CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214231Orig1s000

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA214231
Drug Name:	Dasiglucagon s.c. 0.6 mg
Indication(s):	Treatment of severe hypoglycemia in patients with diabetes aged 6 years and above
Applicant:	Zealand Pharma A/S
Date(s):	Received date: March 27, 2020
	Filing date: May 26, 2020
	PDUFA goal date: March 27, 2021
Review Priority:	Standard
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Keywords: NME, Hypoglycemia, Superiority, Placebo, KM estimates, Time to recovery

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1 EXECUTIVE SUMMARY

The applicant, Zealand Pharma A/S, submitted an original new drug application (NDA) for a new molecular entity (NME), dasiglucagon subcutaneous (SC) 0.6 mg, an anti-hypoglycemic agent. This NDA contained results of nine clinical studies (3 phase I studies, 1 phase II study, 5 phase III studies, 2 safety studies for other indications). The applicant proposed a new indication for treatment of severe hypoglycemia in patients with diabetes aged 6 years and above.

1.1 Brief Overview of Clinical Study

There were three pivotal Phase III placebo-controlled efficacy trials: two trials in adult patients with Type I Diabetes Mellitus (T1DM) (Trials 16137; NCT03378635 and 17145; NCT03688711), and one trial in pediatric (≥ 6 years and <18 years) patients with T1DM (Trial 17086; NCT03667053). In this statistical review, results from three pivotal efficacy trials were mainly evaluated for efficacy and safety.

All three pivotal Phase III studies were randomized, double-blinded, and parallel trials to confirm the clinical efficacy and safety of dasiglucagon for the rescue treatment of severe hypoglycemia. There were active controlled (GlucaGen®) arms in Trials 16137 and 17086, but no formal statistical testing for efficacy was performed for comparing dasiglucagon to GlucaGen®. Safety profiles of GlucaGen® was compared with ones of dasiglucagon.

Primary objective of three pivotal studies was to demonstrate superiority of dasiglucagon compared to placebo administered to patients with T1DM following insulin-induced hypoglycemia. Primary endpoint of three pivotal trials was time to plasma glucose recovery after dosing a single SC injection of study treatment following a hypoglycemic clamp with monitoring at discrete time points (pre-dose, 4, 6, 8, 10 minutes etc.) at the clinic visit. Plasma glucose recovery was defined as first increase in plasma glucose of ≥ 20 mg/dL from baseline without administration of rescue intravenous (IV) glucose. The subjects who are rescued with IV glucose or who has not recovered within 45 minutes irrespective of the use of rescue IV glucose were censored (i.e., set to “not recovered”) at the pre-specified 45 minute from dosing.

1.2 Statistical Issues

There was no major statistical issue. Minor statistical issues are following:

- **Subgroup analysis data and presentation of results**: For the efficacy subgroup analyses, the sponsor pooled the data from two pivotal placebo-controlled adult studies, a phase II dose-finding study and a phase III bridging study. Also, in the integrated summary of efficacy, the sponsor showed the dasiglucagon group results alone in the forest plot without placebo group results as reference. This reviewer disagreed pooling non-pivotal studies into placebo-controlled studies for subgroup analysis because there was no additional placebo group information by adding data of a dose-finding study and a bridging study. This reviewer used the pooled data from two pivotal placebo-controlled adult studies. For a presentation of subgroup analysis, this reviewer suggested a table format of results from both the dasiglucagon group and the placebo group. Tabularized subgroup analysis results will be published in Drug Trials Snapshot given the approval of dasiglucagon (Section 4.1).

- **Cumulative proportions of subjects with recovery over time and presentation in the labeling:** In the proposed labeling, the applicant presented figures of cumulative proportions of subjects with recovery over time from dosing for dasiglucagon group only without the placebo group information. This reviewer suggests illustrating cumulative recovery curves for both dasiglucagon and placebo groups to confirm the difference between groups (Section 3.2.4).
- **Benefit-risk results:** There were higher frequency of nausea and vomiting in the dasiglucagon group compared to the placebo group. Most hypoglycemia as adverse events were of mild or moderate severity and were resolved in short time. Despite the higher frequency of nausea and vomiting, these were clinically common side-effects for glucagon-receptor agonist and were considered relatively mild symptoms compared to potential fatality due to delay of the recovery from severe hypoglycemia (Sections 3.3 and 3.4).

