CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214231Orig1s000

<u>SUMMARY REVIEW</u>

Summary Basis for Regulatory Action

Date	electronic stamp
NDA #	NDA 214231
Applicant	Zealand Pharma
Date of Submission	March 27, 2020
PDUFA Goal Date	March 27, 2021
Proprietary Name	ZEGALOGUE
Established or Proper Name	Dasiglucagon injection
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	Treatment of severe hypoglycemia in patients with diabetes ages six years and above
Applicant Proposed Dosing Regimen(s)	0.6 mg/0.6 mL
Recommendation on Regulatory Action	**Approval**
Recommended Indication(s)/Population(s)	Treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages six years and above
Recommended Dosing Regimen(s)	0.6 mg/0.6 mL

Office of New Drugs (OND) Action Package Material Reviewed/Consulted:	**Names of discipline reviewers; Dates of review**
Clinical Reviewer	Kristen Pluchino 3/10/21
Biostatistics	Yoonhee Kim 11/09/20
Center for Device and Radiologic Health	David Wolloscheck/Rumi Young 2/2/21
Pharmacology Toxicology	Patricia Brundage 12/18/20; 11/23/20
Office of Pharmaceutical Quality	Technical Lead: Muthukumar Ramaswamy 11/27/20, 2/5/21, and 2/23/21
Clinical Pharmacology and Pharmacometrics	SJ Lau/Manoj Khurana 12/10/21 and 3/4/21
Interdisciplinary Review Team for Cardiac Safety Studies	Girish Bende 2/13/20 and 7/28/20
Clinical Cardiology, Division of Cardiology and Nephrology	Preston Dunnmon 10/29/20
Office of Biotechnology Products-immunogenicity review	Faruk Sheikh 12/04/20
Office of Scientific Investigations	Cynthia Kleppinger 11/23/20
Division of Medication Error Prevention and Analysis-human factors and labeling review	Colleen Little/Lolita White 2/24/21; 2/9/21; 1/25/21; 12/11/20
Division of Risk Management	Mei-Yean Chen 1/11/21
Division of Medication Error Prevention and Analysis-proprietary name review	Ariane Conrad 4/29/20
Division of Pediatrics and Maternal Health	Christos Mastroyannis 11/16/20
Office of Prescription Drug Promotion	Samantha Bryant 2/24/21; 1/15/21
Division of Medical Policy Programs-patient labeling review	Sharon Williams 1/21/21

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Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Severe hypoglycemia is a serious medical condition that is most commonly the result of exogenous insulin therapy in patients with diabetes mellitus. Severe hypoglycemia is defined as hypoglycemia requiring assistance from another person because the affected individual is confused or unconscious secondary to neuroglycopenia and cannot take carbohydrates orally. Seizures and coma are not uncommon consequences of severe hypoglycemia. Left untreated, severe hypoglycemia may result in permanent neurologic sequelae or death. Severe hypoglycemia is more common in patients with type 1 diabetes mellitus (T1DM) than type 2 diabetes mellitus (T2DM), but T2DM patients treated with insulin or sulfonylureas are at greater risk than those treated with other antidiabetic agents.

Treatment options include intravenous dextrose, but this option requires administration by a healthcare professional in a hospital or emergency medical setting. Injectable glucagon products are the mainstay of ambulatory treatment of severe hypoglycemia. For many years only glucagon products that required reconstitution by the caregiver before injection were available (although Gvoke which does not require reconstitution and Baqsimi, which is administered intranasally, were both very recently approved for the treatment of severe hypoglycemia). Dasiglucagon is a glucagon analog that acts at the glucagon receptor to increase plasma glucose, but unlike native glucagon, dasiglucagon is stable in aqueous solution, and through its development, the sponsor aimed to provide a ready-to-use treatment option. It is important to note that for these products the goal is not to treat symptoms; symptomatic hypoglycemia without neurologic compromise should be treated with oral intake of a fast-acting source of carbohydrate such as fruit juice. Instead, the objective is to increase blood glucose concentrations rapidly, resolve neuroglycopenia, and prevent the serious complications of neurologic damage and death.

Three adequate and well-controlled clinical studies have established the effectiveness of a single injection of dasiglucagon 0.6 mg for the treatment of severe hypoglycemia in patients with diabetes age 6 and above. Time to plasma glucose recovery, defined as the initial increase in plasma glucose of ≥ 20 mg/dL from baseline during a hypoglycemic clamp procedure, was selected as the primary endpoint for these studies. The endpoint is acceptable because it not only assesses the ability of dasiglucagon to increase blood glucose, but also considers the rapidity of the response. Dasiglucagon demonstrated robust superiority to placebo with a median time to glucose recovery of 10 minutes across the three studies (decreased vs. placebo by two-thirds), and importantly, the drug led to recovery in all subjects, i.e., there were no non-responders. In addition, the increase in plasma glucose achieved by dasiglucagon was numerically similar to the plasma glucose increase observed with the native glucagon active comparator treatment (included in two of the three studies).

The efficacy demonstrated in the clamp studies is expected to result in benefits that include recovery from neuroglycopenia and prevention of complications of neurologic sequelae or death, although these were not directly assessed in the development program. A development program

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that required 'real-world' testing of dasiglucagon vs. an approved glucagon product for assessment of benefit on these clinical outcomes would be infeasible and unnecessary.

Other benefits of dasiglucagon include the 'ready-to-use' product presentations (both a prefilled syringe and an autoinjector) and the 'dual-storage' conditions under which the product is stable. The available product presentations may allow easier administration compared to the older native glucagon products, because no reconstitution is needed. Furthermore, the likelihood of medication errors related to the reconstitution step may be reduced. Dasiglucagon can be stored at room temperature for up to 12 consecutive months providing a portable treatment option for patients.

Findings from the safety program suggest that dasiglucagon does not cause serious harms, but rather that adverse reactions are largely limited to non-serious tolerability issues (headache, nausea, vomiting, and diarrhea). About half of patients will likely experience mild to moderate tolerability issues, but I expect these symptoms will be well-accepted by patients considering the life-saving potential of dasiglucagon use. As glucagon receptor agonism causes inotropic and chronotropic effects, hemodynamic events observed in the clinical studies are almost certainly drug-related but were self-limited and occurred with low frequency. Inclusion of tolerability and hemodynamic information in the Adverse Reactions section of the Prescribing Information is adequate.

The observed safety profile is not unexpected given what is known about native glucagon, and inclusion of the native glucagon active comparator in two of the studies allowed for a demonstration of a similar safety profile between dasiglucagon and native glucagon. Based on a shared mechanism of action with native glucagon, I recommend that dasiglucagon labeling contains the Contraindications and Warnings and Precautions currently included in labeling for native glucagon products (with minor exceptions), but these risks are anticipated to be applicable to very few patients (e.g., risk of hypoglycemia in patients with insulinoma), and importantly, there were no new safety issues identified in this application that warrant Contraindications or Warnings and Precautions beyond what are already contained in glucagon product labels. No REMS or postmarket safety studies are necessary for this product.

As dasiglucagon is a peptide product with seven amino acid modifications from native glucagon, immunogenicity issues require consideration. Although limited, the provided anti-drug antibody (ADA) data suggest that the incidence of antibody formation was low and had no observable clinical consequence. A remaining uncertainty is the immunogenicity risk of repeated dasiglucagon administration, as this was not evaluated in the development program; this potential risk can be monitored with standard pharmacovigilance.

Overall, a highly favorable benefit-risk profile has been demonstrated for dasiglucagon for the proposed indication and under the labeled conditions of use. Dasiglucagon showed clinically meaningful and robust superiority versus placebo in the time to glucose recovery. Rapid recovery of plasma glucose and correction of neuroglycopenia is anticipated to prevent serious complications of severe hypoglycemia. The potentially life-saving benefit conferred by dasiglucagon far outweighs the identified safety issues.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Severe hypoglycemia, defined as hypoglycemia requiring assistance of another person because of neuroglycopenia, is a serious medical condition that occurs in patients with diabetes mellitus that is often a result of insulin treatment. • It occurs in patients with both T1DM and T2DM, although it is more common in patients with T1DM: approximately 22% to 46% of patients with T1DM annually, and 7% to 25% of patients with T2DM who are treated with insulin. • Severe hypoglycemia can lead to seizures, coma, or death.	The likelihood of a serious complication from a severe hypoglycemic episode is expected to increase with the duration and severity of neuroglycopenia. Therefore, the time to resolution of the event is clinically important. 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 needed.
Current Treatment Options	• Current approaches to the treatment of severe hypoglycemia aim to increase blood glucose quickly either by providing exogenous glucose or by increasing endogenous glucose release through breakdown of glycogen in the liver. Glucagon agonists have this latter mechanism of action. • Intravenous dextrose infusion can be administered in a healthcare setting only • Injectable glucagon can be administered in an outpatient setting, but many available formulations require reconstitution. • Intranasal glucagon was recently approved for the treatment of severe hypoglycemia.	Injectable glucagon, which often requires reconstitution prior to use, and intranasal glucagon, are the only treatment options available outside of a healthcare setting. Dasiglucagon would be the first glucagon analog approved in the U.S.
Benefit	• In two adult phase 3 studies (16137 and 17145) and one pediatric phase 3 study (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 studies, the median time to glucose recovery was 10 minutes in the dasiglucagon groups, vs. 35 to 40 minutes in the placebo groups. In the pediatric study, 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 studies 16137 and 17145 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. The experience of this patient is likely attributable to laboratory error. In	Dasiglucagon 0.6 mg was effective in increasing blood glucose levels in a clinically meaningful timeframe without treatment failures. In the postmarket setting, the clinical effect is expected to result in benefits including recovery from neuroglycopenia and prevention of complications of neurologic sequelae or death. The selected dose is appropriate for all indicated patients (age 6 and above) including those with high body mass index. The formulation offers a potentially easier to administer rescue product for emergency use and may reduce the likelihood of certain medication errors related to the reconstitution step, although this benefit was not directly assessed in the clinical

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	contrast, ~72% of subjects in the placebo groups of the adult studies recovered within 45 minutes, and two (4%) received rescue IV glucose. Data from pediatric study 17086 were similar in that all pediatric subjects treated with dasiglucagon achieved glucose recovery within 45 minutes as compared to 64% of subjects achieving recovery in the placebo group. • Efficacy was not meaningfully affected by any demographic or disease characteristics, for example age, or body mass index. • Dasiglucagon will be available in prefilled syringe/autoinjector devices with no requirement for reconstitution of drug product. • In order to support dual storage conditions for dasiglucagon either under refrigeration (2°C to 8°C), or at room temperature (25°C), the Applicant conducted a phase 3 bridging study in subjects with T1DM to evaluate a batch of dasiglucagon stored under the proposed dual storage condition as compared to a batch stored solely under refrigeration. Compared to the drug content stored under refrigeration (0.6 mg), the batch stored under dual storage conditions had a drug content of $^{(b)(4)}$ mg of dasiglucagon. The glucose response for the dual storage batch as compared to the refrigerated batch showed a difference in mean time to plasma glucose recovery of 0.40 minutes (95% CI: -0.08 to 0.88), equivalent to a 24 second delay in plasma glucose recovery. • Efficacy in children under age 6 has not been established.	development program. Dasiglucagon can be stored at room temperature for up to 12 months providing convenience to patients. Benefits are expected to apply to T2DM patients.
Risk and Risk Management	• The size of the safety database was adequate for a single-use emergency product, but the development program was not designed to assess rare safety events or events of long latency. • The most common AEs (occurring in ≥2%) were nausea, vomiting, headache, diarrhea (adults only), and injection site pain. In the pooled adult phase 3 studies, 56.5% and 24.6% of subjects in the dasiglucagon group had nausea and vomiting, respectively; whereas 4.1% and 1.8% of subjects in the placebo group had nausea and vomiting, respectively. Subjects in the GlucaGen arm in study 16137 also had nausea (53%) and vomiting (21%) as AEs. Safety findings were generally consistent with injectable glucagon products, with the exception of a higher incidence of diarrhea among adult subjects.	In the postmarket setting, it is expected that about half of dasiglucagon treated patients will have some gastrointestinal (GI) tolerability issues. The expected frequency of GI tolerability issues, however, should not exceed what patients have experienced with native glucagon. The frequency of adverse events in the hemodynamic grouping was low and in accordance with published literature and labeling for approved native glucagon products. Hemodynamic events, such as GI events, are expected to be mild and self-

