.6%, GlucaGen: 0%, placebo: 5.7%; circled datapoints in Figure 32). One of these subjects (Subject (b) (6) in trial 16137) also experienced a hemodynamic adverse event (bradycardia). As discussed in section 8.5.1 this event may have been due to the administration of metoclopramide for nausea approximately 6 minutes prior to the bradycardia event.

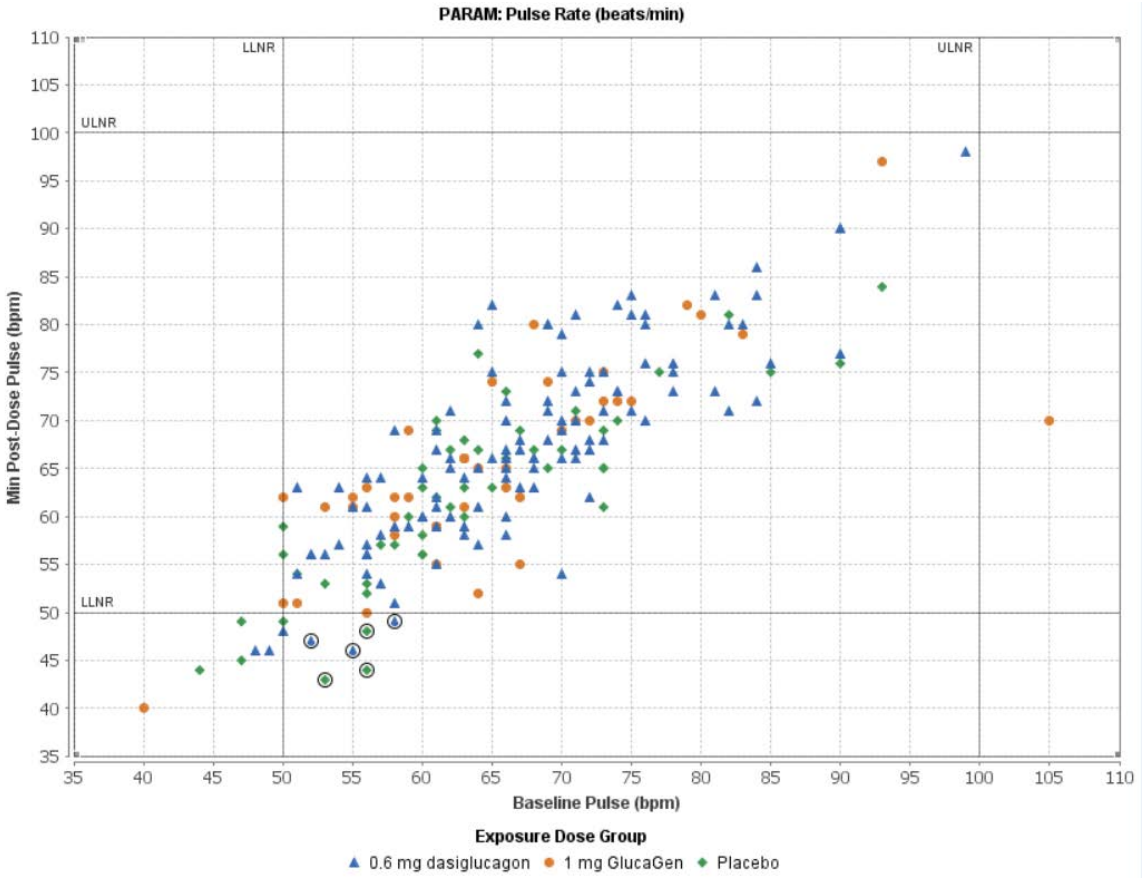
There were three subjects treated with dasiglucagon who shifted from a pre-dose normal to high heart rate (>100 bpm) (dasiglucagon: 2.6%, GlucaGen: 2.3%, placebo: 1.9%) (Figure 33). None of the subjects exposed to dasiglucagon who shifted from 50-100 to >100 bpm experienced a hemodynamic event (an event of orthostatic hypotension was observed in a GlucaGen treated subject).

Figure 31. Heart Rate at Pre-Specified Analysis Timepoints – Placebo-Controlled Pool



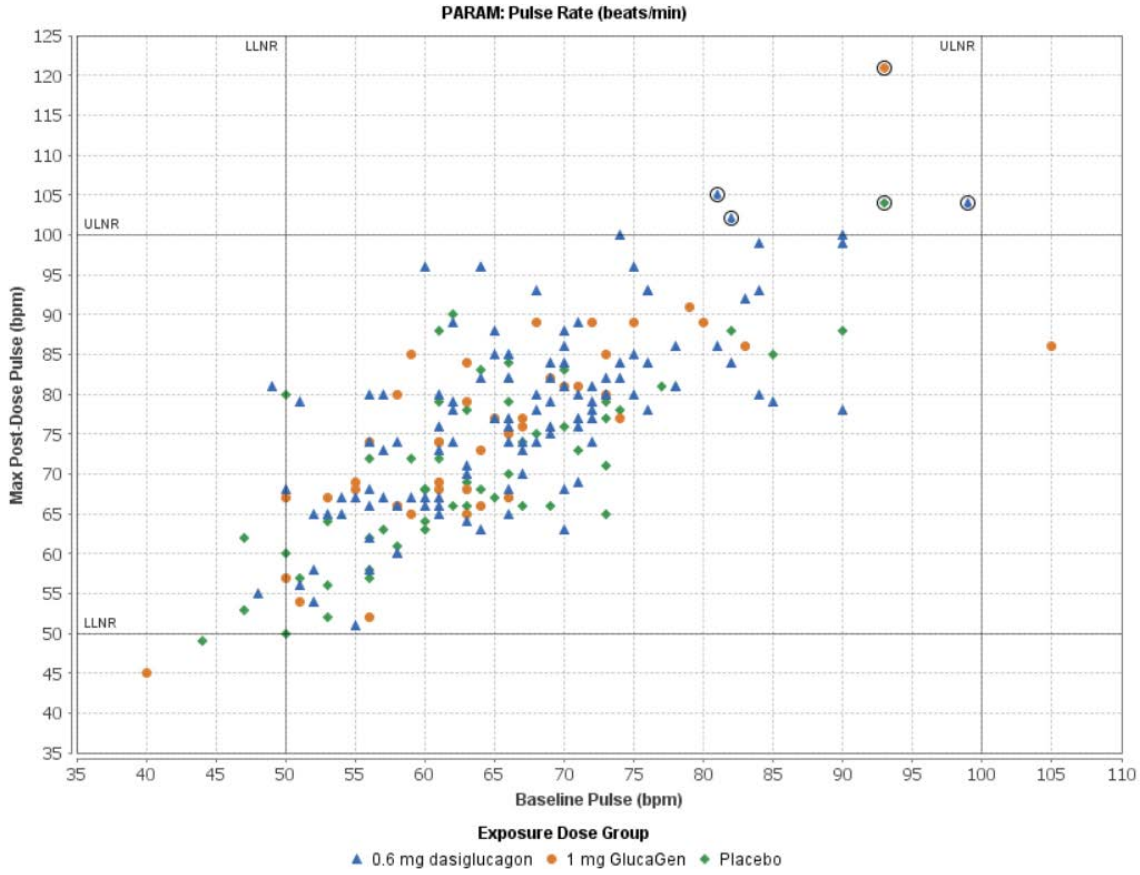
Source: Generated from ADVS dataset by reviewer in JReview

Figure 32. Heart Rate Pre-Dose vs Minimum Post-Dose Value (Pre-Specified Monitoring Timepoints; Dosing Day)– Placebo-Controlled Pool



Source: Generated by reviewer with ADVS dataset in JReview

Figure 33. Heart Rate Pre-Dose vs Maximum Post-Dose Value (Pre-Specified Monitoring Timepoints; Dosing Day)– Placebo-Controlled Pool



Source: Generated by Reviewer from ADVS dataset in JReview

Pediatric Trial 17086

Pediatric data were consistent with the data obtained from adults. Baseline to minimum and maximum post-dose analyses for blood pressure and heart rate were performed for trial 17086 (data not shown). As observed with adults, transient increases or decreases in heart rate and blood pressure were observed in pediatrics. Transient increases/decreases in heart rate and blood pressure did not appear clinically significant, and no dasiglucagon-exposed subjects experienced hemodynamic events (one GlucaGen-exposed subject experienced an AE of hypertension).

Reviewer comment: Overall, blood pressure and heart rate analyses do not demonstrate important differences in central tendency among treatment groups, nor are there concerning outliers. Importantly however, this analysis should be considered in the context of hemodynamic

events observed, as clinically meaningful (i.e., symptomatic but non-serious) changes in heart rate and blood pressure may have occurred at timepoints other than the pre-specified monitoring timepoints represented in the above analyses. As further discussed in 8.5.1, hemodynamic events were AESIs in all phase 3 trials, and analyses of these events will also inform labeling recommendations regarding the impact of dasiglucagon on blood pressure and heart rate. As noted in sections 8.5.1 and 10.1, I recommend information regarding hemodynamic events to be included in Section 6.1 of the PI for dasiglucagon.