1.3 Collective Evidence

- The primary analysis results in Trials 16137, 17145 and Trial 17086 achieved strong statistical significance for testing superiority of dasiglucagon compared to placebo for time to plasma glucose recovery. Median time to plasma glucose recovery of dasiglucagon group was 10 minutes while median time to recovery was 30 to 40 minutes in the placebo group (Table 1, see Section 3.2.4.1).
- All secondary endpoints analyses, supportive efficacy trial analysis and subgroup analysis results demonstrated robust and consistent superiority of dasiglucagon compared to placebo (See Sections 3.2.4.2, 3.2.4.3 and Section 4).
- The pivotal phase III studies for efficacy and safety demonstrated that benefits in reduction of time to plasma glucose recovery outweighs the risk of dasiglucagon (see Section 3.4).

Table 1. Primary Analysis Results: Median time (95% CI) to plasma glucose recovery from severe hypoglycemia

	Trial 16137 *N=82(dasiglucagon) N=43(placebo)*	***Trial 17145*** *N=34(dasiglucagon) N=10 (placebo)*	***Trial 17086*** *N=20 (dasiglucagon) N=11(placebo)*
Dasiglucagon	10 minutes [10, 10]	10 minutes [8,12]	10 minutes [8,12]
Placebo	40 minutes [30, 40]	35 minutes [20, ∞)	30 minutes [20, ∞)

Note: Time to plasma glucose recovery were monitored at pre-dose, 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, and 45 minutes within 45 minute censoring time ˚ All p-values from log-rank test of dasiglucagon vs placebo are < 0.001
**Source: Statistical reviewer's analysis*

1.4 Conclusion and Recommendations

Statistical findings in three adequate and well-controlled pivotal studies for efficacy and safety in adults and children aged 6 years and above provide strong statistical evidence for effectiveness of dasiglucagon S.C. 0.6 mg in reducing time to plasma glucose recovery from severe hypoglycemia. Results from studies reviewed support a new indication for dasiglucagon and adding information in CLINICAL STUDIES section in the label (see Section 5.4).

2 INTRODUCTION

2.1 Overview

A severe hypoglycemia is defined as a decline in plasma glucose to very low values (e.g., below 70 mg/dL or below 54mg/dL) that requires assistance from another person for a recovery. Symptoms and signs of a severe hypoglycemia happen quickly and can cause serious medical consequences such as seizures and death. Severe hypoglycemia episodes may occur more frequent in T1DM population who are usually treated with insulin.

To recover from hypoglycemic state, human glucagon, a peptide hormone, raises the concentration of glucose and fatty acids in the bloodstream. This applicant developed dasiglucagon as NME that is a peptide analog of human glucagon for the treatment of severe hypoglycemia in patients with diabetes mellitus for a ready-to-use glucagon aqueous formulation for SC administration that facilitates convenient and fast dose delivery.

This application was submitted with eleven clinical studies (3 phase I studies, 1 phase II study, 5 phase III studies, 2 safety studies for other indications) to support an indication for dasiglucagon, to treat severe hypoglycemia in patients with diabetes aged 6 years and above. Five phase III studies include two adult studies (Trial 16137; Trial 17145), one pediatric study (Trial 17086), one immunogenicity study (Trial 16136) and a bridging study to evaluate two different storage batches (Trial 17084). Communications between the applicant and the agency regarding efficacy protocols for dasiglucagon were documented under IND127866.

The efficacy evaluation for this statistical review mainly uses results from three pivotal, placebo-controlled trials: two trials in adult subjects with T1DM (Trials 16137 and 17145), and one trial in pediatric subjects (≥ 6 years and <18 years) with T1DM (Trial 17086) (Table 2). Trial 17086 was submitted in line with the agreed initial plan for pediatric study (iPSP) on June 7, 2018. Trial 17086 details were consistent with the iPSP.