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- The severity of these common AEs was generally mild and self-limiting. No serious long-term sequelae were identified, although as noted above the development program did not thoroughly address long-term safety. - Hemodynamic events were observed below the threshold for common adverse events in the placebo-controlled pool and at an incidence of 2.3% in the broad pool analysis. The incidence of hemodynamic events was lower with dasiglucagon than was observed with GlucaGen (5.9%). - No subjects developed ADAs in immunogenicity study 16136 and therefore the clinical consequence of ADA formation is unknown at this time. - Less than 1% (4 of 498 subjects) of dasiglucagon-exposed subjects developed ADAs in the clinical development program.	limiting. These risks are expected to apply to the T2DM population without any significant differences in frequency or severity. The immunogenic potential of dasiglucagon appears low; however, the data are limited. Loss of efficacy of dasiglucagon caused by ADAs and increased risk of hypoglycemia in the postmarket setting due to neutralizing antibodies that are cross reactive to native glucagon are theoretical concerns at this time. In the postmarket setting, patients may use dasiglucagon more than once per year. The long-term immunogenicity risk of repeated dosing over years is unknown. Patients with T2DM generally have a lower risk of immunogenicity than patients with T1DM. The safety of dasiglucagon can be adequately communicated in labeling and monitored via standard postmarket surveillance.

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2.   Background

<u>Analysis of Condition</u>

Diabetes mellitus is a serious chronic medical condition characterized by hyperglycemia and includes two main types of diabetes; T1DM and T2DM. Patients with T1DM have impaired insulin production and secretion, and require insulin treatment for survival, although many patients with T2DM also may require insulin to achieve glycemic control. Insulin therapy and some other antihyperglycemic drugs, most notably sulfonylureas, are associated with the risk of severe hypoglycemia. Severe hypoglycemia is characterized by neurological impairment due to significant neuroglycopenia that requires assistance from another person for recovery and can result in loss of consciousness, seizures, or death. Severe hypoglycemia is more common in patients with T1DM, occurring in approximately 22% to 46% of patients with T1DM annually and 7% to 25% of patients with T2DM who are treated with insulin.

<u>Current Treatment Options</u>

Two general treatment modalities for severe hypoglycemia are currently available: intravenous dextrose and glucagon. Intravenous dextrose requires administration by a healthcare professional in a hospital or emergency medical setting, whereas glucagon is administered via injection or intranasally and can be given by a caregiver outside of a hospital setting. Glucagon increases blood glucose by stimulating hepatic glycogenolysis and gluconeogenesis. Many of the currently approved glucagon products require reconstitution prior to administration, although a recently approved glucagon product, Gvoke, is available in an injectable formulation that does not require reconstitution, and Baqsimi is available for intranasal administration. There are no glucagon analogs currently approved for the treatment of severe hypoglycemia or any other indication. See Table 1.

Table 1: US-Approved Glucagon Products for Treatment of Severe Hypoglycemia

Product	Indication	Route of Administration
Glucagon powder (Baqsimi) NDA 210134	Patients with diabetes ages 4 and up	Intranasal
Glucagon injection (Gvoke) NDA 212097 Xeris Pharmaceuticals	Patients with diabetes ages 2 and up	Subcutaneous injection
Glucagon for injection (GlucaGen) NDA 020918 Novo Nordisk	No age limit	Subcutaneous/intravenous/intramuscular injection Reconstitute before administration
Glucagon for injection NDA 201849 Fresenius Kabi	No age limit	Same as GlucaGen
Glucagon for injection NDA 020928 Eli Lilly	No age limit	Same as GlucaGen

Product Information and Regulatory History

Dasiglucagon is a glucagon analog that consists of 29 amino acids similar to native glucagon; however, it contains 7 substituted amino acids with the goal of improving physical and chemical stability in aqueous solution compared to native glucagon. Zealand Pharma, hereafter referred to as the Applicant, has submitted a new drug application (NDA) under the 505(b)(1) regulatory pathway, seeking approval for dasiglucagon, for the treatment of severe hypoglycemia. The product class is 'glucagon receptor agonist.'

The indication sought for dasiglucagon is: *for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above.* The Applicant is proposing to market only one dose for dasiglucagon of 0.6 mg. The drug-device combination product will be available for administration in two presentations; a prefilled syringe and an autoinjector for subcutaneous injection.

In support of this NDA, the Applicant conducted a total of nine studies, which included eight studies in adults and one study conducted in pediatric subjects. The primary efficacy evaluation was derived from two placebo-controlled studies in adults with T1DM (16137, 17145) and one placebo-controlled study in pediatric patients with T1DM (17086). The Applicant conducted additional studies to evaluate the potential effects of dasiglucagon on the QTc interval to support cardiac safety, a dedicated immunogenicity study to evaluate potential effects of ADAs on safety and efficacy, and a bridging study to support the proposed 'dual-storage conditions' for dasiglucagon (described below).

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommended approval of this NDA for the proposed indication. Dr. Muthukumar Ramaswamy was the lead OPQ reviewer. The Center for Radiologic Health (CDRH) reviewed the device constituent of the drug product and did not find any deficiencies. The Division of Medication Error and Prevention (DMEPA) conducted a human factors validation review which was determined to be acceptable. I concur with the review recommendations.

The drug substance of dasiglucagon is a 29 amino acid peptide, with a free amino group at the N-terminus and a carboxylic acid at the C-terminus. The drug substance is isolated as a hydrochloride salt. Dasiglucagon is an amorphous powder and is freely soluble in water. It has a molecular weight of 3381.6 g/mol (average mass). The empirical formula is $C_{152}H_{222}N_{38}O_{50}$. The chemical structure of dasiglucagon is shown in Figure 1.

Figure 1: Chemical Structure of Dasiglucagon
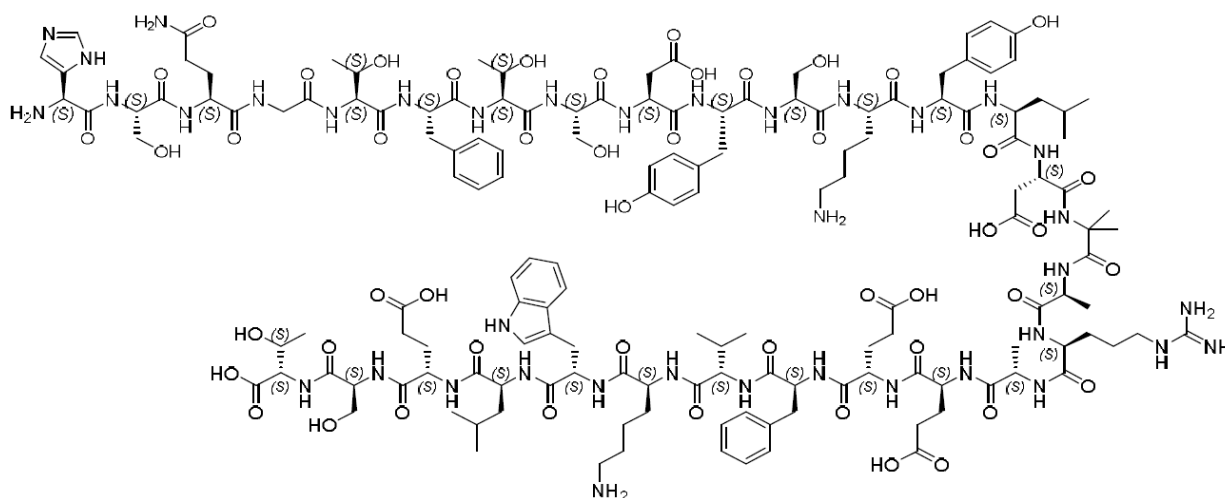
Source: Figure 1 from Applicant's 2.3S Drug Substance

The drug substance is manufactured ⬛ (b) (4) The Applicant has referenced ⬛ (b) (4) Type II DMF ⬛ (b) (4) for all chemistry, manufacturing, and control (CMC) information related to the drug substance. Dr. Joseph Leginus reviewed the CMC information for the drug substance in the NDA submission as well in the DMF ⬛ (b) (4) His review covered the drug substance manufacturing process description, the proposed starting material specifications, control strategy for impurities, characterization data for drug substance and its impurities, reference standard information, test method descriptions and methods validation, drug substance specifications, and stability data provided in the DMF. Based on the data submitted, Dr. Leginus' review concluded that the drug substance information in the DMF and in the NDA is adequate to control the quality of the drug substance used in the drug product manufacturing.

The proposed drug product, dasiglucagon injection, 0.6 mg/0.6 mL, is a clear, colorless, sterile, aqueous solution, which is packaged in a single dose pre-filled syringe or an autoinjector. Dasiglucagon is provided as dasiglucagon hydrochloride and is solubilized in ⬛ (b) (4) tromethamine (tris buffer), sodium chloride, and water for injection, and each mL

contains 1.0 mg of dasiglucagon. The proposed commercial product has the same composition as the one used in the clinical development program. The drug product information was reviewed by Dr. Ramaswamy and was determined to be adequate to support the quality of the proposed product.

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 commitment, were reviewed and determined to be acceptable by OPQ.

The Applicant conducted testing to evaluate long-term storage conditions and provided 36 months of long-term stability data (5°C/60% relative humidity (RH)), 12 months of long-term stability data (25°C/60% RH), and 3 months of stability data under accelerated storage conditions (40°C/65% RH). The product is light sensitive, and storage of the product in the protective case is recommended to prevent exposure to light during shelf-life. The product should not be frozen. Based in part on the provided stability data, Dr. Ramaswamy recommended an expiration period of 36 months when stored at 2-8°C, during which time the drug product can be stored at 25°C for 12 months in the protective case (so-called 'dual-storage conditions'). Other supportive data that the Applicant provided to support the dual-storage condition included a clinical bridging study, discussed in the Efficacy section of this memo. Additionally, the Applicant developed a clinical pharmacology model of dasiglucagon dose and time to glucose recovery to support the proposed shelf-life specifications (b)(4) (b) (4) The clinical pharmacology modeling data are discussed in Section 5.

The process reviewer concluded that the proposed drug product manufacturing process controls are adequate to support the NDA. The composition of the drug product, the drug product manufacturing process, and the packaging system used to manufacture the drug product used in phase 3 clinical and registration stability studies are the same as that proposed for commercial use.

A 704a facilities "desk" review was conducted (rather than an inspection) because of the ongoing COVID-19 pandemic. The overall manufacturing inspection recommendation from the Office of Process Manufacturing Assessment (OPMA) for this NDA is for approval. Post-approval inspections are recommended for (b) (4) Rechon Life Science, which manufactures the finished product (drug-device combination product). For details please refer to the CDRH and OPQ reviews.

The NDA was granted categorical exclusion from submitting environmental assessment. The estimated concentration of the drug substance at the point of entry into the environment would be below 0.1 part per billion and is not expected to significantly affect the quality of the human environment.

Device

There were no changes made to the to-be-marketed devices from what was used in the clinical studies. Dasiglucagon is designed to be delivered via a prefilled syringe or an autoinjector. The autoinjector is loaded with the same PFS, (b) (4) The components, which are identical for the prefilled syringe and autoinjector, are depicted in Figure 2.