8.4.8. Electrocardiograms (ECGs)

This section reviews AEs related to abnormal ECG findings. QT prolongation is specifically reviewed in 8.4.9.

Serial 12-lead ECGs were performed in all trials in the clinical development program for dasiglucagon for the treatment of severe hypoglycemia. ECGs were conducted at screening, follow-up, and on the dosing day. ECG assessments on the dosing day varied per trial, but generally occurred at pre-dose and at 20-, 35-, 45-, 60-, and 300-minutes post-dose timepoints. ECGs were recorded using the site's ECG machine and were evaluated on site by the investigator. The investigator's interpretation of either normal, abnormal/not clinically significant (ANCS), or abnormal/clinically significant (ACS) was entered into the eCRF, and if the investigator interpreted the finding as abnormal (either ANCS or ACS), there was a free-text field where the investigator could specify the finding.

In the broad pool, one dasiglucagon exposed subject had an ECG finding judged as ACS by the investigator (dasiglucagon: 1/316, GlucaGen: 0/151, placebo: 0/53), that was also reported as an AE of 'electrocardiogram T wave inversion,' as described below:

- ID (b) (6): A 24-year-old male subject with T1DM experienced an AE of 'electrocardiogram T wave inversion' after dosing with 0.6 mg dasiglucagon. No medical history was reported for the subject, nor any concomitant medications besides insulin glulisine. The subject was dosed with 0.6 mg dasiglucagon twice, 28 days apart. The subject experienced no AEs in relation to the first dosing. On the second dosing day, the subject experienced T-wave inversion in lead AVF at 20 and 35 minutes after dosing, and T-wave inversion in leads AVF, II, and V3 to V5 at 45 minutes after dosing. No clinical signs were reported, and the subject's vital signs were normal. At 60 minutes after dosing, the inversion was no longer present. The subject had not shown any clinically significant ECG abnormalities during the first treatment sequence (Batch B). No clinically significant abnormal laboratory results or vital signs were reported. The subject completed the trial.

Reviewer comment: This case was also reviewed by the IRT-CS (see review from Dr. Preston

Dunnmon in DARRTS dated October 29, 2020). Asymptomatic transient non-specific ST-T-wave changes can happen for a variety of reasons (e.g. hyperventilation). This event occurred in a single subject without clinical consequence and does not raise a safety concern.

8.4.9. QT

This section reviews the impact of dasiglucagon on the QT interval as assessed in the IV/QTc trial 17144. Assessments of PR and QRS intervals are also reviewed. Supportive ECG data from the placebo-controlled pool are also presented (see 8.4.8 for additional information regarding the ECG methodology (e.g., timepoints) employed for placebo-controlled studies).

IV/QTc Trial 17144

Trial 17144 was a randomized, double-blind, placebo-controlled, dose-escalation study conducted in healthy subjects to evaluate the effect of dasiglucagon on cardiac repolarization (QT interval). A total of 60 adult subjects were randomized, of which 18 received placebo and 36 received dasiglucagon at the following doses: 0.03 mg IV, 0.1 mg IV, 0.3 mg IV, 0.6 mg IV, 0.6 mg SC, and 1.5 mg IV. Replicate 12-lead ECGs were performed at a central ECG laboratory at the following time points: -45, -30 and -15 min and paired with PK samples at 5, 15, 25, 40, 60, 80, 100, 120, 140, 180, 240 minutes and 24 hours post-dose, allowing for a concentration-QTc (C-QTc) analysis.

There were no deaths, SAEs, or AEs leading to discontinuation. No AEs of clinical importance per ICH E14 guidelines (e.g., seizures, significant ventricular arrhythmias, sudden cardiac death) occurred in this study.

There was no trend for a dose-response relationship in the C-QTc analysis over the wide range of dose levels evaluated, and no significant QTc prolongation effect was detected at doses up to 1.5 mg dasiglucagon administered IV over 5 minutes (Table 27).

Reviewer comment: These findings are in accordance with both in vitro and in vivo nonclinical studies, which indicated a low potential for QT prolongation. The results from trial 17144 were reviewed by the Integrated Review Team for Cardiac Safety Studies (IRT-CS), who concluded that no significant QTc prolongation effect of dasiglucagon was detected (see reviews dated February 13 and July 28, 2020 in DARRTS).

Reviewer comment: The Applicant's proposed labeling stating that doses resulting in 5 times the concentration of the recommended therapeutic dose of dasiglucagon do not prolong the QT interval to any clinically relevant extent is acceptable. Note, dose proportionality was only established between 0.1 and 1 mg dasiglucagon in trial 15126 (see clinical pharmacology section 4.5 for additional information), and therefore dose proportionality >1 mg is unknown.

Per the IRT-CS, in the absence of dose proportionality data for the SC route at doses >1 mg, a bioavailability-corrected concentration-based exposure margin is acceptable for the label. Because bioavailability following SC administration is approximately 50%, the Applicant's proposed labeling language is conservative, as the exposure reached with 1.5 mg IV dasiglucagon was ~37 x what was observed with a 0.6 mg SC dose (1,534 pmol/L versus 57,895 pmol/L with 0.6 mg SC and 1.5 mg IV dasiglucagon, respectively).

Regarding other markers of cardiac conduction, no subjects in trial 17144 had post-dose PR or QRS interval outliers in any treatment assignment (defined as a treatment emergent PR interval >200 ms with an increase in ΔPR >25%, or a QRS interval >120 with an increase in ΔQRS >25%).

Table 27. QT Prolongation Analysis Conducted by IRT-CS – Trial 17144

ECG parameter	Treatment	Concentrations (pmol/L)	ΔΔQTcF (msec)	90% CI (msec)
QTc	0.60 mg (SC#)	1,534.0	0.7	(-1.1 to 2.5)
QTc	1.50 mg (IV*)	57,895.6	-0.1	(-4.2 to 3.9)

#administered as a single subcutaneous dose of dasiglucagon
**administered as a single intravenous dose of dasiglucagon using 5 min infusion*
Source: IRT-CS analysis of C-QTc data (review dated February 13, 2020)

Placebo-Controlled Pool

As described in 8.4.8, serial ECGs were conducted in the placebo-controlled trials allowing for additional supportive safety analyses regarding the effects of dasiglucagon on QT, PR, and QRS intervals at the intended dasiglucagon dose, route of administration, and subject population (Table 28). Results obtained from trials 16137 and 17145 were supportive of the results obtained in the IV/QTc trial, with neither trial demonstrating significant changes in QT interval, defined as an upper bound 90% CI of the LS mean less than 10 ms in ΔΔQTcF at 35 minutes-post-dose (the t_{max} of dasiglucagon when administered SC is approximately 35 minutes). Regarding potential outliers of clinical significance, no subjects in any treatment arm had an increase in QTcF of >60 ms from baseline or a QTcF > 480 ms. Two subjects in the placebo-controlled pool exposed to dasiglucagon met the criterion for a PR outlier. The Applicant provided representative ECG tracings to support that these events were misreads of the rhythm and the PR interval by the ECG recorder due to noise/artifact. Therefore, there is no evidence from the placebo-controlled pool for a deleterious drug effect on AV conduction (see review from Dr. Preston Dunnmon in DARRTS dated October 29, 2020).

Table 28. Categorical Analysis of Post-Dose ECG Parameters – Placebo-Controlled Pool

	0.6 mg Dasiglucagon n=116	1 mg GlucaGen n=43	Placebo n=53
QTcF Threshold Parameter - count subjects (%)			
QTcF >450 ms	17 (14.1%)	6 (14.0%)	9 (16.6%)
QTcF >480 ms	0 (0.0%)	1 (2.3%)	0 (0.0%)
QTcF >500 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase from baseline >30 ms	15 (12.5%)	9 (20.9%)	2 (3.6%)
Increase from baseline >60 ms	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR Threshold Parameter - count subjects and %			
> 200 with an increase from baseline >25%	2 (1.6%)	0 (0.0%)	0 (0.0%)
Heart Rate - count subjects and %			
<50 with a decrease from baseline >25%	0 (0.0%)	0 (0.0%)	1 (1.8%)
>100 with an increase from baseline >25%	2 (1.6%)	1 (2.3%)	0 (0.0%)
QRS Threshold Parameter			
>120 with an increase from baseline >25%	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Generated by reviewer with ADEG dataset in JReview (CMH adjusted)

QT Prolongation Events (broad pool)

A SMQ for Torsade de Pointes/QT prolongation (broad scope) was used to identify events related to QT prolongation in the broad pool. Two events were captured; one event of syncope (GlucaGen) and one event 'QT interval prolonged' (dasiglucagon) (dasiglucagon: 1/316, GlucaGen: 1/151, placebo: 0/53). The detailed subject narrative for the subject who experienced an event of QT prolongation is shown below:

- Subject (b) (6): A 53-year-old male subject in trial 16136 (immunogenicity trial) with T1DM experienced a prolonged QT interval after administration of 0.6 mg dasiglucagon. Concomitant medications included insulin lispro and insulin glargine for T1DM, pantoprazole for GERD, and rosuvastatin for dyslipidemia. At screening and baseline, QTc was 462 and 455 ms, respectively, and the values remained at this level for 45 min after dosing. At 60 and at 240 minutes post-dose, QTc increased to 470 and 480 ms, respectively. The investigator judged the event to be moderate in severity and probably related to investigational product. The investigator decided to withdraw the subject from further dose administrations.