All three pivotal Phase III studies were randomized, double-blinded, placebo-controlled and parallel trial to confirm the clinical efficacy and safety of dasiglucagon in the rescue treatment of severe hypoglycemia. Trials 16137 and 17086 used pre-filled syringe, and trial 17145 used auto-injector for a ready-to-use aqueous formulation, dasiglucagon. There were active controlled (GlucaGen®) arms in Trials 16137 and 17086, but no formal statistical testing for efficacy was performed for comparing dasiglucagon to GlucaGen®.

In addition to the pivotal efficacy trials, the relevant primary efficacy results of dasiglucagon from a supportive efficacy trial, a bridging study (Trial 17084) for testing the non-inferiority of dual storage batch to the reference batch (refrigerated condition) that is used for all other clinical trials for dasiglucagon were reviewed. Full evaluation of two different batches can be found in the clinical and clinical pharmacology reviews of this NDA.

Table 2 shows the summary of three pivotal efficacy trials (Trials 16137, 17145, and 17086) and a bridging study (Trial 17084) for study design, sample size, randomization ratio and primary/secondary endpoints.

Table 2. Summary of Efficacy Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size (Randomization ratio)	Endpoints (Analysis)
16137 Phase III Pre-filled syringe	Pivotal efficacy trial R, DB, M, PBO- & AC-controlled parallel arm stratified by injection site (abdomen/ buttocks/thigh)	N=170 (2:1:1) dasiglucagon: 84* placebo: 43 GlucaGen: 43 **2 subjects were not treated.*	Primary endpoint: Time to plasma glucose recovery defined as first increase in plasma glucose of ≥ 20 mg/dL from baseline without rescue IV glucose (*stratified log-rank test and KM estimates)* Secondary endpoints: Plasma glucose recovery within 30, 20, 15 and 10 minutes without rescue IV glucose (Fisher's exact test) Plasma glucose change from baseline at 30, 20, 15 and 10 minutes or at the time of rescue (ANCOVA) (PD) Time to first plasma glucose concentrations ≥ 70mg/dL without administration of rescue IV glucose
17145 Phase III Auto-injector	Pivotal efficacy trial R, DB, M, PBO-controlled parallel arm stratified by injection site (buttocks/deltoid)	N=45 (3:1) dasiglucagon: 34 placebo: 11* **1 subject was not treated.*	
17086 Phase III Pre-filled syringe Pediatric study (≥ 6 and <18 years)	Pivotal efficacy trial R, DB, M, PBO- & AC-controlled parallel arm stratified by age group (6 to 11, 12 to 17) & injection site (abdomen/thigh)	N=42 (2:1:1) dasiglucagon: 21* placebo: 11 GlucaGen: 10 **1 subject was not treated.*	
17084† Bridging study Phase III Pre-filled syringe	Supportive efficacy trial R, DB, crossover Batch A (reference: refrigerated condition) & Batch B (test: dual storage condition)	N=90* dasiglucagon 0.6 mg *87 subjects in Batch A only are used for integrated subgroup analysis.	Primary endpoint: Time to plasma glucose recovery defined as first increase in plasma glucose of ≥ 20 mg/dL from baseline without rescue IV glucose (ANOVA including factors center, sequence, patient

			within sequence, period, and treatment) NI margin= 2 min

*Note: R Randomized; DB Double-Blind; M Multicenter; PBO Placebo; AC Active Control; KM Kaplan-Meier; CMH Cochran Mantel-Haenszel; ANCOVA Analysis of covariance; NC Not Calculated; NI Non-inferiority; PK Pharmacokinetics; PD Pharmacodynamics
† The relevant part of Trial 17084 (primary efficacy results only) was reviewed in this statistical review.
**Source: statistical reviewer's analysis*

2.2 Data Sources

The applicant submitted materials for this review electronically in the electronic common technical document (eCTD) format which were archived under the network path location: \\CDSESUB1\evsprod\NDA214231\214231.enx

Datasets in ADAM and STDM formats with clinical study reports are in the eCTD sequence number #001 (\\CDSESUB1\evsprod\NDA214231\0001\m5\datasets). Datasets of each trial are located under each trial folder: "ZP4207-16137" for Trial 16137, "ZP4207-17145" for Trial 17145, "ZP4207-17086" for Trial 17086, and "ZP4207-17084" for Trial 17084. Datasets for the integrated study for safety and integrated study for efficacy including subgroup analysis using the pooled data are under the folder of "iss-ise".