Figure 2: Prefilled Syringe Components

(b) (4)

Source: CDRH review

The prefilled syringe consists of a rigid needle shield, ⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) the drug product, a 1mL glass syringe with staked needle, and the plunger rod with stopper. See Figure 3.

Figure 3: Pre-Filled Syringe Components

(b) (4)

Source: CDRH review

The autoinjector has the same primary container closure for the drug product solution as the prefilled syringe. The components include a yellow needle guard, cap, the prefilled syringe, ⬛⬛⬛⬛⬛⬛ (b) (4) ⬛⬛⬛⬛⬛⬛ . See Figure 4.

Figure 4: Dasiglucagon Autoinjector Components

(b) (4)

Source: CDRH review

The Applicant conducted human factors validation studies in order to support that intended users could understand product instructions and appropriately administer the dose using both device presentations. The validation study results were reviewed by DMEPA, and their review identified use errors with some critical tasks. For the autoinjector presentation, there were errors associated with 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, one use error related to failure to remove the cap, and five use errors related to removal of the autoinjector prior to full dose delivery. For the prefilled syringe presentation, there were three use errors in which participants dropped the device while opening the protective case, and one use error where the user did not expose bare skin and injected through clothing. 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. DMEPA also found the final version of the Instructions For Use to be acceptable.

In addition, DMEPA identified concerns regarding   (b) (4)
                                                              and recommended
that the Applicant remove this feature from the submission. The Applicant agreed.   (b) (4)
                                                              DMEPA concluded that the
conducted verification testing was still applicable to the prefilled syringe   (b) (4)

4. Nonclinical Pharmacology/Toxicology

The nonclinical program for dasiglucagon was designed to support both acute and chronic indications (dasiglucagon is also being evaluated for use in a dual-hormone artificial pancreas device). For this NDA, only a single-dose rescue indication is proposed by the Applicant.

The review of the submitted nonclinical data was completed by Dr. Patricia Brundage. Based on the nonclinical data reviewed, Dr. Brundage recommends approval. Findings from Dr. Brundage's review are summarized here. I concur with the review recommendations.

In summary, dasiglucagon caused an increase in heart rate and gastrointestinal effects (i.e., diarrhea and vomiting) in the dog after a single dose at clinically relevant exposures. These effects are due to G-protein coupled glucagon receptor (GCGR) activity and are expected to occur with clinical use of dasiglucagon.

The Applicant conducted a range of both in vitro and in vivo studies to evaluate the pharmacologic effects of dasiglucagon. The in vitro potency of dasiglucagon was comparable to native glucagon at the GCGR in humans, as well as in nonclinical species. There did not appear to be any off-target activity, given the absence of activity at any of the 239 G-protein coupled receptors that were evaluated. The pharmacodynamic effects of dasiglucagon were evaluated following subcutaneous (sc) administration in rats, dogs, and rabbits. Single sc doses of dasiglucagon caused increased blood glucose levels, similar to glucagon, although the effects of dasiglucagon were generally more prolonged when compared to glucagon.

The Applicant conducted safety pharmacology studies to assess the effects of single subcutaneous doses of dasiglucagon on cardiovascular, neurological, and respiratory function. Although dasiglucagon caused tachycardia in dogs at clinically relevant exposures (1X clinical exposure; Cmax basis), which was also observed with repeated dosing, this finding is attributable to the established positive inotropic effect of GCGR agonism. In vitro evaluation of eight human cardiac ion channels (including hERG) indicates dasiglucagon has a low potential for QT prolongation in vivo. No other significant clinical safety concerns were identified.

Absorption, distribution, metabolism, and excretion studies showed that dasiglucagon (as well as native glucagon) has a relatively short half-life, high clearance, and low volume of distribution across species following single sc dosing. Clearance of dasiglucagon appears to be through proteolytic degradation in the liver, kidney, and blood, similar to native glucagon.

The repeat dose toxicity of dasiglucagon was evaluated in Crl:CD1(ICR) mice for up to 13 weeks, Wistar rats for up to 26 weeks, and beagle dogs for up to 39 weeks. Dasiglucagon caused treatment-related effects in the heart, kidney, and liver, attributable to GCGR agonism. In the dog, gastrointestinal effects (loose feces) were noted, and in rats, transient freezing absences, in which the animals went into a sleep-like state and remained either motionless or exhibited a slow movement towards a resting place, were observed. The freezing absences were only observed in rats with repeat dosing and appeared to be related to the peak plasma exposures of dasiglucagon. In a follow-up study to further evaluate the freezing episodes, native glucagon (5 mg/kg) was also shown to elicit freezing absences, indicating that the freezing absences are likely related to GCGR activity, although a definite mechanism was not established. Similar findings have not been observed clinically, and the finding is of limited relevance for the proposed single-dosing indication.

Anti-drug antibodies (ADAs) were detected in mice, rats, and dogs exposed to dasiglucagon, with cross reactivity to endogenous glucagon observed in ADA-positive rats and dogs. However, ADAs had no effect on dasiglucagon exposure or pharmacodynamic activity in rats, dogs, or mice dosed for 13 weeks. Increased drug exposure at the end of dosing was observed only in rats that had been dosed

chronically. The nonclinical reviewer noted that this finding is suggestive of sustaining antibodies. The relevance to humans is unknown.

In nonclinical fertility and embryonic and fetal development studies, there were no effects on reproductive performance or fertility indices in male and female rats at exposures up to 364 to 625 times clinical exposure. There was also no teratogenicity 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). When given to pregnant rabbits at mid and high doses (20X clinical exposure), dasiglucagon caused fetal external, visceral, and skeletal malformations (cleft palate, malrotated hindlimbs, hyperflexed forepaws, acephalostomia, anencephaly, microglossia and/or hydrocephaly), which were not clearly related to maternal toxicity. At the high dose (100X clinical exposure), a dose at which maternal toxicity was induced in terms of decreased body weight gain, lower fetal body weights and delayed bone ossification were also observed. In rats, the mid- and high-doses (475X clinical exposure) were associated with reductions in maternal body weight gain that were also associated with reductions in fetal body weight and delayed bone ossification; however, fetal survival was not affected and there were no fetal malformations. Based on the standard battery of two in vitro and one in vivo GLP genetic toxicology studies, dasiglucagon was not mutagenic or clastogenic. Carcinogenicity studies were not required to support the proposed indication.

To support the proposed long-term storage conditions, a 28-day toxicity study in rats, a single-dose pharmacodynamic study, and an in vitro study were conducted to demonstrate that the toxicity profile of a degraded dasiglucagon formulation was comparable to that of the non-degraded formulation. These studies found no notable differences in GCGR activity between batches, indicating that the degradation products/impurities should not significantly impact the toxicologic and pharmacodynamic effects of the drug product.

5.   Clinical Pharmacology

Based on the reviewed clinical pharmacology data Dr. Lau and Dr. Khurana from the Office of Clinical Pharmacology recommend approval of dasiglucagon for the proposed indication. Because the to-be-marketed formulation of dasiglucagon was used in the primary efficacy studies, no Office of Study Integrity and Surveillance (OSIS) inspections were requested or performed for this application. Dr. Lau stated that overall, the bioanalytical method validation of dasiglucagon PK was acceptable.

Clinical pharmacology data for dasiglucagon were obtained from three phase 1 studies in healthy volunteers (one of which was an IV/QTc study), one phase 1 study in subjects with T1DM, a phase 2 dose selection study, two phase 3 placebo-controlled studies in adults and one phase 3 placebo-controlled study in pediatrics. The phase 1 studies (except for the IV/QTc study) used a different formulation from the to-be-marketed formulation, and therefore, were not used to establish the PK/PD properties of dasiglucagon for labeling. For a complete listing of clinical studies conducted by the Applicant see Appendix 1.

The key PK/PD parameters for dasiglucagon are summarized in Table 2. Dasiglucagon may be administered into the abdomen, buttock, thigh, or upper arm. No dose adjustment is necessary for age, gender, body weight, race, organ impairments, injection site, or drug interaction.

Table 2: Key Pharmacological and Pharmacokinetic Properties of Dasiglucagon

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

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

[1] Study 17144
[2] Studies 15126, 16137, 17145, 16136, and 17084 [adult]; Study 17086 [pediatric]
[3] Studies 15126, 16137, 17145, 16136, and 17084 [adult]; Study 17086 [pediatric]
[4] Studies 15126 and 17084
[5] Studies 15126 and 17084[adult]; Study 17086 [pediatric]
[6] Study 15126
[7] Study 13-149
* The Applicant reported 16 proteolytic metabolites of dasiglucagon. Within vivo rats and dogs studies, the data indicate that dasiglucagon is mainly cleared through the blood, liver, and kidney via proteolytic degradation pathways like that of glucagon.
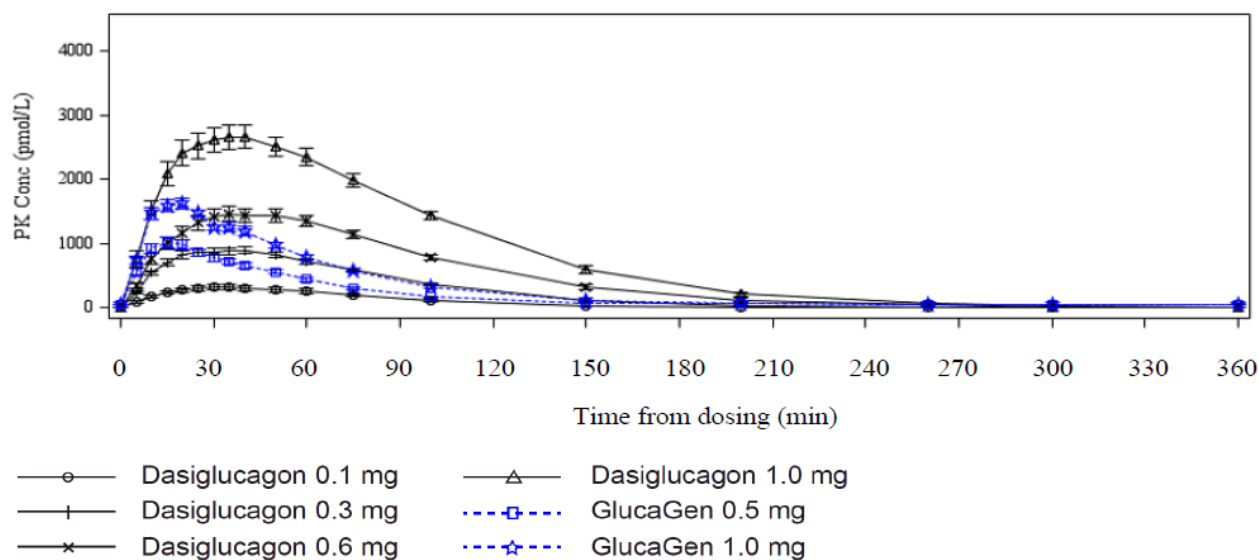*Source: Table 1 from Clinical Pharmacology review*

Dose Selection

The Applicant selected a 0.6 mg dose to investigate in phase 3 studies. This selection was based on the phase 2 dose finding study 15126. Study 15126 was a randomized, double-blind study of a single dose of sc dasiglucagon administered to T1DM subjects with insulin-induced hypoglycemia, in which

various doses of dasiglucagon (0.1, 0.3, 0.6, and 1.0 mg sc) were compared to a single dose of GlucaGen (0.5 and 1.0 mg sc).

In study 15126, the PK profile of dasiglucagon demonstrated an increase in plasma dasiglucagon concentrations following sc administration, with a C_{max} of 1570 pmol/L (mean) and t_{max} of 35 minutes (median) for the 0.6 mg dose of dasiglucagon. The plasma concentrations thereafter decreased with a half-life of approximately 0.5 hours. See Figure 5.