Reviewer Comment: Subject (b) (6) had a borderline prolonged QTc interval at screening and in pre-dose ECG assessments (462 and 455 ms, respectively). QTc interval increased to a maximum of 25 ms from baseline at 240 min post-dose. The half-life and C_{max} of dasiglucagon are approximately 35 and 30 minutes respectively, and dasiglucagon is expected to be eliminated by

240 min post-dosing. Given the subject had borderline prolonged QT at baseline and that the timing of the event was not related to important PK parameters, this event is not likely related to dasiglucagon administration. This case was also independently reviewed by the IRT-CS, who concluded that the event appears unrelated to dasiglucagon administration.

Pediatrics and QT Assessment

In pediatric trial 17086, dasiglucagon plasma concentrations were measured on the dosing day pre-dose and at 10, 20, 30, 40, 60, 90, 140, 220, and 300 minutes post-dose. A peak concentration of 1330 ± 724 pmol/L (n=20; T_{max}: ~0.5 h, half-life: 0.7 h) was observed in the pediatric population. Slightly higher peak concentrations were observed in the younger age group (n=8; 1644 pmol/L in 6 to 11 years) compared to that observed with the older age group (n=12; 919 pmol/L in 12 to 17 years). Nonetheless, PK data in pediatrics is well within the range that is covered by the assessment performed in adults in trial 17144. Therefore, it is reasonable to extrapolate results observed in the IV/QTc trial 17144 to pediatrics (see IRT-CS review dated July 28, 2020 in DARRTS). Additionally, no events related to QT prolongation or AEs in the SOC "cardiac disorders" were reported in pediatric trial 17086. Review of box and whisker plots in JReview did not identify treatment emergent QTcF outliers in dasiglucagon exposed pediatric subjects (data not shown).

8.4.10. Immunogenicity

Overview

ADA assessments were conducted in all nine trials in the clinical development program for severe hypoglycemia (see Table 2) as well as in two trials (b) (4) representing a total of 11 trials and 498 subjects exposed to dasiglucagon (370 adults with T1DM, 20 pediatrics with T1DM, and 108 healthy subjects). An additional 212 subjects in the above-noted trials were exposed to exogenous native glucagon.

Assay validation reports utilized by the Applicant in the assessment of ADAs were reviewed by Dr. Faruk Sheikh (OBP/CDER), who determined that the anti-dasiglucagon antibody (ADA) binding assay, anti-glucagon antibody binding assay, cross-reactivity and titering assay for analyzing antibodies to dasiglucagon, and neutralizing antibody (NAbs) assays (to dasiglucagon and glucagon) are sufficient for the purpose of this application. Refer to Dr. Sheikh's review memorandum dated December 4, 2020 for additional information regarding assay validation.

Note, dasiglucagon is approximately 75% homologous to glucagon, and there is the potential for ADAs to develop to epitopes that may be unique to dasiglucagon or to epitopes that are conserved between glucagon and dasiglucagon. Should the latter occur, positivity would be expected in both anti-dasiglucagon and anti-glucagon binding assays. Likewise, should a subject

have (or develop) anti-glucagon antibodies, positivity in both assays may occur depending on the specific epitope that is being targeted.

Immunogenicity Assessment

In total, four of 498 subjects (0.8%) who were ADA-negative at baseline developed ADAs after dasiglucagon administration (Table 29). The four ADA-positive subjects included two subjects from single-dose trials (16137, 17086), one from the dose-finding cross-over trial of a single dose of dasiglucagon and GlucaGen (15126), and one from a supportive multi-dose cross-over trial of dasiglucagon and glucagon (Eli Lilly) (b) (4) (16098). One of the four ADA-positive subjects was a pediatric subject (subject (b) (6) in 17086). Given the small number of ADA-positive subjects, statistical analysis for the impact of ADA formation on PK/PD, efficacy and/or safety was not performed. Instead, subject narratives for these subjects were reviewed individually.

Table 29. Summary of Subjects who Became ADA-Positive After Dasiglucagon Exposure

Trial - Study Population - Subject ID	Dose	- Cross Reactivity - Neutralizing Activity	ADA-negative timepoint
15126 - T1DM adults - (b) (6)	0.3 mg single dose dasiglucagon	- No - Not determined	Not determined
16098* - T1DM adults - (b) (6)	- 8 doses of dasiglucagon (0.03 - 0.6 mg) - 3 doses of 1 mg glucagon	- Yes - Yes	7 months
16137 - T1DM adults - (b) (6)	0.6 mg single dose dasiglucagon	- No - No	17 months
17086 - T1DM pediatrics - (b) (6)	0.6 mg single dose dasiglucagon	- No - No	Subject remained ADA-positive at 18-month timepoint

** This subject also tested positive for anti-glucagon antibodies*
Source: Compiled by reviewer

No immunogenicity-related AEs were identified for any of the four subjects who tested positive for ADAs. As noted above, two subjects who tested positive for ADAs were enrolled in crossover studies and therefore were administered both dasiglucagon and native glucagon. Regarding subject (b) (6) from dose finding trial 15126, this subject was administered 0.3 mg dasiglucagon, and then subsequently tested positive for ADAs five days later in a sample obtained on the GlucaGen dosing day. Because of methodologic issues NAbs were not assessed, but cross-reactive (to native glucagon) antibodies were negative. This subject experienced an AE of hypoglycemia on the same day that was not adequately explained by the Applicant (plasma glucose of 34 mg/dL approximately 6 hours post-GlucaGen dosing; treated with IV glucose), but

it is unlikely that the hypoglycemia AE was related to ADAs because of the timing of the event and lack of cross-reactive antibodies in this subject.

Subject (b) (6) was enrolled in trial 16098 (b) (4) and received eight doses of dasiglucagon (0.03-0.6 mg; 4 mg/dL formulation) and three doses of glucagon for injection (Eli Lilly) subcutaneously in eight treatment days over a 21-day timeframe. On the first three dosing days, the subject was administered both dasiglucagon and native glucagon on the same day. Initial samples were ADA-negative, whereas the result from the ADA sample taken at the follow-up visit (45 days after first dosing day and 24 days after last dosing day), was positive for both anti-dasiglucagon and anti-glucagon antibodies. NAbs were positive for both glucagon and dasiglucagon neutralizing activity. At a follow-up visit about 3.5 months after last dosing, the sample was negative for anti-glucagon antibodies but remained positive for anti-dasiglucagon antibodies. At an additional follow-up visit performed about 7 months after last dosing the serum sample was negative for anti-dasiglucagon antibodies.

Reviewer Comment: Any impact of the neutralizing activity of the antibodies in this sample on safety and efficacy cannot be determined from these data. Trial 16098 was not designed to evaluate the impact of ADA positivity on PK/PD, and this subject was not exposed to dasiglucagon after becoming ADA positive. Due to the cross-over nature of the study and the high degree of amino acid sequence homology between dasiglucagon and glucagon, the ADA-positivity result cannot be specifically assigned to either dasiglucagon or glucagon treatment. No other ADA-positive subjects developed NAb responses during the treatment and follow-up periods, which suggests that either subject-specific factors, multiple doses, and/or the drug switching protocol may have been responsible for the observed NAb development. Overall, the available data are not sufficient to draw any firm conclusions.

Immunogenicity Trial 16136

No ADA-positive samples were observed in immunogenicity trial 16136, which was a phase 3, randomized, double-blind, parallel-group safety trial to evaluate the immunogenicity of dasiglucagon and GlucaGen administered SC in patients with T1DM. Subjects were randomized to receive either 0.6 mg dasiglucagon (57 subjects) or 1.0 mg GlucaGen (54 subjects) three times within a two-week period, and then were assessed for ADA-positivity for approximately 15 weeks. This trial also intended to follow ADA-positive subjects for PK/PD sampling to determine the impact of ADAs on efficacy and safety; however, this planned evaluation was unable to proceed due to the lack of ADA positive subjects.