In addition to the sponsor's analyses, this reviewer independently verified the descriptive statistics, plots and analyses results using SAS (modified from the sponsor's code) and R language.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted data of high quality and made it possible for the statistical reviewer to reproduce their results of pre-specified primary analysis as well as sensitivity analyses for efficacy. For data integrity, this reviewer checked derived variables from STDM to ADAM datasets and basic statistics. The primary endpoint was in the "adtte.xpt" file of each trial folder (variable paramcd="TTPCR"(Trial 16137)/ "T2PGRP"(Trial 17145)/ "PGLRECP"(Trial 17086)). There was no issue for data and analysis quality except the different naming of variables and parameters across trials for the same variable.

3.2 Evaluation of Efficacy

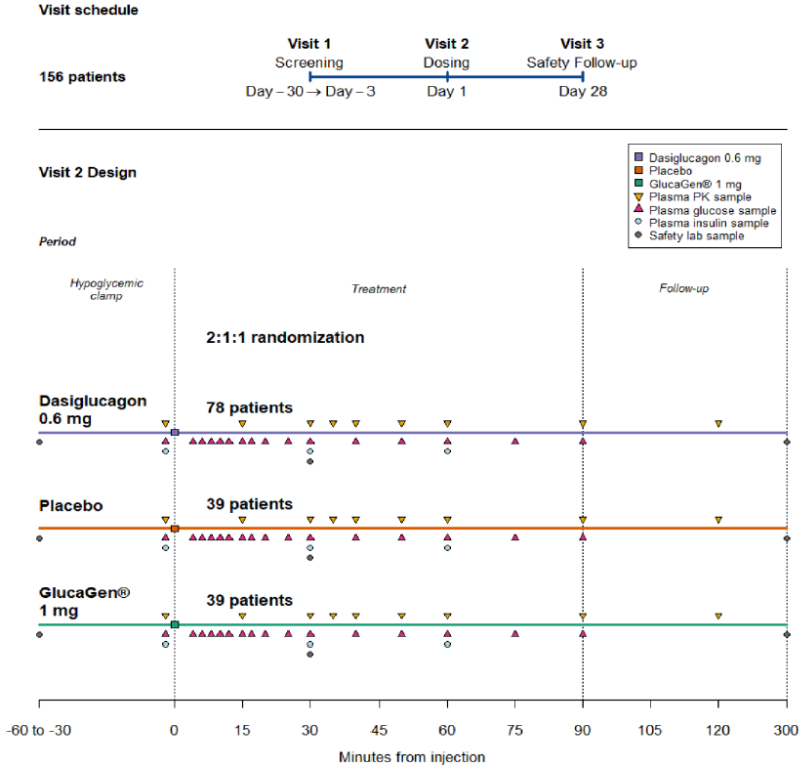
3.2.1 Study Design and Endpoints

Key study design features for all three efficacy trials were summarized in Table 2 (Section 2.1). Three pivotal efficacy trials (Trials 16137, 17145 and 17086) have identical visit schedules of three clinic visits during the trial; 1) screening visit, 2) dosing visit and 3) 28 day follow-up visit.

The study design scheme for the trial 16137 is illustrated in Figure 1 represented as an example for study designs of pivotal efficacy trials.

At the dosing visit, investigational product dosing was injected followed by a hypoglycemic clamp (insulin infusion) procedure to induce a controlled hypoglycemic state. Hypoglycemic clamp is a controlled induction of hypoglycemia using intravenous administration of insulin. During this hypoglycemic clamp procedure, a plasma glucose value was targeted between ≥ 45 mg/dL and < 60 mg/dL in the two adult trials (Trials 16137 and 17145), whereas a higher value was targeted between ≥ 54 mg/dL and < 80 mg/dL in pediatric trial 17086. If the subjects went into that targeted region defined as "severe hypoglycemia", then the investigational product was dosed as a rescue treatment.