Figure 5: Mean Dasiglucagon and GlucaGen plasma concentration profiles by dose - Study 15126

Data represent the mean values plus/minus the standard error of the mean.
Cross-reference: Trial 15126, Figure 14.2.2.3.2

Source: Figure 3-1 from Applicant's Summary of Clinical Pharmacology studies

Table 3 shows the summary statistics for plasma glucose parameters from study 15126. Although the 0.6 mg dose has a lower AUE_{0-30} min compared to the 1.0 mg dose, the more clinically relevant parameters are the time to plasma glucose increasing by at least 20 mg/dL and the reaching equal to or above 70 mg/dL. For these parameters there is no apparent difference between 0.6 mg and 1.0 mg. In addition, it is evident from Figure 6 that the plasma glucose concentration remains above normal, i.e., in the hyperglycemia range, for a longer time for the 1.0 mg dose vs. the 0.6 mg dose, an effect that is particularly undesirable for a patient with diabetes. Therefore, I agree that the Applicant's selection of 0.6 mg as the phase 3/to-be-marketed dose is acceptable. It is also notable that the 0.6 mg dose of dasiglucagon produces a glucose increase similar to the marketed product GlucaGen (native glucagon).

Table 3: Summary statistics of plasma glucose PD parameters as arithmetic mean (standard deviation) and median (range) for tmax, TPG≥70mg/dL, and TPG increase≥20mg/dL

Treatment Dose No. of patients	$AUE_{0\text{-}30min}$ [mg*h/dL]	AUE [mg*h/dL]	CE_{30min} [mg/dL]	CE [mg/dL]	t_{max} [h]	$T_{PG\geq70mg/dL}$ [min]	$T_{PG\ increase\geq20mg/dL}$ [min]
ZP4207							
0.1 mg N = 5	12.9 (5.21)	344 (149)	66.1 (23.8)	102 (33.7)	1.25 (0.833-1.67)	10.0 (2.00-17.0)	14.0 (11.0-27.0)
0.3 mg N = 16	20.9 (6.13)	666 (247)	93.4 (23.7)	174 (44.6)	1.67 (1.00-2.50)	6.00 (0.000-13.0)	10.0 (7.00-20.0)
0.6 mg N = 17	21.1 (6.10)	788 (165)	98.2 (25.0)	190 (32.2)	1.67 (1.67-4.33)	6.00 (0.000-9.00)	9.00 (6.00-16.0)
1.0 mg N = 16	24.1 (5.18)	895 (213)	100 (20.3)	209 (40.2)	2.50 (1.67-2.50)	6.00 (0.000-9.00)	9.00 (7.00-15.0)
GlucaGen							
0.5 mg N = 17	22.1 (5.48)	462 (273)	93.5 (21.4)	142 (42.6)	1.00 (0.667-5.00)	6.00 (0.000-9.00)	10.0 (6.00-13.0)
1.0 mg N = 33	21.9 (5.74)	566 (232)	96.5 (21.9)	166 (42.5)	1.25 (0.833-6.12)	7.00 (0.000-10.0)	10.0 (5.00-15.0)

$AUE_{0\text{-}30min}$ and AUE = area under the plasma glucose (PG) excursions above baseline from 0-30 minutes and 0-last available measurement; CE_{30min} = PG excursion at 30 minutes; CE = maximum PG excursion; t_{max} = time to maximum PG excursion; $T_{PG\geq70mg/dL}$ = time to achieve a PG of ≥70 mg/dL; $T_{PG\ increase\geq20mg/dL}$ = time to achieve a PG increase of ≥20 mg/dL

Source: Trial 15126's synopsis

Figure 6: Mean plasma glucose concentration following single doses of Dasiglucagon and GlucaGen - Study 15126
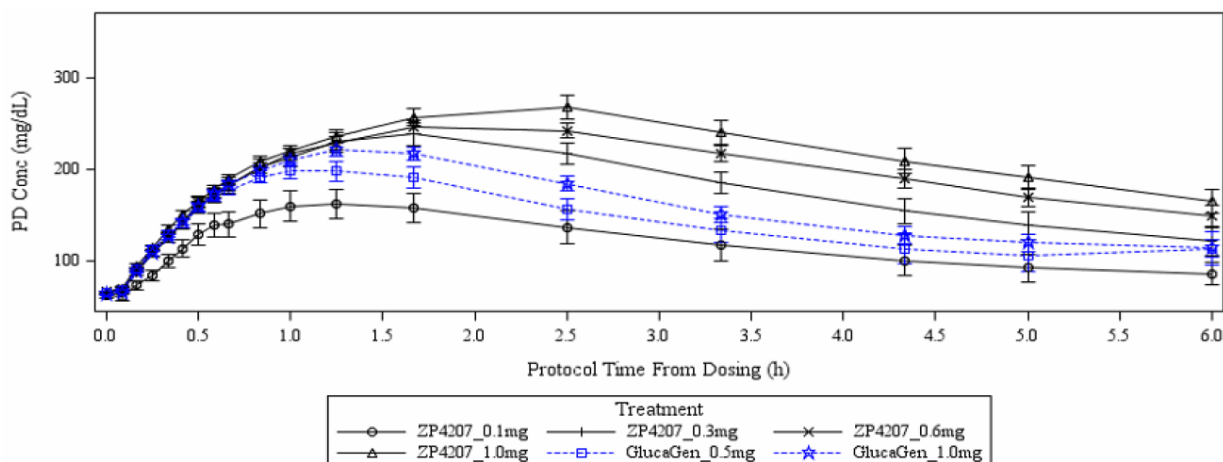
SEM: standard error of the mean
BK 02SEP2016 12:21

Source: Figure 11-3 from Applicant's CSR for Study 15126

Additionally, as dasiglucagon is a peptide product that degrades in aqueous solution, the applicant proposed a 69-105% shelf-life specification that could potentially allow a dose as low as 0.41 mg of dasiglucagon. To support the proposed shelf-life, the Applicant developed a model of dasiglucagon dose and time to glucose recovery utilizing data from study 15126. For a dasiglucagon dose of 0.40 mg, the model predicts a delay in recovery time by approximately 40.8 seconds. The clinical

pharmacology reviewer, Dr. S. J. Lau, concluded that the delay in recovery time is small and the proposed shelf-life specification is acceptable. I agree with this conclusion.

Population PK

The Applicant also conducted a population pharmacokinetic covariate analysis, to support the dasiglucagon dose selection based on the phase 2 data, i.e., only one dose option regardless of body weight or other intrinsic factors. The model was then refined with data from the five phase 3 studies (including the adult and pediatric studies) in order to quantify the impact of specific covariates on dasiglucagon PK. The effects of individual covariates on dasiglucagon exposure (relative to the exposure predicted for a typical male or female subject aged ≥24 years, weighing 78 kg with eGFR of 95 mL/min/1.73 m² who received a 0.6 mg dose of dasiglucagon) were estimated for the sub-populations shown in Figure 7 (blue symbols). For all sub-populations, apart from subjects with eGFR of 30 mL/min/1.73 m² and the relative exposure for a 6-year-old, the estimated AUC ratios fell within the 95% CI (0.55 to 1.30) of exposures predicted for subjects within the analysis dataset.

Figure 7: Effect of covariates on dasiglucagon exposure- Population pharmacokinetic Modeling

	Estimated AUC ratio (95% CI)
Analysis population, 0.6 mg	0.93 [0.55;1.3]
eGFR: 30 mL/min/1.73 m2	1.25 [1.09;1.43]
eGFR: 45 mL/min/1.73 m2	1.16 [1.06;1.26]
eGFR: 75 mL/min/1.73 m2	1.05 [1.01;1.09]
Body weight: 60 kg	1.22 [1.18;1.25]
Body weight: 100 kg	0.83 [0.81;0.85]
Batch: dual storage	0.87 [0.84;0.89]
Injection site: thigh	0.69 [0.62;0.75]
Injection site: buttocks or deltoid	0.86 [0.81;0.91]
Age: 16 years	0.78 [0.7;0.86]
Age: 12 years	0.67 [0.56;0.78]
Age: 6 years	0.5 [0.33;0.68]
16 years and 60 kg	0.93 [0.84;1.02]
12 years and 40 kg	0.97 [0.81;1.13]
6 years and 20 kg	1.14 [0.78;1.51]

Source: Figure 7 from Applicant's CSR study 19077

Because the predicted dasiglucagon exposures were calculated following the change of a single covariate, this estimate did not consider that pediatric subjects have a lower body weight and higher eGFR than the typical adult. For this reason, the Applicant also predicted the exposures for pediatric patients considering correlations between age, body weight, and renal function (green symbols, Figure

7). The exposures predicted for 16, 12, and 6-year-old subjects were similar to exposures predicted for a typical adult subject.

QT Assessment

I agree with the language recommended by the QT-IRT for the product label: At a dose resulting in 5 times the concentration of the 0.6 mg dasiglucagon subcutaneous dose, ZEGALOGUE does not prolong the QT interval to any clinically relevant extent. This language is based primarily on an IV-QT study which is described in detail in Dr. Pluchino's review.

Phase 3 Supportive PD Data

The two phase 3 adult studies (16137 and 17145) and the pediatric phase 3 study (17086) included PK/PD assessments. The study designs for the adult studies were similar, as both were randomized, blinded, parallel-group studies; however, 16137 also utilized a GlucaGen treatment arm, whereas 17145 did not. These studies are discussed in detail in Section 6 of this memo.

The PD profiles of dasiglucagon from both studies demonstrated increases in plasma glucose following administration of dasiglucagon, with a mean change from baseline of 24 mg/dL at the 10-minute timepoint in both studies with no apparent increase in the placebo groups. The $AUE_{0-30min}$ was 21 mg*h/dL for dasiglucagon and 20 mg*h/dL for GlucaGen, as compared to 3.6 mg*h/dL for placebo in study 16137. Similarly, in study 17145, the $AUE_{0-30min}$ was 19.9 for dasiglucagon and 2.7 mg*h/dL for placebo. See Figure 8.