Bridging Trial

ADAs may also develop towards peptide degradation products of dasiglucagon, so it is noteworthy that no ADA-positive samples were observed in bridging study 17084, which

included the analysis of samples from a batch of dasiglucagon (Batch B) (b) (4)

Treatment-boosted antibodies

A total of five subjects had pre-existing antibodies, as tested by the anti-dasiglucagon assay. As these subjects has not been previously exposed to dasiglucagon, presumably these subjects had anti-glucagon antibodies that tested positive in the ant-dasiglucagon antibody binding assay. These five subjects were assessed for treatment boosting of their ADA responses (defined as a five-fold increase in titer from baseline). No subjects experienced a treatment boosted antibody response (greatest titer increase was 2.3-fold).

Reviewer Comment: Although the immunogenic potential of dasiglucagon could, in theory, be higher than native glucagon because of the seven amino acid substitutions introduced into the native peptide chain, the available data suggest that the immunogenic potential of dasiglucagon is low, with no subjects demonstrating ADA-positivity in immunogenicity trial 16136, which was specifically designed to assess immunogenicity after multiple doses over 15 weeks. Of the ADA positive subjects in other trials, no immunogenicity-related AEs were reported. Regarding the single subject with cross-reactive and NAbs, no clinical consequence was identified. Furthermore, the ADA-positive results in this subject cannot be conclusively determined to be due to dasiglucagon treatment. Limited evidence suggests that the incidence of ADA formation to dasiglucagon may be similar to native glucagon, as the current USPI for glucagon for nasal inhalation (Baqsimi, Eli Lilly) reports that 2% of patients developed treatment-emergent glucagon antibodies.

Overall, although the immunogenicity risk for the proposed single-dose indication is expected to be low based on the data reviewed herein, the available data may not be fully predictive of real-world use of dasiglucagon where it will be used on an as-needed basis for the treatment of severe hypoglycemia, and the clinical consequence of NAbs is unknown. In theory, NAbs that develop towards native glucagon could impact a patient's endogenous response to hypoglycemia. This would be expected to primarily impact patients with T2DM as these patients have a preserved counter-regulatory response to hypoglycemia (as opposed to patients with T1DM, who are likely to have a compromised counter-regulatory response to hypoglycemia). Despite this, these concerns are hypothetical at this point. Based on the available information, standard postmarket surveillance appears reasonable to monitor the risk of immunogenicity. Loss of efficacy after repeated dosing due to immunogenicity should be considered if postmarketing reports of 'ineffective product' are identified frequently. Reports of hypoglycemia that may indicate a loss of endogenous glucagon response should also be monitored.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hemodynamic Events

Methods

Exogenously administered native glucagon has been shown to exert inotropic and chronotropic effects on the heart, and therefore dasiglucagon treatment may also result in temporary changes in heart rate and/or blood pressure for some patients. Signs of clinically relevant hypotension or hypertension and changes in heart rate, collectively termed hemodynamic events, were pre-specified as AESI in all phase 3 trials and defined as follows:

- Post-dose clinical signs or measured vital signs indicating a clinically significant drop in blood pressure including signs of orthostatic hypotension, vasovagal responses or bradycardia.
- Post-dose changes in heart rate or blood pressure considered an event of hypo- or hypertension as judged by the investigator.

To identify hemodynamic events, the Applicant developed a post-hoc customized MedDRA query (CMQ). The PTs included were based on a selection of High Level Group Terms (HLGT) and High Level Terms (HLT) chosen to capture clinical signs or measured vital signs indicating clinically significant changes in blood pressure or heart rate, with the exclusion of the PT of "dizziness," which the Applicant stated is non-specific and can be associated with a wide variety of conditions such as hypoglycemia. Hemodynamic events were recorded in a specific AESI form in the eCRF that collected additional information regarding the event such as heart rate, blood pressure, glucose level, and ECG information at the time of the event.

Reviewer comment: The Applicant's approach to collecting information via an AESI form in the eCRF in phase 3 trials appears reasonable to have collected meaningful information regarding the event. The applicant included PTs in the HLGT 'decreased and non-specific blood pressure disorders and shock' and PTs within the following HLTs: cardiac signs and symptoms, heart rate and pulse investigations, vascular hypertensive disorders not elsewhere classified (NEC), vascular tests NEC (including blood pressure), rate and rhythm disorders NEC, and accelerated and malignant hypertension. I have reviewed these PTs and agree that they are appropriate for the identification of hemodynamic events. Regarding the Applicant's exclusion of the PT of 'dizziness' there were 9/316 and 4/151 events of dizziness in dasiglucagon and GlucaGen exposed subjects, respectively, that occurred within 12 hours dosing in the broad pool (no events of dizziness were observed with placebo). Events of dizziness did not coincide with other AEs that could indicate a hemodynamic event aside from the events already captured by the Applicant's post-hoc CMQ.

Broad Pool

In the broad safety pool, seven subjects treated with dasiglucagon (2.3%) and nine subjects treated with GlucaGen (5.9%) were identified who experienced at least one hemodynamic event within 12 hours of dosing, as captured by Applicant's post-hoc CMQ for hemodynamic events (described above). No events occurred in the placebo groups (Table 30). Events in all treatment arms had an onset of approximately 1–3 hours after administration. The majority of the events were associated with gastrointestinal symptoms. No events were serious or led to study withdrawal.

Table 30. Hemodynamic Events within 12 Hours Post-Dose by SOC/PT (Applicant's Post-Hoc CMQ) - Broad Pool

	≥0.6 mg Dasiglucagon n=316	1 mg GlucaGen n=151	Placebo n=53
Subject with at least one AE - count (%)	**7 (2.3%)**	**9 (5.9%)**	**0 (0%)**
Vascular disorders	**3 (1.1%)**	**6 (3.9%)**	**0 (0%)**
Hypotension	2 (0.7%)	2 (1.3%)	0 (0%)
Hypertension	1 (0.4%)	2 (1.3%)	0 (0%)
Orthostatic hypotension	0 (0%)	1 (0.7%)	0 (0%)
Circulatory collapse	0 (0%)	1 (0.6%)	0 (0%)
Cardiac disorders	**2 (0.6%)**	**1 (0.6%)**	**0 (0%)**
Palpitations	1 (0.4%)	0 (0%)	0 (0%)
Bradycardia	1 (0.2%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	1 (0.6%)	0 (0%)
Nervous system disorders	**2 (0.6%)**	**1 (0.6%)**	**0 (0%)**
Orthostatic intolerance	1 (0.4%)	0 (0%)	0 (0%)
Presyncope	1 (0.2%)	0 (0%)	0 (0%)
Syncope	0 (0%)	1 (0.6%)	0 (0%)
Investigations	**0 (0%)**	**1 (0.6%)**	**0 (0%)**
Blood pressure decreased	0 (0%)	1 (0.6%)	0 (0%)

Source: Generated by reviewer in JReview with ADSL and ADAE datasets; CMH weighing from Applicant's analysis

Narratives of the hemodynamic events that occurred following dasiglucagon treatment were reviewed individually and additional details for each event are summarized in Table 31. Five of the seven events that occurred in dasiglucagon-exposed subjects (events of hypotension, hypertension, palpitations, and orthostatic intolerance) resolved without intervention or action being taken by the investigator. They were transient in nature, lasting from 5 to 115 minutes in duration, and categorized as mild in severity by the investigator. Subjects who experienced palpitations and orthostatic intolerance also experienced hypoglycemia at the time of event (blood glucose 56 mg/dL), and it is possible that hypoglycemia could have contributed or caused the event.