Figure 1. Study Design for ZP4207-16137 (Trial 16137)



Source: The sponsor's clinical study reports for Study ZP4207-16137 page 20

For evaluation of the clinical efficacy (primary and secondary endpoints), plasma glucose were collected and assessed at pre-dose, and at 4, 6, 8, 10, 12, 15, 17, 20, 25 (except Trial 17086), 30, 40 (except Trial 17086), 45 (except Trial 16137), 50 (except Trial 17086), 60, 75 (except Trial 17086), 90 (except Trial 17086) minutes after dosing at the clinic visit on dosing day. The actual time of blood sampling was also recorded.

The primary endpoint in all three pivotal efficacy trials was the time to plasma glucose recovery defined as first increase in plasma glucose of ≥ 20 mg/dL from baseline without administration of rescue intravenous (IV) glucose. The subjects who are rescued with IV glucose within 45 minutes or who has not recovered within 45 minutes irrespective of the use of rescue IV glucose

were censored (i.e., set to “not recovered”) at the pre-specified 45 minute from dosing. The censoring time, 45 minutes was pre-determined during the IND communication stage with the Agency.

As the occurrence of the intercurrent events (rescue therapy) and failure of treatment are incorporated into assessment of the primary endpoint, this reviewer sees that the composite strategy is the proper estimand in these trials for adults and children of 6 years and above with T1DM.

Key secondary endpoints were identical across the three pivotal efficacy trials.

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

A pharmacodynamic (PD) endpoint of time to first plasma glucose concentrations ≥ 70 mg/dL without administration of rescue IV glucose was also included in this review because the severe hypoglycemia is defined as < 70 mg/dL and this reviewer thinks this endpoint is also clinically meaningful for the efficacy of dasiglucagon.

Trial 17084 (trial initiation date March 26, 2019) is a randomized and double-blinded bridging study in cross-over design including 28 days follow-up between periods to show non-inferiority of the efficacy of dasiglucagon stored at the intended dual storage condition (Batch B) relative to dasiglucagon stored at refrigerated condition (Batch A) as reference as used in other clinical trials. The primary endpoint for efficacy was time to plasma glucose recovery same as pivotal efficacy trials. The primary endpoint was evaluated in this review as supportive evidence of efficacy of dasiglucagon. The pre-specified non-inferiority (NI) margin was 2 minutes. This NI margin (see details in Section 3.2.4.3) was pre-specified based on placebo-controlled treatment effect from the Trial result 16137 (trial completion date May 25, 2018) after the Type C meeting on November 16, 2018 with the Agency.

3.2.2 Statistical Methodologies

Analysis population

For statistical analysis for efficacy evaluation, full analysis set (FAS) that is all randomized patients who received at least one dose of investigational products was used. Due to relative shorter time of follow-up to assess the primary endpoint using plasma glucose sampling of 90 minutes at the clinic visit on dosing day, there were no missing data in terms of primary and secondary endpoints.

Statistical analysis method for primary endpoint

For all three pivotal efficacy trials, two-sided log-rank test stratified by stratification factors (injection sites for Trials 16137 and 17145; injection sties and age groups for Trial 17086) was

performed to evaluate treatment difference between dasiglucagon and placebo to show the superiority of dasiglucagon. For Trials 16137 and 17086, no formal statistical testing for dasiglucagon compared to GlucaGen® was performed.

Kaplan-Meier (KM) estimates for median time to recovery and corresponding 95% confidence interval (CI) were used to present the results in each group. Confidence interval was calculated using the intervals on the log hazard (conf.type=log-log option in Survfit function in R).

Recovery (Survival) Time Ratio

In addition to presenting the median time to recovery with 95% CI in each group, since plasma glucose were collected at discrete time such as pre-dose, and at 4, 6, 8, 10, 12, 15, 17, 20, 25 etc. post-dose, the sponsor performed a discrete-time Cox Proportional Hazard (CPH) model with treatment group and stratification factors as categorical effects and baseline plasma glucose as continuous covariate as an additional analysis and showed the hazard ratio (HR) in terms of summary statistic of comparison for two groups in Trials 16137 and 17145 (adult studies) .