Figure 8 : Plasma glucose change from baseline - Studies 16137 and 17145
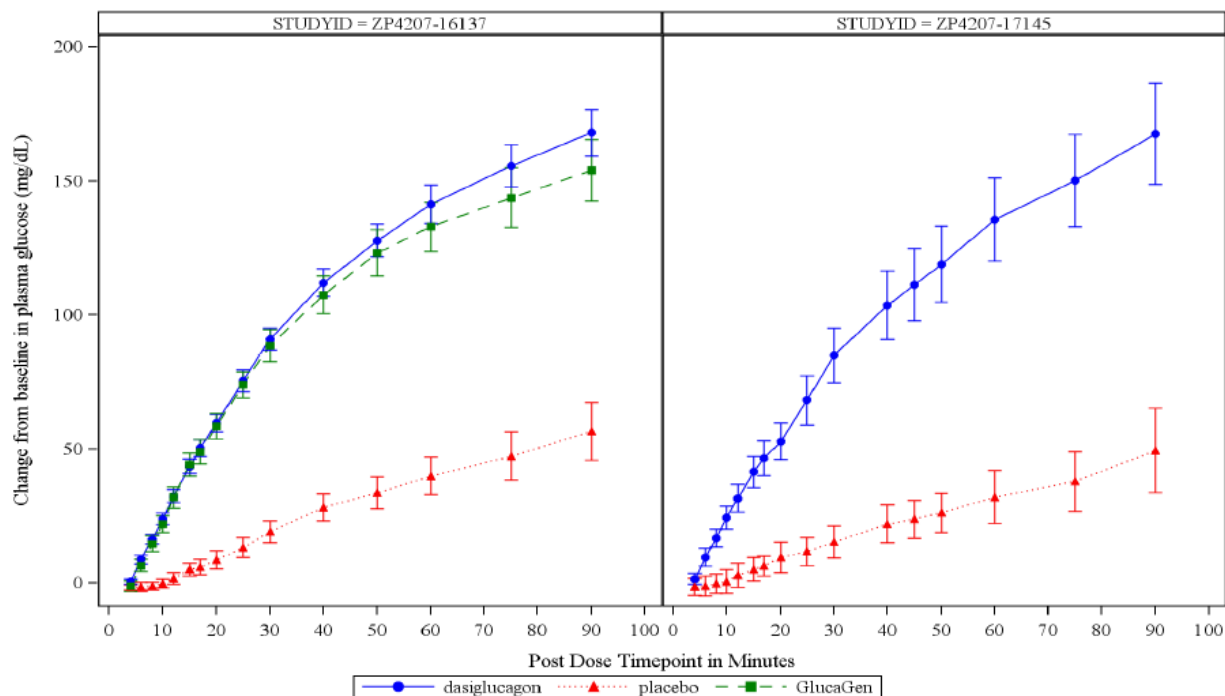
Notes: Trial 16137: N=168; Trial 17145: N=44. Error bars represent 95% confidence intervals of the mean. For patients receiving rescue IV glucose, the last recorded plasma glucose value prior to receiving rescue IV glucose is carried forward.
Cross-reference: Appendix 6.3, Figure 2.32

Source: Figure 3-1 from Applicant's ISE

In pediatric phase 3 study 17086, following administration of dasiglucagon 0.6 mg, the observed $AUE_{0-30min}$ for the dasiglucagon, GlucaGen 1 mg, and placebo treatments were 22.8, 19.7, and 1.8 mg*h/dL, respectively (Figure 9).

Figure 9: Mean (with standard error of mean) plasma glucose concentration profiles following single SC doses of dasiglucagon, GlucaGen, and placebo
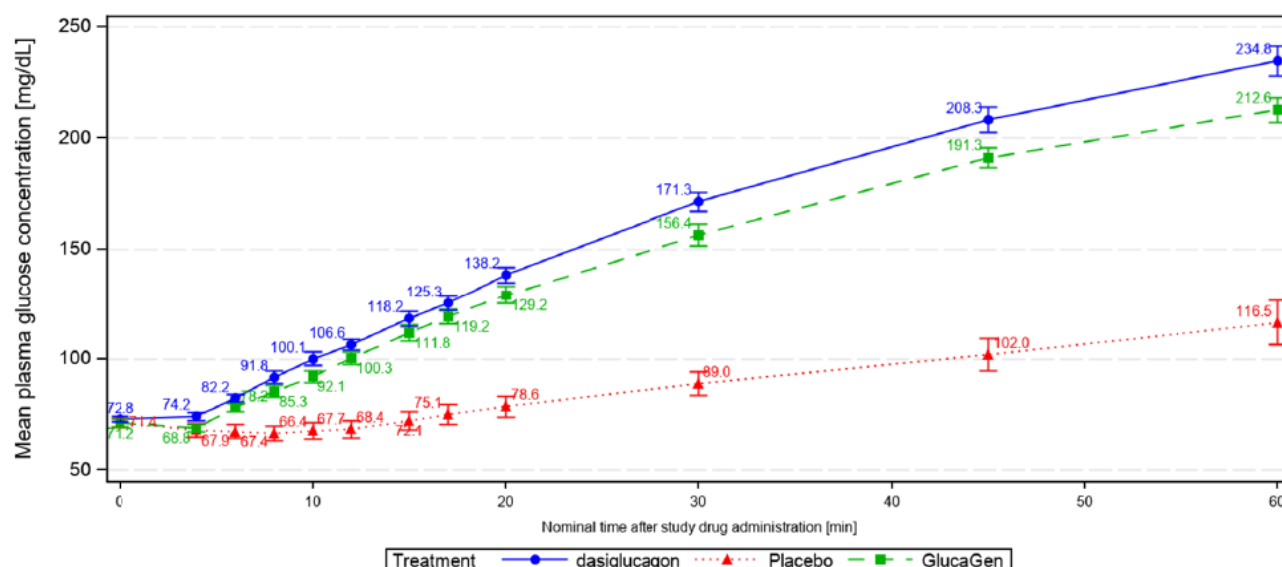
Source: Trial 17086's report Figure 11.7

Overall, the clinical pharmacology data support the proposed single 0.6 mg dose of dasiglucagon, as this dose provides adequate efficacy coverage for the broad body weight range in patients 6 years of age and above.

6.   Clinical/Statistical-Efficacy

Dr. Yoonhee Kim conducted the statistical review for this NDA, and Dr. Kristen Pluchino conducted the clinical efficacy review. Both Dr. Kim and Dr. Pluchino recommend approval of this NDA.

The Applicant has provided substantial evidence of effectiveness of dasiglucagon from three adequate and well controlled (placebo) clinical studies. As outlined in Table 4, studies 16137 and 17145 were conducted in adult patients with T1DM and study 17086 was designed to study pediatric patients age 6 and older. The primary endpoint for all three of these studies was time to plasma glucose recovery defined as first increase in plasma glucose of ≥20 mg/dL. I agree with Dr. Pluchino that this endpoint is acceptable to establish efficacy; faster recovery from hypoglycemia is desirable to prevent permanent neurologic sequelae of neuroglycopenia, and therefore, an endpoint that considers time, in addition to the plasma glucose increase, is clinically meaningful.

This memo will also briefly review the bridging study (17084) conducted to support the proposed dual storage conditions. For a complete listing of clinical studies conducted by the Applicant, see Appendix 1.

According to both Drs. Kim and Pluchino, data quality for the efficacy analyses was good. In addition, the Office of Scientific Investigations (OSI) conducted an inspection of two domestic sites (representing three clinical sites for studies being used to support efficacy) and a remote regulatory

assessment of the Applicant foreign site in support of this application. Overall, the inspectional findings support validity of data as reported by the Applicant.

Study Design - 16137 and 17145

Studies 16137 and 17145 had similar but not identical study designs. Both studies were blinded (to patient and investigator, but not to staff administering IMP), randomized, parallel design studies comparing the efficacy and safety of dasiglucagon for insulin-induced hypoglycemia in adult patients with T1DM. In study 16137, subjects were randomized 2:1:1 to dasiglucagon, GlucaGen, or placebo, whereas in study 17145, subjects were randomized 3:1 to dasiglucagon or placebo. Study 16137 utilized a prefilled syringe and study 17145 utilized an autoinjector to administer dasiglucagon and placebo. Different injection sites were used in each study. The primary endpoint of both studies was time to plasma glucose recovery, which was defined as the first increase in plasma glucose ≥20 mg/dL from baseline without administration of rescue IV glucose. Subjects who required rescue with IV glucose were censored (i.e. set to "not recovered) at 45 minutes from dosing (which was pre-specified).

At the study visit, subjects were given an IV infusion of insulin, which was stopped once blood glucose levels reached <60 mg/dL, with a target plasma glucose level of 55 mg/dL. The investigational product (i.e., dasiglucagon, GlucaGen, or placebo) was administered, and blood glucose levels were measured pre-dose, and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 50, 60, 75 and 90 minutes after dosing. If a subject experienced an 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, then post-treatment rescue IV glucose was administered.

Study Design - 17086

Study 17086 was a randomized, blinded, multi-center study in pediatric patients aged 6 years to <18 years old with T1DM. Subjects were randomized 2:1:1 to dasiglucagon, GlucaGen, or placebo administered via pre-filled syringe. As with the adult studies, the primary endpoint was the time to plasma glucose recovery, as described above. Subjects who required rescue with IV glucose were censored (i.e. set to "not recovered) at 45 minutes from dosing.

At the study visit, subjects were given an IV infusion of insulin which was stopped once blood glucose levels reached <80 mg/dL. The investigational product (i.e., dasiglucagon, GlucaGen, or placebo) was administered if the plasma glucose remained ≥54 mg/dL. Blood glucose levels were measured pre-dose, and at 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 45, and 60 minutes after dosing. If a subject experienced an escalation of 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, then post-treatment rescue IV glucose was administered.

Study Population

Phase 3 studies supporting efficacy in the development program included only subjects with T1DM. Subjects with T2DM were not included because of the potential confounding effect of endogenous insulin production on the euglycemic clamp procedure. Clinical practice guidelines for treatment of severe hypoglycemia do not distinguish between treatment of patients with T1DM and T2DM, and

the mechanism of action of dasiglucagon is relevant to both populations; therefore, I agree with Drs. Lau and Pluchino that the efficacy outcome of the development program is applicable to both populations.

The applicability of the data to the US population is acceptable. In study 16137, only 15% of subjects randomized were from the US, but in study 17145, all 34 subjects enrolled were from the US. In the pediatric study 29/41 (71%) of the subjects were from the US.

Phase 3 protocols included extensive exclusion criteria, many of which were probably overly conservative. I agree with Dr. Pluchino that, although unnecessary, the implementation of these criteria is not expected to affect the efficacy evaluation or generalizability of the results or safety conclusions. Additional 'dosing day' exclusion criteria applied to the day of the euglycemic clamp procedure. These are routine methods of ensuring reliable and consistent results for the clamp procedure and should also not affect generalizability of efficacy and safety results. I do not recommend any additional labeling language to address these factors.

Statistical Methods

For all three studies supporting efficacy, the Applicant used a two-sided log-rank test (with stratification factors injection sites for studies 16137 and 17145; injection sites and age groups for study 17086) to evaluate treatment differences between dasiglucagon and placebo. Although GlucaGen was included as a treatment arm in studies 16137 and 17086, no formal statistical testing was conducted comparing dasiglucagon to GlucaGen.

The Applicant used Kaplan-Meier (KM) estimates for median time to plasma glucose recovery, as well as a Cox Proportional Hazard model with treatment group and stratification factors as categorical effects, and baseline glucose as a continuous covariate. Sensitivity analyses were conducted for the primary endpoint, which included linearly interpolated time between assessed time points to estimate the patient's actual time of recovery.

Because the primary endpoint, time to recovery, is a beneficial outcome, in addition to confirming the analyses performed by the Applicant, Dr. Kim also conducted a survival time ratio analysis, as the hazard ratio is better applied for hazardous outcomes such as death. If the recovery time ratio is less than 1, then the results are interpreted as in favor of dasiglucagon because the recovery time becomes shorter with the group change from placebo. Please refer to the reviews of Drs. Kim and Pluchino for details.

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 changes from baseline at 30, 20, 15 and 10 minutes were analyzed using an Analysis of Covariance (ANCOVA) model. Type 1 error was controlled at a one-sided 0.025 level for multiplicity across the primary and secondary endpoints.

Phase 3 Study Results

The disposition of subjects in the 3 adequate and well-controlled studies is displayed in Table 4.

Table 4: Subject Disposition in Efficacy Studies

		Randomized	Treated (Full Analysis Set)	Completed
Study 16137	Dasiglucagon 0.6 mg	84*	82	82
	Placebo	43	43	43
	GlucaGen	43	43	43
Study 17145	Dasiglucagon 0.6 mg	34	34	34
	Placebo	11*	10	10
Study 17086	Dasiglucagon 0.6 mg	21*	20	20
	Placebo	11	11	11
	GlucaGen	10	10	10

As indicated, four subjects withdrew after randomization but prior to being treated with the investigational product; however, all subjects treated with the investigational product remained in the study until completion.
Source: adapted from Statistical Reviewer's analysis

The median times to plasma glucose recovery (95% CI), as well as the number of subjects rescued and subjects censored in studies 16137, 17145, and 17086 are presented in Table 5. The K-M curves are plotted for study 16137 in Figure 10. The curves appear similar for the other studies and are shown in Drs. Kim and Pluchino's reviews.