Table 31. Details for Hemodynamic Events after Dasiglucagon Treatment Within 12 Hours Post-Dose – Broad Pool

Trial - ID -Dose	PT	- Onset Post-Dose - Duration	Other symptoms	Selected Vitals	Additional Info
16137 - (b) (6) - 0.6 mg	Presyncope	-77 min - 3 min	Bradycardia, nausea, sweating, paleness	Screening: 52 bpm Pre-dose: 68 bpm Time of event: 40 bpm End of event: 54 bpm 90 min: 65 bpm	- See detailed narrative below
16137 - (b) (6) - 0.6 mg	Bradycardia	- 138 min - 1 min	Nausea, loss of consciousness, sweating	Pre-dose: 55 bpm Time of event: 30 bpm End of event: 46 bpm 300 min: 46 bpm	- See detailed narrative below
16136 - (b) (6) - 0.6 mg	Hypertension	- 90 min - 30 min	None	Pre-dose: 151/94 mmHg Time of event: 162/100 mmHg 120 min: 143/95 mmHg	- Detected at planned vital sign measurement - No action taken to resolve
16136 - (b) (6) - 0.6 mg	Hypotension	- 124 min - 74 min	Nausea	Pre-dose: 138/73 mmHg Time of event: 111/65 mmHg	- Detected at planned vital sign measurement - No actions taken to resolve
16136 - (b) (6) - 0.6 mg	Hypotension	- 88 min - 76 min	None	Pre-dose: 122/80 mmHg Time of event: 100/68 mmHg	- Detected at planned vital sign measurement - No action taken to resolve
15126 - (b) (6) - 1 mg	Orthostatic intolerance	- 102 min - 5 min	Nausea	Time of Event: 68 bpm, 120/78 mmHg	- No action taken to resolve - Glucose was 56 mg/dL at the time of event
15126 - (b) (6) - 0.6 mg	Palpitations	- 90 min - 115 min	Dizziness, nausea, headache	No vital data from time of event; normal vitals at scheduled timepoints.	- No action taken to resolve - Glucose was 56 mg/dL at the time of event

Source: Compiled by reviewer with information from ISS Table 2-21 and ISS Appendix 9

There were two hemodynamic events where investigator intervention occurred, which were also categorized moderate in severity by the investigator, as detailed below:

- Subject (b) (6): A 33-year-old female subject with T1DM in trial 16137 experienced an AE of presyncope after dosing with 0.6 mg dasiglucagon. The subject's heart rate was 52 and 68 bpm at screening and pre-dose, respectively. The event of presyncope occurred approximately 1 hour and 15 minutes after dosing and was associated with bradycardia, nausea, sweating, and paleness. At the start of the event, the subject's pulse was 40

bpm. The subject's legs were raised in a supine position, and symptoms resolved within three minutes. The investigator considered the event of presyncope to have been caused by bradycardia.

- Subject (b) (6): A 48-year-old male subject with T1DM in trial 16137 experienced an AE of bradycardia after dosing with 0.6 mg dasiglucagon. The subject's heart rate was 55 bpm pre-dose. The subject was connected to a cardiac monitor at the time of the event, enabling the trial staff to observe the event of bradycardia. Approximately two hours after dosing the subject experienced nausea, which was treated with 10 mg metoclopramide. Six minutes after start of the IV infusion of metoclopramide, and approximately 2 hours and 20 minutes after dosing with dasiglucagon, the subject's heart rate decreased to 30 bpm and the subject lost consciousness. Chest compressions were performed, heart rate increased to over 40 bpm, and the subject regained consciousness. The loss of consciousness lasted approximately 30 seconds. At all ECG measurements on the dosing day, including pre-dose ECG, the subject was found to have sinus bradycardia.

Reviewer comment: Subject (b) (6) experienced presyncope in the setting of bradycardia, nausea, sweating, and pallor; although baseline heart rate was low, drug-relatedness to the further drop in heart rate cannot be excluded. For subject (b) (6), the event of bradycardia occurred six minutes after staring IV administration of metoclopramide. The USPI for metoclopramide lists cardiac AEs of hypotension, hypertension, supraventricular tachycardia, bradycardia, fluid retention, acute congestive heart failure, possible AV block. Autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac arrhythmias) can also occur. The subject's pre-dose heart rate was below the normal range. A causal relationship between administration of dasiglucagon and the event of bradycardia cannot be excluded, but the administration of metoclopramide may equally well account for or contribute to this event. This event was also independently reviewed by the IRT-CS (review dated February 28, 2019), who concluded that the event appears related to metoclopramide administration and not dasiglucagon.

Reviewer comment: Given the results from the broad pool showing an increased incidence of hemodynamic events compared to placebo, data from supportive trials in healthy subjects demonstrating events with dasiglucagon doses 1.0-2.0 mg (reviewed below), and given that changes in heart rate and blood pressure are documented consequences of exogenous native glucagon, dasiglucagon may have a causal relationship with the hemodynamic events described in this review. Importantly however, the overall incidence of hemodynamic events was low (dasiglucagon: 2.3%; GlucaGen: 5.9%; placebo 0%), and events were transient in nature and generally resolved without intervention. As with other approved glucagon products for the treatment of severe hypoglycemia, labeling appears appropriate to inform patients and

prescribers about the possibility of clinically relevant changes in heart rate/blood pressure when taking dasiglucagon.

Pediatric Subjects

There were no hemodynamic events in dasiglucagon-exposed pediatric subjects over the entire observation period (one event of hypertension occurred in the placebo arm) as assessed using the Applicant's post-hoc CMQ for hemodynamic events.

Supportive Trials in Healthy Subjects

Trials conducted with healthy subjects in the development program of dasiglucagon for severe hypoglycemia included three phase 1 studies: trial 14013 Part 1, trial 15007, and IV/QTc trial 17144 (see Table 2 for an overview of study designs). Doses of dasiglucagon in these studies varied from 0.03 – 2.0 mg. Hemodynamic events were pre-specified AESIs only in trial 17144.

Six healthy subjects experienced hemodynamic AEs (dasiglucagon: 5/108 subjects (4.6%), GlucaGen: 1/16 subjects (6.2%), placebo 0/24 (0%) subjects within the 12-hour post-dose time period). Most of these events were categorized as hypotension. All events occurred with dasiglucagon doses higher than the intended 0.6 mg dose.

Reviewer comment: These data in healthy volunteers generally corroborate the results from the analyses using the placebo-controlled and broad pool that showed a small increase in hemodynamic events. Again, such events are proposed to be listed in Section 6 of the PI as Adverse Reactions. The higher risk increase relative to placebo in this analysis versus the placebo-controlled and broad pool analyses could possibly be related to the higher dose of dasiglucagon used the healthy volunteer studies, although caution is needed when attempting to draw conclusions based on cross-trial comparisons.

8.5.2. Hypersensitivity

Methods

Hypersensitivity and allergic reactions that have been reported with glucagon products include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. Therefore, a SMQ for Hypersensitivity (narrow scope) was performed utilizing the broad pool to identify AEs related to hypersensitivity. As noted in 8.3.2, MedDRA version 22.0 was used for all queries.

Broad pool

The SMQ identified two subjects exposed to dasiglucagon who experienced AEs related to hypersensitivity (dasiglucagon: 0.6%, GlucaGen: 1.9% placebo: 0%). The two AEs had PTs of 'dermatitis contact' and 'infusion site rash,' which appear related glucose/insulin infusion during the hypoglycemic clamp given the verbatim terms reported, which were "reaction to adhesive" and "IV rash," respectively.

Pediatric Trial 17086

No AEs related to hypersensitivity were identified by the Hypersensitivity SMQ (narrow scope) in dasiglucagon-exposed subjects (dasiglucagon: 0%, GlucaGen: 16.7%, placebo: 0%).

8.5.3. Injection Site Reactions:

Methods

Injection site reactions have been reported as commonly occurring adverse reactions in the labeling of some injectable native glucagon products (e.g., Gvoke, Fresenius Kabi glucagon for injection, etc.). To this end, local tolerability assessments at pre-specified timepoints occurred in all trials in the broad pool. A dedicated local tolerability assessment form that was included the eCRF detailed that the investigators should assess for the following at pre-specified timepoints: spontaneous pain, pain on palpation, itching, redness, edema, induration/infiltration, and/or other. In the placebo-controlled pool injection sites were assessed at pre-dose, and 30- 120-, and 300-minutes post-dose and at the follow-up safety visit. To investigate the relationship between dasiglucagon and injection site reactions, the Applicant developed a post-hoc CMQ, which included all PTs in the following HLTs: administration site reactions, application site reactions, injection site reactions.

Reviewer comment: The Applicant's approach for collecting clinically meaningful information during trials for the evaluation of ISRs is acceptable. Regarding the Applicant's post-hoc CMQ, it is noteworthy that the CMQ excludes the HLT of 'infusion site reactions,' which includes PTs of infusion site extravasation and infusion site rash, which were AEs observed in the placebo-controlled pool in the SOC 'general disorders and administration site conditions.' However, these AEs appear related to IV infusion of insulin/glucose during the hypoglycemic clamp procedure given the verbatim terms of IV infiltration and IV site rash. Therefore, the Applicant's post-hoc CMQ appears appropriate to identify events that may be specific to SC dasiglucagon administration.

Placebo-controlled pool

Table 32 shows the ISRs identified by the Applicant's post-hoc CMQ within 12 hours of dosing in the placebo-controlled pool. A low percentage of subjects experienced ISRs in all treatment

groups, with the percentage of events being comparable between dasiglucagon and placebo (dasiglucagon: 3.2%, GlucaGen 7.0%, placebo: 3.6%). Events generally had an onset within one hour of dosing and lasted less than two hours.