Since the primary endpoint is time to recovery that is a beneficial outcome rather than hazardous outcome such as death, the hazard ratio was not intuitively understood for the time to plasma glucose recovery. To better understand, this reviewer borrowed the concept of a survival time ratio from the parametric survival model[1] with log-normal distribution for a comparison of time to plasma glucose recovery in two groups. With time to recovery in the placebo group as a reference, the survival time ratio will be the ratio of time to recovery in the dasiglucagon group over one in the placebo group. In this review, the "recovery" time ratio is used in lieu of the survival time ratio. If the recovery time ratio is less than 1, then the results are interpreted as a favor to dasiglucagon because the recovery time becomes shorter with the group change from placebo. Parametric Survival Model (psm) function in the R package, rms v.6.6 was used to calculate the survival time ratio.

Statistical analysis method for secondary endpoints

For secondary endpoints, Fisher's exact test was performed for comparing the proportion of subjects of plasma glucose recovery within 30, 20, 15 and 10 minutes after injection and an analysis of covariance (ANCOVA) test was performed for plasma glucose change from baseline at 30, 20, 15 and 10 minutes after injection.

Multiplicity adjustment

Type I error was controlled at a one-sided 0.025 level for multiplicity across primary and secondary endpoints. Hierarchical inferential testing was performed using the same order of the primary and key secondary endpoints.

Sensitivity analyses

[1] Frank E. Harrell, Regression Modeling Strategies (second edition, springer) 466, 468 page

The sponsor performed sensitivity analyses for the primary endpoint using 1) linearly interpolated time between assessed time points, 2) without censoring for subjects who required rescue IV glucose and 3) with censoring at the time of administration of rescue IV glucose. This reviewer validated the results as an additional analysis using the actual collected time of plasma glucose. The primary endpoint incorporated the intercurrent events and the failure of treatment as a penalty (censoring at the maximum time, 45 min), there was no additional concerns of bias of treatment effect. Also, because there was no missing data for all three pivotal studies (see Section 3.2.3), there were no concerns of handling missing data in the evaluation of efficacy.

A bridging study of two different storage batches of dasiglucagon (supportive efficacy, non-inferiority study)

For a bridging study, Trial 17084, time to plasma glucose recovery was analyzed by an analysis of variance (ANOVA) model including sequence, subject within sequence, period, and treatment as factors. The sponsor used the linearly interpolated time points between the 2 time points using per protocol analysis set (PPS). This reviewer used assessed timepoints which were same as other pivotal trials using full analysis set (FAS) for a validation. Non-inferiority of dasiglucagon Batch B (dual storage) relative to that of dasiglucagon Batch A (refrigerated condition) was demonstrated if the upper limit of the 2-sided 95% CI for the mean treatment difference between Batch A and B did not exceed NI margin of 2 minutes.

The NI margin of 2 minutes was based on the treatment effect of dasiglucagon in Batch A compared to placebo from Trial 16137. This margin preserved 93% of placebo-adjusted median time upper limit (30 mins) resulted from the observed median time to recovery in Trial 16137 (40 minutes [95% CI: 30, 40] in the placebo group;10 minutes [95% CI: 10, 10] in the dasiglucagon group; see details in Section 3.2.4). Because mean treatment difference in time to recovery, instead of median time to recovery, is used for Trial 17084, 2 minute NI margin preserved 92% of placebo-adjusted mean time upper limit (26 mins) calculated from observed mean time to recovery: 34.6 minutes (95% CI: 31.7, 37.4) in the placebo group; 10.5 minutes (95% CI: 9.8, 11.1) in dasiglucagon group. Because of large preserved fraction in both median time and mean time to recovery treatment effect, NI margin of 2 minutes was reasonable to test non-inferiority of Batch B in the reference of Batch A numerically.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A patient disposition for three pivotal efficacy trials are summarized in Table 3. All randomized subjects who received at least one dose of investigational products completed the trial. A few subjects withdrew consents after randomization but before injecting the investigational products because of clamp procedure did not reach to the targeted plasma glucose range or subject's decision. All randomized and treated subjects were assessed for efficacy endpoints and completed trials with a 28-day follow up period.