For all three studies, the results were statistically significant and demonstrate the superiority of dasiglucagon compared to placebo (all log-rank test two-sided p-values <0.001). In study 17145, one subject in the dasiglucagon treatment group received rescue glucose treatment at 10 minutes following study product administration based on the presence of hypoglycemic symptoms and a plasma glucose of 39.6 mg/dL at 5 minutes. Importantly however, the 10-minute plasma glucose drawn simultaneously to the administration of rescue glucose was 63.1 mg/dL, which represented an increase from baseline of 20 mg/dL. As the subject received rescue glucose, the subject was censored, but I do not consider this subject a treatment failure.

The recovery time ratio was 0.29 for all three studies, which indicates a reduction in recovery time by greater than two-thirds. The hazard ratios and recovery time ratios are also shown, with hazard ratios >1 and recovery time ratios <1 representing a shorter time to recovery for dasiglucagon over placebo.

For all secondary endpoints, dasiglucagon demonstrated superiority to placebo, supporting the primary endpoint. See Drs. Kim and Pluchino's reviews for details.

The median time to recovery (95% CI) for GlucaGen was similar to dasiglucagon; 12 minutes (10, 12) in study 16137, and 10 minutes (8, 12) in study 17086.

Table 5: Time to Plasma Glucose Recovery – Studies 16137, 17145, 17086

	Study 16137 *N=82 (dasiglucagon)* *N=43 (placebo)*	*Study 17145* *N=34 (dasiglucagon)* *N=10 (placebo)*	*Study 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 because of no recovery or having rescue IV glucose within 45 minutes after dosing; ** only for a reference because of 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: adapted from Table 7 in the Statistical Review

Figure 10: Study 16137- K-M Plot of Cumulative Proportions of Subjects with Recovery
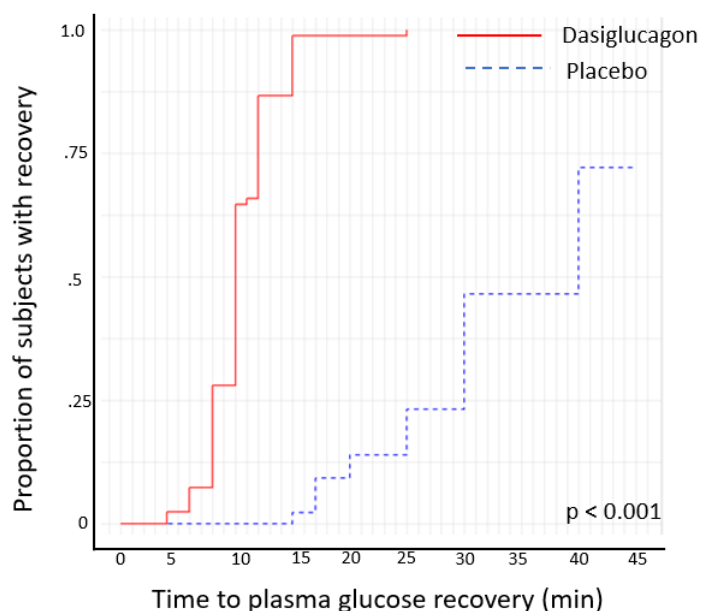
Source: Statistical reviewer analysis (with modified formatting)

In pediatric study 17086, the median time to plasma glucose recovery among dasiglucagon treated subjects was similar between the younger and older age groups. Refer to Table 6.

Table 6: Time to Plasma Glucose Recovery by Age Group- Study 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 because of no recovery or having rescue IV glucose within 45 minutes after dosing; NE: Not estimable
Source: Statistical reviewer's analysis

Because of the nature of the study designs, there were no missing data for the primary endpoint for any of the three studies. Dr. Kim replicated the sensitivity analyses performed by the Applicant and confirmed the robustness of the superiority findings for dasiglucagon compared to placebo for median time to recovery of plasma glucose.

Subgroup analyses

No important treatment-by-subgroup interactions were observed using pooled data from the two adult studies: 16137 and 17145 (Table 7). There appears to be a trend of increasing recovery time with increasing age among dasiglucagon treated subjects. Nevertheless, even in the oldest age quartile, recovery time with dasiglucagon treatment is adequate.

Table 7: Time to Plasma Glucose Recovery by Subgroups – Adult Placebo-Controlled Pool

Subgroup 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: Dr. Pluchino's review

Data from pediatric study 17086 were analyzed separately from the adult data. Similar to adults, no important interactions were observed in the pediatric cohort. Please see Table 21 in Dr. Pluchino's review. Notably, however, Dr. Pluchino noted that the Applicant limited enrollment to subjects weighing ≥20 kg, which is approximately 50th percentile for pediatric patients at 6 years of age. Furthermore, although the study was designed to enroll subjects ages 6 to 17, the youngest subject enrolled was 7 years of age. I agree with Dr. Pluchino that the efficacy results from the pediatric study do not suggest that any difference in efficacy would be evident between patients at age 6 vs. 7, and that the 0.6 mg dose is highly likely to be effective in patients with body weight less than 20 kg.

Dual-Storage Conditions

To support dual storage conditions for dasiglucagon   (b) (4)   under refrigeration (2°C to 8°C) and 12 months at room temperature (25°C)), the Applicant conducted bridging study 17084 in patients with T1DM to evaluate recovery time for a batch of dasiglucagon stored under the proposed dual storage condition (Batch B) as compared to a batch stored solely under refrigeration (Batch A). The study utilized a euglycemic clamp procedure similar to the phase 3 efficacy studies discussed above and was designed to test non-inferiority (NI) of Batch B to Batch A.

The NI margin was based on the entire treatment effect (M1) observed when comparing placebo and a dasiglucagon batch stored under refrigerated conditions. The treatment effect was determined from the phase 3 study 16137 in which the median observed time to recovery was 40 minutes (95% CI: 30, 40) in the placebo group and 10 minutes (10, 10) in the dasiglucagon group, resulting in an M1 of 30 minutes. When recalculating time to recovery in study 16137 applying interpolation, the mean interpolated time to recovery was 9.2 minutes (8.7, 9.7) for dasiglucagon and 32.3 minutes (29.2, 35.4) for placebo, resulting in an M1 of 23.1 minutes. Based on clinical judgement the Applicant set the NI margin at 2 minutes, resulting in a preserved fraction of 93% (without interpolation) and 91% (with interpolation). Traditionally, the preserved proportion of effect is often set at 50%. I agree with the Applicant that because dasiglucagon is an emergency use product, preserving over 90% of the effect is appropriate.

Compared to the drug content of Batch A   (b) (4)   Batch B had a drug content of   (b) (4)   mg of dasiglucagon. Using the Applicant's primary analysis population (PPS) and linearly interpolated timepoints, the difference between Batch B versus Batch A was 0.4 minutes (95% CI: -0.08, 0.88)

equivalent to a 24 second delay in plasma glucose recovery. These results were replicated by Dr. Kim, who also performed an analysis using the FAS population and observed time to recovery (without interpolation), and the difference was 0.59 minutes (0.01, 1.17). As the upper limits of the 95% CI for the mean difference in time to recovery were all within the NI margin of 2 minutes, the non-inferiority of Batch B to Batch A was established. See Table 8.

I agree with the reviewers that the estimated difference in time to recovery is clinically acceptable. From these data, it can be concluded that a patient using dasiglucagon, immediately prior to the expiration date, after being stored under dual-storage conditions, would only experience an average 0.4 min delay in recovery (up to 1.17 minutes) compared to dasiglucagon at the end of shelf-life stored under refrigerated conditions. The advantage of being able to store the product at room temperature and have it on hand in case of an emergency far outweighs the observed delay in recovery.

Table 8: Time to Plasma Glucose Recovery for Batch A vs. Batch B- Study 17084

	Analysis Population	Recovery Time	Batch A	Batch B	Difference in minutes (Batch B vs. Batch A)
			Mean (SD)	Mean (SD)	Mean (95% CI)
Applicant's primary	PPS*	Interpolated	9.21 (2.34)	9.61 (2.89)	0.40 (-0.08, 0.88)
FDA's primary	FAS**	Observed	10.28 (2.94)	10.84 (3.29)	0.59 (0.01, 1.17)

* PPS : Per protocol set (N=82) 2 subjects had intermittent missing values, so these subjects were excluded.
** FAS : N=90; n=87 for each batch, 6 subjects had only one batch data for period 1, no imputation was performed on missing data for period 2
Source: adapted from Table 12 from the Statistical Review

7. Safety

The assessment of safety was conducted by Dr. Pluchino. In this memo I will briefly review the overall safety findings and discuss selected safety findings of special interest for this product. Please refer to Dr. Pluchino's review for a detailed discussion of safety results. Dr. Pluchino notes that the quality of the safety submission was adequate, and the key safety findings were reproducible and able to be confirmed using the submitted datasets.

Description of the Pooling Strategy

The safety profile of dasiglucagon was assessed via review of safety data from placebo-controlled efficacy studies 16137 and 17145 (i.e. the placebo-controlled pool). Data from pediatric study 17086 was evaluated independently. Additionally, a secondary pool, referred to as the 'broad pool,' consisting of all available data from studies conducted in adult subjects with T1DM exposed to dasiglucagon ≥0.6 mg, was used for additional supportive safety analyses. See section 8.1 of Dr. Pluchino's review for additional information regarding the pooling strategy.

Because potential bias may be introduced because of differences in randomization ratios (Simpson's paradox), Cochran Mantel Haenszel (CMH) weighting was used for pooled data (placebo-controlled and broad pools) to present adjusted incidences. The Applicant's use of CMH weighting was reviewed by Dr. Yoonhee Kim, the statistical reviewer, who confirmed the weights applied to each study. Considering the short half-life of dasiglucagon of approximately 30 minutes, a 12-hour post-

dose cutoff was used for identification of treatment-emergent adverse events. There is precedent for following this approach; see Section 6 of Gvoke PI (glucagon injection, NDA 212097).

Relevant Characteristics of the Safety Population

Relevant issues have been previously discussed in the context of the efficacy evaluation. The subject population was adequately representative of the US population and included a sufficiently broad range of demographic and disease characteristics. Also as noted previously, phase 3 studies in the development program included only subjects with T1DM, not T2DM. Safety results from T1DM subjects are relevant to the T2DM population and adequate to inform safety for both populations. In fact, immunogenicity tends to be a greater safety issue among T1DM patients than T2DM patients because of the autoimmune nature of the etiology of T1DM.

Overall Exposure

During the clinical development program for dasiglucagon, a total of 466 patients were exposed to dasiglucagon at doses ranging from 0.01 to 2.0 mg, of whom 358 had T1DM. The rest were healthy volunteers. There were 390 patients out of the total of 466 patients who received doses ≥0.6 mg of dasiglucagon, the to-be-marketed dose. There were 20 pediatric patients with T1DM out of the total 358 patients. See Appendix 1 for a complete table of studies conducted with dasiglucagon. The size of the safety database is adequate for a single dose, emergency-use product.

Deaths

There were no deaths reported among dasiglucagon exposed subjects.

Serious Adverse Events

There was one reported serious adverse event (SAE) of severe hypoglycemia in a 64-year-old male with T1DM from immunogenicity study 16136. Dr. Pluchino describes the case narrative in detail, but it appears that the subject injected more prandial insulin than his carbohydrate intake required and then was unable to self-correct. The episode occurred 26 hours after the dasiglucagon dose and was not proximally related. I agree with Dr. Pluchino's assessment that the severe hypoglycemia occurred because of a mismatch of insulin administered versus insulin required and inability to consume oral glucose in a timely fashion and was not caused by the study drug.

Dropouts /discontinuations due to Adverse Events

No adverse events (AEs) led to withdrawal in the placebo-controlled pool or the pediatric study.