Table 32. ISRs within 12 Hours Post-Dose (Applicant Post-Hoc CMQ) – Placebo-Controlled Pool

	0.6 mg Dasiglucagon n=116	1 mg GlucaGen n=43	Placebo n=53
TEAE Flag - count subjects and % with data	**4 (3.2%)**	**3 (7.0%)**	**2 (3.6%)**
General disorders and administration site conditions	**4 (3.2%)**	**3 (7.0%)**	**2 (3.6%)**
Injection site erythema	2 (1.6%)	2 (4.7%)	2 (3.6%)
Injection site pain	3 (2.3%)	0 (0.0%)	0 (0.0%)
Injection site edema	0 (0.0%)	1 (2.3%)	0 (0.0%)

Source: Generated by reviewer in JReview with ADSL and ADAE datasets; CMH weighing from Applicant's analysis

Similar results were obtained with an analysis for ISRs utilizing the broad pool (data not shown).

Pediatric Trial 17086

ISRs that occurred in pediatric trial are shown in Table 33. ISR events were reported for 5% of subjects (i.e., 1 subject) following dasiglucagon administration and 30% of subjects following GlucaGen; no events occurred in the placebo group. In light of the limited size of the pediatric safety database, ISRs were identified manually versus via the Applicant's post-hoc CMQ.

Table 33. ISRs within 12 Hours Post-Dose – Pediatric Trial 17086

	0.6 mg Dasiglucagon n=20	1.0 mg GlucaGen n=10	Placebo n=11
General disorders and administration site conditions	**1 (5.0%)**	**3 (30.0%)**	0 (0%)
Injection site erythema	0 (0%)	3 (30.0%)	0 (0%)
Injection site pain	1 (5.0%)	0 (0%)	0 (0%)
Injection site induration	0 (0%)	1 (10.0%)	0 (0%)
Injection site edema	0 (0%)	1 (10.0%)	0 (0%)

Source: Generated by reviewer in JReview with ADSL and ADAEP datasets

8.5.4. Hepatic and Renal Events

Hepatic

A SMQ (drug-related hepatic disorders – comprehensive search [broad scope]) was performed with the broad pool and the pediatric trial to capture AEs associated with drug-related liver disorders. No events were identified.

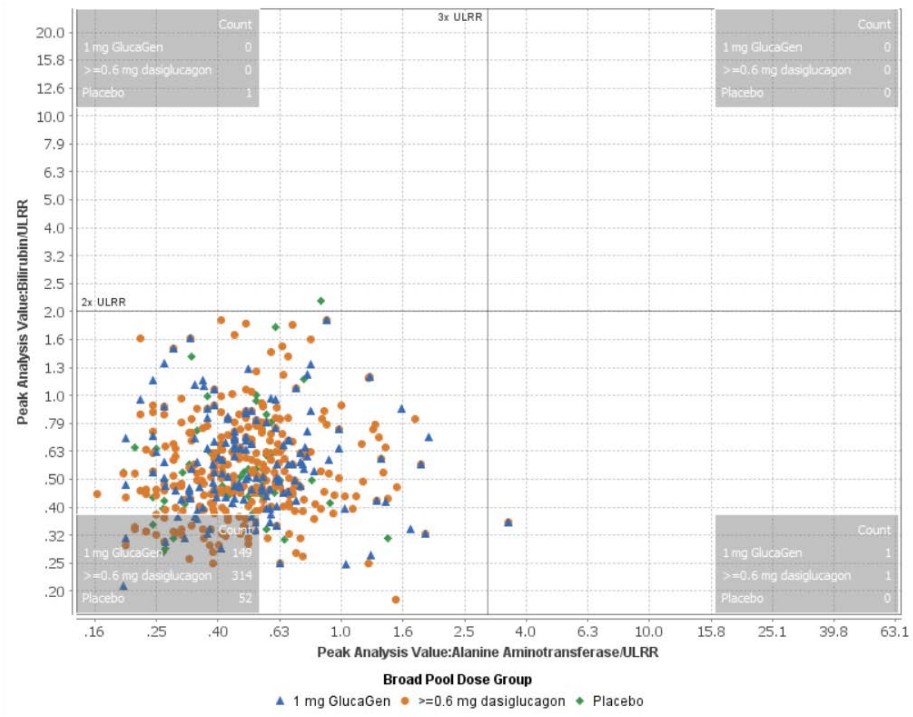
There were no Hy's law cases in the broad pool, defined as ALT/AST >3x ULN and total bilirubin >2x ULN (Figures 34 and 35). As shown in Figure 34, one subject in trial 14013 Part 2 who was exposed to a single dose of 0.7 mg dasiglucagon and a single dose of 1.0 mg GlucaGen demonstrated ALT >3xULN. The following narrative was provided:

- ID (b) (6): A 41-year-old male subject with T1DM in trial 14013 Part 2 had a transient elevation in hepatic function markers. The subject had an ALT outlier value of 171 U/L at an unscheduled visit that took place five days after the safety follow-up visit, which decreased to 96 U/L at a second (final) unscheduled visit that took place nine days after the safety follow-up visit. At the safety follow-up visit, the subject had an ALT value (57 U/L) and an AST value (93 U/L) that were above the normal range. The AST value was also above the normal range at the first unscheduled visit (76 U/L) but not the second (36 U/L). At all other time points in the trial, ALT and AST measurements were within the normal range. No AEs were reported for this subject. The investigator attributed the event to the subject engaging in intensive muscular exercise (weightlifting) prior to the follow-up visit.

Reviewer comment: This event is likely unrelated to dasiglucagon given that there was no discernable pattern of transaminase values and given a potential alternative etiology (i.e. strenuous exercise).

Reviewer comment: Overall, the absence of AEs captured by the SMQ for drug related hepatic disorders, the lack of a signal from liver enzyme chemistry tests in the broad pool, and the lack of a known liver safety issue with marketed glucagon products suggest that single-dose administration dasiglucagon does not have a liver safety signal.

Figure 34. Hy's Law Plot, Alanine Transaminase (ALT) vs. Bilirubin – Broad Pool



Source: Generated by reviewer in JReview with ADEX and ADLB datasets

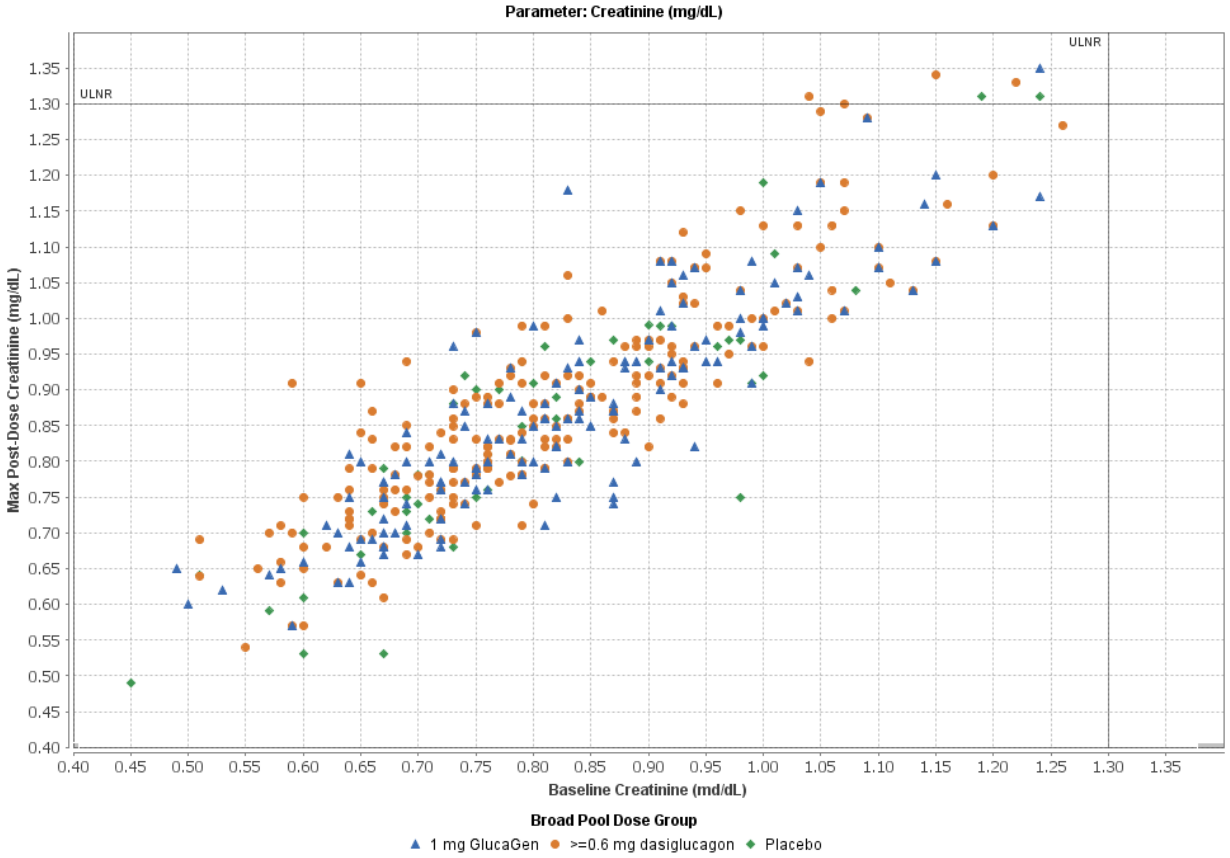
Figure 35. Hy's Law Plot, Aspartate transaminase (AST) vs. Bilirubin – Broad Pool

Source: Generated by reviewer in JReview with ADEX and ADLB datasets

Renal

A SMQ (acute renal failure [broad scope]) was performed with the broad pool and the pediatric study to capture AEs related to acute renal failure. No AEs related to acute renal failure were identified. There were no creatinine outliers of clinical significance (>2x ULN; Figure 36).