Table 3. Patient Disposition in Pivotal Efficacy Trials

		Randomized	***Treated (Full Analysis Set)***	***Completed***
Trial 16137	*Dasiglucagon 0.6 mg*	84*	82	82

	Placebo	43	43	43
	GlucaGen	43	43	43
Trial 17145	*Dasiglucagon 0.6 mg*	34	34	34
	Placebo	11**	10	10
Trial 17086	*Dasiglucagon 0.6 mg*	21***	20	20
	Placebo	11	11	11
	GlucaGen	10	10	10

*In Trial 16137, one subject withdrew consent and one subject had adverse event and withdrew consent after randomization before administration of investigational products. **In Trial 17145, one subject did not want to continue the study and withdrew consent after randomization before administration of investigational products. ***In Trial 17086, one subject did not agree to reschedule the dosing visit.
**Source: statistical reviewer's analysis*

In a bridging study, Trial 17084, total of 92 subjects were randomized in 1:1 ratio for each batch cross-over combination (Table 4). After first treatment, 2 subjects discontinued treatment due to an adverse event of vomiting, 3 subjects discontinued due to subjects' decision and 1 patient was unable to visit.

Table 4. Patient Disposition for Trial 17084 for dasiglucagon Batch A and Batch B

Number of subjects	***Batch A->B***	***Batch B->A***
Randomized	46	46
Treated 1st batch	45	45
Treated 2nd batch	42	42
Completed	42	41

**Source: statistical reviewer's analysis*

Major baseline characteristics by treatment arm for three pivotal efficacy trials are summarized in Table 5 (adult studies) and Table 6 (a pediatric study). Overall, majority of population were whites and younger than 65 years old. In Trial 17145, more males than females were randomized in the placebo arm, and all subjects were from USA. There was no issue with the submitted randomization scheme and code for Trial 17145. Because sample size was small in each trial, the impact of imbalanced proportion of subgroups to efficacy of dasiglucagon were investigated in the subgroup analysis using the pooled adult studies (see details in Section 4.1).

Table 5. Demographics and Baseline Characteristics- Adult studies, Trial 16137 & Trial 17145

	Trial 16137			***Trial 17145***	
	Dasiglucagon N=82	***Placebo N=43***	***GlucaGen N=43***	***Dasiglucagon N=34***	***Placebo N=10***
Age					
Mean (SD)	39.2 (12.1)	28 (13.1)	40.2 (11.5)	42.4 (13.5)	36.5 (12.8)
Median (min, max)	37 (18, 71)	36 (18, 65)	38 (23, 66)	40.5 (24,69)	32.5 (18, 55)
< 65 years (%)	79 (96%)	42 (98%)	41 (96%)	32 (94%)	10 (100%)
≥ 65 years (%)	3 (4%)	1 (2%)	2 (4%)	2 (6%)	0 (0%)
Sex					
Male (%)	50 (61%)	27 (63%)	28 (65%)	18 (53%)	9 (90%)
Female (%)	32 (39%)	16 (37%)	15 (35%)	16 (47%)	1 (10%)
Ethnicity					

Hispanic or Latino (%)	2 (2%)	2 (5%)	3 (7%)	4(12%)	3 (30%)
Not Hispanic/Latino (%)	80 (98%)	41 (95%)	40 (93%)	30 (88%)	7 (70%)
Race					
White (%)	76 (93%)	39 (91%)	39 (91%)	34 (100%)	7 (70%)
African American (%)	1 (1%)	1 (2%)	2 (5%)	0	1 (10%)
Others (%)	5 (6%)	3 (7%)	2 (5%)	0	2 (20%)
Region					
USA (%)	12 (15%)	6 (14%)	6 (14%)	34 (100%)	10 (100%)
Out of USA (%)	70 (85%)	37 (86%)	37 (86%)	0	0
Injection Site					
Abdominal region	28 (34%)	13 (30%)	15 (35%)	0	0
Buttock	27 (33%)	15 (35%)	13 (30%)	18 (53%)	6 (60%)
Thigh	27 (33%)	15 (35%)	15 (35%)	0	0
Deltoid	0	0	0	16 (47%)	4 (40%)
Baseline HbA1c(%)					
Mean (SD)	7.5 (0.95)	7.2 (0.7)	7.4 (0.97)	7.2 (0.89)	7.2 (0.88)
Baseline Plasma glucose (mg/dL)					
Mean (SD)	58.9 (5.6)	58.8 (4.4)	58.5(5.1)	55.6(5.1)	55.7(3.2)

**Source: extracted from clinical study reports for Study ZP4207-16137 & Study ZP4207-17145*

In a pediatric study, Trial 17086, almost 40% of subjects were 6 to 11 years old age group and all subjects were whites except 2 subjects.