Treatment-emergent Adverse Events (TEAEs)

Studies 16137 and 17145 (Placebo-controlled pool)

Dr. Pluchino discussed that dasiglucagon has a half-life of approximately 30 minutes, and a 12-hour post-dose data flag was used in the analysis to enrich for AEs that were more likely related to dasiglucagon as compared to AEs that may have occurred during the study observation period (a time

frame of approximately four weeks) but may be unrelated to dasiglucagon treatment. I agree with this approach to the safety evaluation.

AEs reported by subjects within 12 hours of dosing (Table 9) were similar between the dasiglucagon arm (65.6%) and GlucaGen arm (67.4%), and higher than in the placebo arm (15.9%). The most common AEs that were more frequent in the dasiglucagon arm vs. placebo were nausea, vomiting, diarrhea, and headache. Comparatively, the frequency of these AEs appears similar to GlucaGen. Of note, these AEs are labeled for other approved glucagon products (with the exception of diarrhea). The AEs of nausea, vomiting, and diarrhea, and headache were non-serious and resolved without sequelae. I consider these to be temporary tolerability issues rather than important safety concerns, and labeling in section 6 of the PI is adequate to inform of these adverse reactions. Injection site reactions also appear to occur more frequently with dasiglucagon than with placebo or GlucaGen, although numbers of events are small, limiting conclusions. Again, these were non-serious and self-limiting and can be conveyed in section 6 of labeling.

Table 9: AEs by System Organ Class Occurring at a Frequency of ≥2% and more than Placebo within 12 Hours of Dosing, Preferred Term - 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%)
Nervous system disorders	**15 (12.8%)**	**6 (14.0%)**	**2 (3.6%)**
Headache	13 (11.2%)	5 (11.6%)	2 (3.6%)
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%)

Source: Adapted from Table 23 of Dr. Pluchino's Clinical Safety Review

AEs that occurred in <2% of dasiglucagon-exposed subjects within 12 hours of dosing that were clinically meaningful (i.e., symptomatic but non-serious) included one event of bradycardia and one event of presyncope. See the "hemodynamic events" section for additional information and comments on labeling recommendations. Otherwise, AEs occurring within 12 hours of dosing in the adult placebo-controlled pool were unremarkable; please refer to Dr. Pluchino's review for a listing of these AEs.

Study 17086 - Pediatric Study

As in the placebo-pool, the highest incidence of reported AEs within 12 hours of dasiglucagon dosing were gastrointestinal disorders, with nausea and vomiting the most frequently reported PTs, with a greater incidence of gastrointestinal AEs reported by 12- to 17-year-old subjects in the dasiglucagon group. Diarrhea was a commonly reported AE in the adult placebo-controlled pool, but it was not reported by pediatric subjects. For a tabulation of AEs reported in at least 2% of subjects (and more frequently with dasiglucagon than placebo), see Table 10. Otherwise, AEs occurring within 12 hours of dosing in the pediatric study were unremarkable. Please refer to Dr. Pluchino's review for a listing of these AEs.

Table 10: AEs by System Organ Class Occurring within 12 Hours of Dosing ≥2% and more than Placebo, Preferred Term, Age Group - Study 17086

	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%)
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%)

Source: Adapted from Table 26 from Dr. Pluchino's Clinical Safety Review

In her review, Dr. Pluchino also evaluated adverse events that occurred over the entire observation period (rather than with the 12-hour cutoff) for both adult and pediatric pools. These analyses did not change the overall safety conclusions. Please refer to Dr. Pluchino's review for details.

Subgroups

Overall, Drs. Kim and Pluchino found no evidence of important safety by subgroup interactions.

With respect to gastrointestinal tolerability, additional analyses of nausea and vomiting by age subgroup may suggest a trend towards increasing nausea and vomiting with younger age (data shown in Dr. Pluchino's review). This finding is inconclusive but interesting in light of the efficacy by subgroup analysis shown in Table 7, which suggests a faster time to recovery for younger age groups. One could surmise that gastrointestinal symptoms are associated with faster recovery time rather than specifically drug-related.

As discussed previously the Applicant limited enrollment in study 17086 to subjects weighing ≥20 kg, which is approximately 50th percentile for patients 6 years of age. Therefore, dasiglucagon may be administered to pediatric patients <20 kg in the postmarket setting. No apparent relationship was observed between body weight and AEs, and subjects with lower body weight appear to have a similar safety profile as the general pediatric pool. Therefore, the restriction on body weight in study 17086 does not appear to present a safety concern based on available information, and no additional labeling language is warranted.

<u>Laboratory Findings</u>

Dr. Pluchino conducted extensive analyses of common chemistry and hematology parameters. There were no notable outliers with apparent relationship to dasiglucagon dosing. With the exception of leukocyte counts, no changes in central tendencies for any laboratory value were observed. Dr. Pluchino found that 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 11). Dr. Pluchino also notes that transient increases in leukocyte count have been characterized in the literature following glucagon treatment, but do not appear clinically meaningful. I agree that this observation is not a clinical concern for this NDA. I also do not recommend labeling this information in section 6 of the PI because prescribers will not be following hematologic parameters during dasiglucagon therapy.

Figure 11: Leukocytes over Screening, Dosing, and Follow Up – Placebo-Controlled Pool
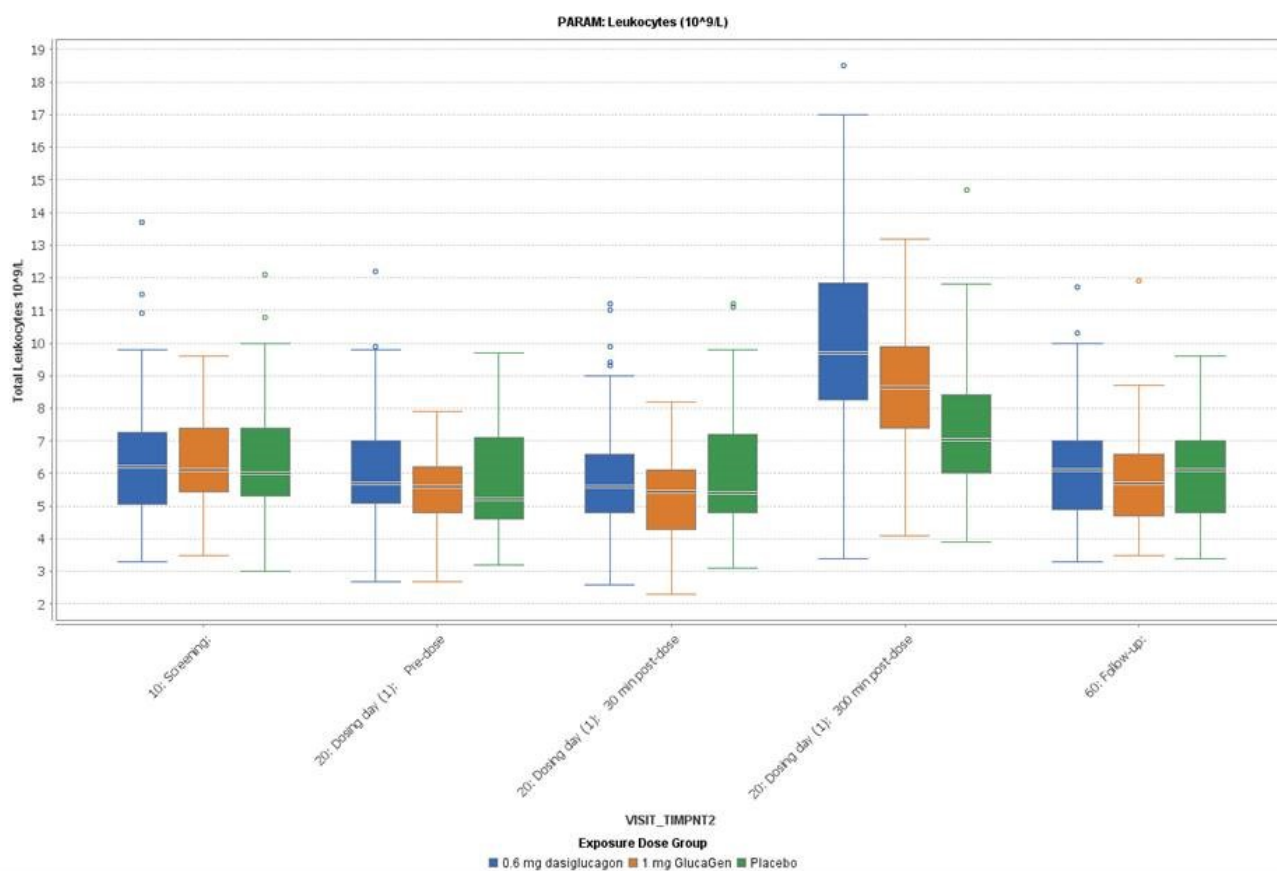
Source: Dr. Pluchino's review

<u>Routine Vital Sign Monitoring</u>

Because exogenous glucagon can cause inotropic and chronotropic effects, blood pressure and heart rate were carefully monitored during the phase 3 studies; vital signs were measured pre-dose (i.e., prior to initiation of the hypoglycemic clamp) and at 30, 90, and 300 minutes post-dose. Dr. Pluchino conducted analyses based on mean changes and categorical shifts from pre- to post-dose (any timepoint after dosing). Please see her review for details. I agree with the conclusion that blood pressure and heart rate analyses do not demonstrate important differences in central tendency among treatment groups, nor are there concerning outliers observed at the pre-specified monitoring timepoints.

Reported Hemodynamic Events

The Applicant designated hemodynamic events, including hypotension, hypertension, and changes in heart rate, as adverse events of special interest during the phase 3 development program. In the broad pool, the incidence of hemodynamic events was 2.3% in the dasiglucagon arm, 5.9% in the GlucaGen arm, and there were no events in the placebo arm. Given the known hemodynamic effects of this drug class and the disparity in the frequency of these adverse events between treatment groups, these are highly likely to be causally related to dasiglucagon. Of note, however, no hemodynamic events were categorized as SAEs; and none led to subject withdrawal in the dasiglucagon arm. Additionally, all events were transient and most resolved without intervention. There were no hemodynamic events in the dasiglucagon group in the pediatric study. Hemodynamic events will be included in section 6 of the PI.

Electrocardiograms

Serial 12-lead ECGs were performed in all studies 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. The timing of ECG assessments varied per study, but generally occurred pre-dose and at 20, 35, 45, 60, and 300 minutes post-dose timepoints. In the broad pool, one dasiglucagon exposed subject had an ECG finding judged as 'abnormal/clinically significant' by the investigator (dasiglucagon: 1/316, GlucaGen: 0/151, placebo: 0/53), that was also reported as an AE of 'electrocardiogram T wave inversion.' There were no symptoms associated with the event. Both Drs. Pluchino and Dunnmon (cardiology consultant) concluded that this single event of asymptomatic, transient non-specific ST-T-wave changes does not raise a safety concern. Their conclusion is reasonable.

Immunogenicity

The Applicant submitted immunogenicity assessments obtained from 11 clinical studies, in which 498 subjects were exposed to single or multiple doses of dasiglucagon, and 212 subjects were exposed to GlucaGen, including studies conducted with dasiglucagon for other indications. The Applicant also conducted a dedicated phase 3 randomized, double-blind, parallel-group immunogenicity study in 111 subjects, of whom 57 subjects were exposed to 0.6 mg dasiglucagon and 54 subjects were exposed to 1.0 mg GlucaGen, three times within a two-week period, who were then assessed for anti-drug antibody (ADA)-positivity at approximately 5, 9, and 15 weeks after the initial dose.[1]

No important AEs that reasonably could be caused by immunogenicity or hypersensitivity were reported.