Figure 36. Pre-Dose to Maximum Post-Dose Creatinine Values – Broad Pool



Source: Generated by reviewer in JReview with ADEX and ADLB datasets

8.6. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroup utilizing the placebo-controlled pool were performed to evaluate whether commonly occurring adverse events (nausea, vomiting, headache, diarrhea, and injection site pain) differed importantly between subgroups (Table 34). Females experienced a higher percentage of gastrointestinal events as compared to males in the dasiglucagon group (higher percentages of nausea and vomiting were also observed in females in the placebo group, but the low event rate limits interpretability). Additionally, a trend for increased nausea with decreased age was observed in the analysis by age quartile. Regarding race, almost all subjects in the placebo-controlled pool were White, limiting the interpretability of this data. There were no noteworthy differences in injection site pain between subgroups (data not shown).

Table 34. Safety Analyses by Demographic Subgroups - Placebo-Controlled Pool

	% of Population	Nausea		Vomiting		Headache		Diarrhea	
		Dasiglucagon	Placebo	Dasiglucagon	Placebo	Dasiglucagon	Placebo	Dasiglucagon	Placebo
Sex									
- Male	60%	33/66 (50%)	1/36 (3%)	13/66 (20%)	0/36 (0%)	8/66 (12%)	0/36 (0%)	1/66 (2%)	0/36 (0%)
- Female	40%	33/50 (66%)	1/17 (6%)	16/50 (32%)	1/17 (6%)	5/50 (10%)	2/17 (12%)	5/50 (10%)	0/17 (0%)
Age									
- ≥18 to <65	96%	65/111 (59%)	2/52 (4%)	29/111 (26%)	1/52 (2%)	12/111 (11%)	2/52 (4%)	5/111 (5%)	0/52 (0%)
- ≥65 to <75	4%	1/5 (20%)	0/1 (0%)	0/5 (0%)	0/1 (0%)	1/5 (20%)	0/1 (0%)	1/5 (20%)	0/1 (0%)
- Q1: ≥18 to <31	28%	23/28 (82%)	0/19 (0%)	8/28 (29%)	0/19 (0%)	3/28 (11%)	2/19 (11%)	1/28 (4%)	0/19 (0%)
- Q2: ≥31 to <38	22%	20/28 (71%)	0/10 (0%)	10/28 (36%)	0/10 (0%)	4/28 (14%)	0/10 (0%)	2/28 (7%)	0/10 (0%)
- Q3: ≥38 to <49	25%	13/32 (41%)	1/10 (10%)	8/32 (25%)	1/10 (10%)	3/32 (9%)	0/10 (0%)	1/32 (3%)	0/10 (0%)
- Q4: ≥49 to <75	25%	10/28 (36%)	1/14 (7%)	3/28 (11%)	0/14 (0%)	3/28 (11%)	0/14 (0%)	2/28 (7%)	0/14 (0%)
Race									
- White	92%	63/110 (57%)	2/46 (4%)	27/110 (25%)	1/46 (2%)	13/110 (12%)	2/46 (4%)	6/110 (5%)	0/46 (0%)
- Black/African American	2%	1/1 (100%)	0/2 (0%)	0/1 (0%)	0/2 (0%)	0/1 (0%)	0/2 (0%)	0/1 (0%)	0/2 (0%)
- Asian	3%	1/3 (33%)	0/2 (0%)	1/3 (33%)	0/2 (0%)	0/3 (0%)	0/2 (0%)	0/3 (0%)	0/2 (0%)
- Other	3%	1/2 (50%)	0/3 (0%)	1/2 (50%)	0/3 (0%)	0/2 (0%)	0/3 (0%)	0/2 (0%)	0/3 (0%)

Source: Applicant's analysis (with modified formatting)

8.7. Specific Safety Studies/Clinical Trials

See 8.4.9 regarding the IV/QTc trial 17144. No other specific safety studies were conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

In nonclinical studies, dasiglucagon was not mutagenic or clastogenic in a standard battery of genotoxicity tests: bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, rat bone marrow micronucleus. Although nonclinical carcinogenicity studies were not required to support this indication, a preliminary review of a 26-week carcinogenicity study performed (b) (4) did not indicate that dasiglucagon is carcinogenic or tumorigenic. There is currently no concern for carcinogenicity for dasiglucagon when intended for single-dose administration.

8.8.2. Human Reproduction and Pregnancy

There are no available data on dasiglucagon use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, daily subcutaneous administration of dasiglucagon to pregnant rabbits and rats during the period of organogenesis did not cause adverse developmental effects at exposures 7 and 709 times the human dose of 0.6 mg based on AUC, respectively (see nonclinical section 4.4 and Dr. Patricia Brundage's review for additional information).

Reviewer comment: Untreated hypoglycemia in pregnancy can cause complications and may be fatal if untreated. It is reassuring that prolonged experience over several decades with use of glucagon based on published observational studies and postmarketing reports has not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Given the lack of significant nonclinical findings and given that untreated severe hypoglycemia could have significant consequences for both mother and fetus, dasiglucagon should not be withheld from pregnant women because of concern about its effect on the developing fetus.

8.8.3. Pediatrics and Assessment of Effects on Growth

Safety in the pediatric population age 6 and older is discussed above.

This is an emergency use drug product that will not be used chronically, and an impact on growth is not expected. Dasiglucagon should not be withheld because of concerns about growth. Glucagon rescue products are already approved for use in pediatrics for the treatment of severe hypoglycemia.

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

Overall, dasiglucagon is not likely to be abused since it does not appear to produce dependence effects, and I have no clinical concern that abuse potential needs to be evaluated for this product. Nevertheless, a post-hoc CMQ designed by the Applicant to capture AEs related to abuse potential identified one event with the PT 'somnolence' that occurred a day after dosing. As this subject also experienced a non-treatment emergent event of somnolence, this event is not concerning. Because dasiglucagon has a short half-life, treatment of overdose is symptomatic, primarily for nausea, vomiting, hypertension, and hypokalemia. Hyperglycemia after dasiglucagon treatment may also need to be managed, although it is expected to be self-limited.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Dasiglucagon is not currently marketed in any region.

8.9.2. Expectations on Safety in the Postmarket Setting

AEs occurring in ≥2% of subjects treated with dasiglucagon are similar to common events listed in the labeling for other rescue glucagon products (e.g., nausea, vomiting, headache, and injection site pain) and therefore expectations for safety in the postmarket setting are anticipated to be similar to other glucagon products.

8.9.3. Additional Safety Issues From Other Disciplines

No approvability issues have been identified from other disciplines.

8.10. Integrated Assessment of Safety

The primary safety analysis presented in this review is based on a pooled dataset comprised of two, phase 3, placebo-controlled trials (16137 and 17145) that were also used to support

efficacy conducted in adults with T1DM. A secondary pool, referred to as the 'broad pool' was created with all available data from studies conducted in adult subjects with T1DM exposed to dasiglucagon at doses ≥0.6 mg to perform additional safety analyses. Pediatric trial 17086, which was a phase 3, placebo-controlled trial in pediatrics with T1DM, was assessed separately because it is not appropriate to pool adult and pediatric populations for safety analyses for this application. The submitted safety database is adequate for the proposed indication in the proposed populations.

Adverse events occurring in ≥2% of adult subjects treated with dasiglucagon included nausea, vomiting, headache, diarrhea, and injection site pain. These are events that would be expected with glucagon receptor agonism or with an injectable product and are also expected pharmacodynamic effects based on nonclinical data. With the exception of diarrhea, AEs observed with dasiglucagon are also observed with marketed native glucagon products. Additionally, the incidence of adverse events and the types of events reported were comparable between dasiglucagon and GlucaGen which is reassuring that the safety profile of dasiglucagon with regards to common AEs is similar to native glucagon.