The immunogenicity assays utilized in the clinical studies were reviewed by the Office of Biotechnology Products (OBP) reviewer, Dr. Faruk Sheikh. The validated assays included the anti-dasiglucagon antibody binding assay, anti-glucagon antibody binding assay, cross-reactivity and titering assay for assessment of antibodies to dasiglucagon, and neutralizing antibody assays for

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[1] The trial included the following periods: A screening period from Day -30 to Day -3, a treatment period from Day 0 (randomization) to Day 14 with IMP administered SC on Day 0, Day 7, and Day 14, a follow-up period after the end of treatment, with follow-up visits on Day 35, Day 60, and Day 104 (the end-of-trial visit).

antibodies to dasiglucagon and glucagon. Dr. Sheikh determined that the validated assays were suitable for their intended purpose.

In the 11 clinical studies, four out of the 498 subjects (0.8%) who were ADA-negative at baseline developed ADAs following administration of dasiglucagon. Of the four dasiglucagon-exposed subjects who were ADA+, two were from single-dose studies (16137, 17086), one was from dose-finding study (15126), and one subject was from a multiple-dose study conducted in support of a separate dual-hormone artificial pancreas indication (16098). The ADA+ subject from study 16098 received eight doses of dasiglucagon and three doses of native glucagon over the study period and subsequently tested positive for anti-dasiglucagon and anti-glucagon antibodies at the follow up visit (24 days after last dosing). This subject was also found to have cross-reactive and neutralizing antibodies to both glucagon and dasiglucagon. The subject remained positive for anti-dasiglucagon antibodies (although the sample was negative for anti-glucagon antibodies) at a study visit 3.5 months after last dosing and was negative at an additional follow-up visit at 7 months after last dosing. Importantly however, no clinical consequence was identified. Furthermore, according to the OBP reviewer, because of the cross-over nature of the study and the high degree of amino acid sequence homology between dasiglucagon and glucagon, the ADA-positive result cannot be specifically attributed to either dasiglucagon or glucagon treatment. The other three ADA+ subjects did not have cross-reactive or neutralizing antibodies, and no immunogenicity AEs were reported for any of the four subjects who were positive for ADAs.

In the dedicated immunogenicity study (16316), no ADA+ samples were observed. Although the study intended to assess the effects of ADA on efficacy and safety, the lack of ADA+ subjects did not permit the planned evaluation.

In conclusion, the overall incidence of ADA+ was low and there were no AEs related to immunogenicity, although the data are somewhat limited as discussed above. Potential risks caused by immunogenicity in the postmarket setting include excess hypoglycemia and/or inadequate glucose response to dasiglucagon. In theory, NAbs that develop towards native glucagon could impact a patient's endogenous counter-regulatory response to hypoglycemia, and antibodies directed against dasiglucagon specifically could interfere with its activity. Dr. Pluchino recommends that standard postmarket surveillance (pharmacovigilance) appears reasonable to monitor the risk of immunogenicity related to dasiglucagon, and I agree with her recommendation.

In terms of labeling, inclusion of immunogenicity data in section 6 of the Prescribing Information is appropriate.

8. Advisory Committee Meeting

An advisory committee meeting was not held for this application. Although the product is a new molecular entity, the efficacy evaluation was straightforward (three adequate and well controlled studies with consistent results), and no safety issues arose during the review that would benefit from input from an advisory committee.

9. Pediatrics

The Applicant conducted a pediatric assessment for children aged 6 to less than 18 years of age (study 17086) and based on these data, I recommend approval for dasiglucagon for the proposed indication in children down to six years of age. In the agreed iPSP, the Applicant had requested a deferral for study in children aged ≥1 to <6 years of age and a waiver in children less than one year of age. The Division and the PeRC agree with the proposed waiver. A PREA postmarketing requirement will be issued for the deferred study at the time of approval.

In the prescribing information, the Applicant has proposed the following indication for dasiglucagon: "for the treatment of severe hypoglycemia in adult and pediatric patients with diabetes aged 6 years and above." Although the Applicant intended to enroll pediatric patients aged 6 years and older, the youngest subject enrolled in pediatric study 17086 was 7 years old. However, I agree that the submitted data support the use of dasiglucagon for the proposed indication for pediatric subjects aged 6 and older, as there is no reason to believe that efficacy would differ between patients 6 and 7 years old, and as noted by Dr. Pluchino, safety analyses showed that age had no impact on the safety of the product.

10.   Other Relevant Regulatory Issues

Pregnancy, Lactation, and Human Fertility

The Division of Pediatrics and Maternal Health was consulted for pregnancy and lactation labeling recommendations. Dr. Mastroyannis noted that severe hypoglycemia is common during pregnancies in Type I diabetic women. Pregnant women with type 1 diabetes have three to five times more hypoglycemic episodes than during the period prior to pregnancy.

Dr. Mastroyannis concluded the following:
-There are no data of use of dasiglucagon in pregnant women. Prolonged experience over several decades with use of glucagon based on published observational studies and postmarketing reports have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks associated with untreated severe hypoglycemia in pregnancy. Dasiglucagon should not be withheld during pregnancy.

-There is no information to provide to the prescriber regarding pregnancy testing, contraception, or effects on fertility. With no demonstration of adverse developmental effects in the animal offspring, pregnancy testing and contraception is unnecessary.

-No publications on clinical experience with dasiglucagon and its effects of human fertility were found. Animal reproductive studies of administration of dasiglucagon injection did not show any adverse effects on fertility. DPMH recommends that subsection 8.3 Females and Males of Reproductive Potential is omitted from dasiglucagon labeling.

Proprietary Name Review

The Applicant has proposed the proprietary name ZEGALOGUE. This name was reviewed by Dr. Colleen Little of DMEPA, who found the name acceptable.

Review of the Descriptor 'Hypopal' for the Autoinjector

The Applicant proposed using the descriptor ████ (b) (4) in labeling in reference to the autoinjector. Samantha Bryant from the Office of Prescription Drug Promotion recommended removal of this descriptor because it is promotional in tone and may minimize the risks associated with the drug. The concern stemmed primarily from the word ████ (b) (4) which in their view denotes a 'friendly' tone. I agree with removing the descriptor ████ (b) (4) from the product labeling.

Efficacy in the Postmarket Setting and Other Relevant Benefits

Dasiglucagon 0.6 mg was effective in increasing blood glucose levels in a clinically meaningful timeframe without evidence of treatment failure. In the postmarket setting, dasiglucagon is anticipated to have a treatment effect similar to that observed within the context of the clinical development program, once the injection is administered. In the postmarket setting, dasiglucagon will be administered by a caregiver, and minor delays in dose delivery may be expected, compared to doses administered by well-trained clinical study personnel. Notably, however, as discussed in section 4.6, the Applicant provided human factors validation data to confirm that caregivers are able to understand and use the devices appropriately and remaining potential use errors can be mitigated by patient labeling, including a detailed Instructions For Use.

In addition, in the postmarket setting, the increase in plasma glucose is expected to result in benefits that include recovery from neuroglycopenia and prevention of complications of neurologic sequelae or death, although these were not directly assessed in the development program. A development program that required 'real-world' testing of dasiglucagon vs. an approved glucagon product for assessment of benefit on these clinical outcomes would be infeasible and unnecessary.

As dasiglucagon will be available in prefilled syringe/autoinjector devices, it offers the potential for greater ease of administration with a lower potential for certain types of medication errors, e.g., errors related to reconstitution, as compared to glucagon products that require reconstitution. Additionally, dasiglucagon can be stored either under refrigeration or at room temperature (dual-storage conditions) allowing for flexible storage options.

Financial Disclosures

Dr. Pluchino concluded that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.

Compliance with Good Clinical Practice (GCP)

The COVID-19 global pandemic limited the ability to conduct a foreign onsite GCP inspection for the Applicant (Denmark). A remote regulatory assessment revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted, and no Form FDA-483 was issued. No other GCP issues were identified by Dr. Pluchino.

Data Quality and Reliability

Both Drs. Kim and Pluchino noted that data quality ranged from excellent (efficacy data) to adequate (safety data). The Office of Scientific Investigations (OSI) inspected two domestic clinical

investigator sites (representing three clinical trial sites). OSI identified regulatory deficiencies in one clinical site, and a Form FDA-483 was issued for not always obtaining the permission of both parents as per 21 CFR 50.53. I agree with Dr. Pluchino that the violation should not impact safety and efficacy analyses.

Labeling

There are no outstanding labeling issues, and final agreed upon labeling may be included in the NDA approval letter. Labeling recommendations are included throughout this review. Additional recommendations are noted in the following paragraphs.

Several Contraindications and Warnings and Precautions are included in labeling for native glucagon: Contraindications for patients with pheochromocytoma, insulinoma, and in patients with known hypersensitivity to dasiglucagon, Warnings and Precautions including a 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, and necrolytic migratory erythema (NME). Although the pertinent adverse reactions were not observed in dasiglucagon studies, patients with these risk factors would not have been eligible for the dasiglucagon studies. Similar labeling is warranted for dasiglucagon based on the shared mechanism of action with native glucagon (glucagon receptor agonism). The Applicant has proposed *not* to include NME in the Warnings and Precautions, as NME is associated with continuous intravenous infusion, which would not be applicable for dasiglucagon administered as a single injection, and this is acceptable. In addition, according to labeling guidelines, a Contraindication for patients with a known hypersensitivity to dasiglucagon is not appropriate, as hypersensitivity reactions were not observed in the development program. Hypersensitivity is not related to the mechanism of action.

The recommendation in section 2 of the Prescribing Information to administer a second dose if there is no response after 15 minutes is based on class labeling for glucagon products and is theoretical in nature. Although there are no available data testing this dosing strategy, the benefit of resolution of severe hypoglycemia is considered to outweigh any theoretical risk of overdosing of a glucagon receptor agonist, including dasiglucagon.

11.   Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No REMS is recommended for dasiglucagon. No serious safety concerns associated with the use of dasiglucagon were identified that would require a REMS. The identified risks can be adequately conveyed in the product labeling, and none of these risks warrants a boxed warning. The Division of Risk Management in the Office of Surveillance and Epidemiology concurs with this recommendation.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Under the authority of the Pediatric Research Equity Act (PREA), a PMR will be issued for a study to evaluate safety, efficacy, and PK/PD of dasiglucagon in pediatric patients with T1DM age ≥1 year to <6 years. The pediatric study requirement for ages 0 to less than 1 year are waived because necessary

studies are impossible or highly impracticable due to the low incidence of type 1 diabetes mellitus in patients below 1 year of age.

<u>Other</u>

Post-approval inspections are recommended for ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ (b) (4) ⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛⬛ Rechon Life Science, which manufactures the finished product (drug-device combination product). For details please refer to the CDRH and OPQ reviews.

Appendix 1

Listing of Clinical Studies in Dasiglucagon Clinical Development Program for Severe Hypoglycemia

Study ID	Description	Design (Glycemic status at dosing)	Dosing (Randomization)	Study Endpoints	No. of subjects completed	Study Population
Studies to Support Safety and Efficacy						
16137	A phase 3, randomized, double-blind, study 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 study 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, study 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 ($\geq$6 to <18 years)
Supportive Studies to Support Safety and/or Efficacy						
16136	**Immunogenicity** - A phase 3, randomized, double-blind, safety study 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 study evaluating the efficacy and safety of single doses of two dasiglucagon batches. The study 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	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

	program).					
15126	**Dose Finding** - A phase 2, randomized, double-blind study 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 Study** – A phase 1, randomized, double-blind, placebo-controlled, study 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 Study** - A phase 2b, randomized, placebo-controlled, double-blind study 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 study 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

Source: Table 2 from Dr. Pluchino's clinical review

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I was involved in the preparation of this memo and agree with its content.