Exogenously administered native glucagon has been shown to exert transient inotropic and chronotropic effects on the heart, and therefore hemodynamic effects were pre-defined AESIs in all phase 3 trials. An assessment of the broad pool demonstrated an increased incidence of hemodynamic events post-dasiglucagon treatment (2.3%) vs. placebo (0.0%), although lower than the incidence of events observed with GlucaGen treatment (5.9%). Hemodynamic events that did occur were transient in nature and generally resolved without intervention. As with approved native glucagon products, potential risks related to hemodynamic events can be effectively mitigated with labeling.

As a therapeutic peptide product, dasiglucagon has the potential to induce immunogenicity. No ADA-positive subjects were observed in trial 16136, which was designed to elicit immunogenicity and subsequently evaluate the impact of ADAs on PK/PD properties. ADA assessments were conducted in all nine trials in the clinical development program for severe hypoglycemia as well as two supportive trials (b) (4) representing a total of 498 subjects exposed to dasiglucagon in 11 trials. In total, four subjects (three adult and one pediatric) who received dasiglucagon developed ADAs, corresponding to an incidence of <1%. No immunogenicity related AEs were reported in ADA-positive subjects. Overall, the immunogenicity of dasiglucagon appears low, and standard postmarket surveillance appears reasonable to monitor the risk of immunogenicity should dasiglucagon be approved.

If approved, dasiglucagon would be the first glucagon analog marketed for any indication, and therefore there is the potential for unknown risks that may occur with future use of the drug (e.g., rare events that were not identified in the premarket setting). Importantly however, these risks are currently hypothetical in nature, and information presented in this submission

indicates that the safety profile of dasiglucagon is consistent with the well-characterized safety profile of native glucagon. Additionally, the information presented in this application is supportive of the proposed indication, (b) (4) (b) (4). Standard surveillance appears sufficient to monitor for significant events in the postmarket setting.

In conclusion, the analysis presented in this review characterizes the safety profile of 0.6 mg dasiglucagon when intended for single-dose administration for the treatment of severe hypoglycemia. Adverse reactions identified can be adequately addressed with labeling, and outstanding uncertainties can be addressed by standard postmarketing surveillance.

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting conducted for this application. Although dasiglucagon is an NME, the efficacy endpoint was straightforward and well accepted, and there were no controversial efficacy or safety issues that would benefit from an advisory committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling negotiations with the applicant are ongoing at the time of this review. Negotiations that have occurred thus far are summarized below.

Indications and Usage (Section 1)

1. The Applicant has proposed dasiglucagon to be indicated for the treatment of severe hypoglycemia in adult and pediatric patients aged 6 years and above. This is supported by the efficacy demonstrated in adult and pediatric subjects as reviewed in 6.1, 6.2, and 6.3.

Dosage and Administration (Section 2)

The proposed dose in adults and pediatric patients aged 6 years and above is 0.6 mg administered subcutaneously in the abdomen, buttocks, thigh, or deltoid. This is supported by the clinical development program and proposed labeling appears generally adequate. The following additional information has been added to Section 2.1 during negotiations: If there has

been no response after 15 minutes, an additional dose of ZEGALOGUE from a new device may be administered while waiting for emergency assistance.

Contraindications (Section 4)

The Applicant proposed that dasiglucagon should be contraindicated in patients with insulinoma or pheochromocytoma, or in patients with known hypersensitivity to dasiglucagon or any of the excipients. As hypersensitivity reactions were not observed in the clinical development program (see 8.5.2), it was recommended that this contraindication be removed as not to restrict access to this potentially life-saving therapeutic. A Warning and Precaution for hypersensitivity and allergic reactions was retained.

Warnings and Precautions (Section 5)

The Applicant proposed the following Warnings and Precautions:

- Substantial Increase in Blood Pressure in Patients with Pheochromocytoma
- Hypoglycemia in Patients with Insulinoma
- Hypersensitivity and Allergic Reactions
- Lack of Efficacy in Patients with Decreased Hepatic Glycogen

The proposed Warnings and Precautions are in accordance with other approved glucagon products and appear appropriate.

Adverse Reactions (Section 6)

The Applicant proposed to present common adverse reactions as those occurring in >5% of subjects and more frequently than with placebo based on data from the placebo-controlled pool and pediatric trial 17086. To provide additional information regarding potential adverse reactions, this was updated to a threshold of ≥2%. Additionally, the following statement was added to the labeling to provide specific information on the hemodynamic events observed in the clinical development program for dasiglucagon: *Other adverse reactions in patients treated with dasiglucagon within 12 hours of treatment include: hypertension, hypotension, bradycardia, presyncope, palpitations, and orthostatic intolerance*.

Pediatric Use (Section 8.4)

This section (as well as Sections 6.1, 12.2, and 14) was updated to reflect the actual age of pediatric patients enrolled in trial 17086 (i.e. 7-17 years) versus the enrollment criteria for this trial (i.e. 6-17 years).

Geriatric Use (Section 8.5)

This section has been updated to state that clinical studies included too few patients 65 years of age and older to determine whether they respond differently from younger adult patients.

Clinical Studies (Section 14)

The Applicant proposed to present data from placebo-controlled adult trials and pediatric trial 17086 in text, table, and figure formats. The Applicant's proposed approach to presenting efficacy data is generally reasonable, with labeling negotiations thus far consisting of adding glucose recovery data for patients in the placebo group to the proposed figures and the addition of additional details regarding the trial design and baseline characteristics of study participants.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was deemed necessary for dasiglucagon.

12. Postmarketing Requirements and Commitments

There were no clinical issues identified that should be addressed by a post-marketing requirement (PMR) or commitment (PMC) aside from the pediatric study required under the Pediatric Research Equity Act (PREA). For further information see the action letter for this application.

13. Appendices

13.1. References

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13.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): 14013, 15007, 15126, 16051, 16098, 16136, 16137, 17084, 17086, 17144, 17145

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 133		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3 Supplementary Data

Supplementary Table 1. Summary of Withdrawals in Dasiglucagon-Exposed Subjects – Broad Pool

Trial -Subject ID	PT for AE leading to withdrawal	Summary Narrative
16136 - (b) (6)	Vomiting	A female subject aged 27 years developed mild nausea and vomiting 1.5 hours after dosing with 0.6 mg dasiglucagon on the first dosing day in immunogenicity trial 16136. The events were treated with 10 mg metoclopramide orally. The vomiting resolved after about 10 minutes and the nausea resolved after 10.5 hours. Two hours after dosing the subject additionally developed a mild headache, lasting for 10 hours. The subject was withdrawn from additional dosing. The subject completed one of three post-dose immunogenicity assessments (follow up visit #1) but did not complete the final safety assessment.
16136 - (b) (6)	QT Prolongation	This subject was withdrawn from additional dosing by the investigator after the first dosing day in immunogenicity trial 16136 but completed the safety follow-up visit. See 8.4.9 for additional information regarding this event.
16136 - (b) (6)	Headache	A female subject aged 60 years experienced a moderate event of headache at an unknown time after the first dosing day in immunogenicity trial 16136, which resolved 3 days later. The subject was withdrawn from additional dosing but completed the safety follow-up visit.
17084 - (b) (6)	Vomiting	A female subject aged 35 years developed moderate nausea 1.7 hours after 0.6 mg dasiglucagon administration on the first dosing day in bridging trial 17084, which was treated with metoclopramide and lasted approximately 30 minutes. Approximately 4 hours after dosing, the subject experienced mild vomiting, which lasted 1 hour and 20 minutes. More than 2 hours after the mild vomiting resolved, the subject developed moderate vomiting. The vomiting continued intermittently for 15.5 hours. The subject withdrew from additional dosing but attended the follow-up safety visit.
17084 - (b) (6)	Vomiting	A female subject aged 31 years experienced vomiting leading to withdrawal after the first dosing day with 0.6 mg dasiglucagon in bridging study 17084. Between 2 and 3 hours after dosing on the first dosing day, the subject experienced mild events of nausea, vomiting, diarrhea, and headache. The first three events resolved within 3.5 hours, while the headache lasted for more than 7 hours. Approximately 6.5 hours after drug administration the subject experienced a mild event of nausea and a single episode of vomiting. The nausea lasted until the next day. The next day the subject experienced a further episode of mild vomiting. The subject withdrew from additional dosing but attended the follow-up safety visit.

15126 - (b) (6)	Vomiting	A subject experienced AEs on the first dosing day in the crossover, dose-finding trial 15126 after administration of 0.6 mg dasiglucagon. A mild AE of headache occurred 1 hour after investigational product administration and lasted 2 hours. Moderate AEs of nausea and vomiting occurred after approximately 1.5 and 2 hours and lasted 5 and 4.5 hours, respectively. Another mild AE of headache occurred after 6 hours and 20 minutes and lasted 4 hours and 15 minutes. The subject withdrew from additional dosing but attended the follow-up safety visit.

Source: Compiled by Reviewer with information from ISS Appendix 9 and IRs dated August 17 and 31, 2020

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