Table 6. Demographics and Baseline Characteristics- Pediatric study, Trial 17086

	Dasiglucagon N=20	***Placebo N=11***	***GlucaGen N=10***
Age			
Mean (SD)	12.3 (3.4)	12.8 (3.3)	12.4 (3.5)
Min, Max	7, 17	7, 17	7, 17
6 - 11 years (%)	8 (40%)	4(36%)	4(40%)
12 – 17 years (%)	12 (60%)	7 (64%)	6 (60%)
Sex			
Male (%)	10 (50%)	5 (46%)	8 (80%)
Female (%)	10 (50%)	6 (54%)	2 (20%)
Ethnicity			
Hispanic or Latino (%)	4 (20%)	2 (20%)	1 (10%)
No Hispanic or Latino (%)	16 (80%)	9 (80%)	9 (90%)
Race			
White (%)	19 (95%)	10 (91%)	10 (100%)
Others (%)	1 (5%)	1 (9 %)	0
Region			
USA (%)	13 (65%)	9 (82%)	7 (70%)
Out of USA (%)	7 (35%)	2 (18%)	3 (30%)
Injection site			
Abdominal skin	9 (45%)	5 (45%)	5 (50%)
Thigh	11 (55%)	6 (55%)	5 (50%)
Baseline HbA1c(%)			
Mean (SD)	7.6 (1.1)	7.8 (1.2)	7.8 (1.2)
Baseline Plasma glucose (mg/dL)			
Mean (SD)	73 (5.5)	72 (6.9)	71 (6.1)

**Source: extracted from clinical study reports for study ZP4207-17086*

3.2.4 Results and Conclusions

3.2.4.1 Primary endpoint: Time to plasma glucose recovery

For three pivotal efficacy trials, the primary endpoint is time to plasma glucose recovery defined as first increase in plasma glucose of ≥ 20 mg/dL from baseline within 45 minutes during the hypoglycemic clamp procedure without administration of rescue IV glucose.

The results of primary endpoint presented as the median time to recovery (95% CI) with the number of rescued subjects and the number of censored subjects are summarized in Table 7. All results were significant to demonstrate the superiority of dasiglucagon compared to placebo (all log-rank test 2-sided p-values < 0.001).

More number of subjects in the placebo group than the dasiglucagon group were censored due to no recovery within 45 minutes in all three trials. Five out of 12 censored subjects in the placebo group were recovered after 45 minutes (at 50, 60, 75, 75, 90) in Trial 16137, one censored subject in the placebo group recovered at 75 minutes in Trial 17145 and two subjects in the placebo group recovered at 60 minutes in Trial 17086.

Since primary endpoint is time to recovery, the shorter the recovery time, the better, therefore, a HR > 1 or a recovery time ratio <1 favors the dasiglucagon group over the placebo group. Hazard ratios from a discrete-time Cox proportional hazard model for Trial 16137 and Trial 17145 were 111 and 10, respectively. Recovery time ratios from parametric survival model were consistent across all pivotal trials as 0.29. It indicates that when the treatment group changes from placebo to dasiglucagon, the recovery time decreased by more than two-thirds.

Table 7. Primary Results: Time to Plasma Glucose Recovery from Severe Hypoglycemia

	Trial 16137 *N=82(dasiglucagon) N=43(placebo)*	***Trial 17145*** *N=34(dasiglucagon) N=10 (placebo)*	***Trial 17086*** *N=20 (dasiglucagon) N=11(placebo)*
Dasiglucagon			
Number of subjects rescued[*]	0	1	0
Number of subjects censored[†]	0	1	0
Median time (95% CI)	10 minutes [10, 10]	10 minutes [8,12]	10 minutes [8,12]
Min, Max	4, 25 minutes	4, 45 (30[††]) 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,∞)	30 minutes [20,∞)
Min, Max	15, 25 minutes	20, 45 minutes	17, 45 minutes
Hazard Ratio (95%CI)[‡]	111 (38, 330)	10 (4, 34)	51 (6, 424)[**]
Recovery Time Ratio (95%CI) [‡‡]	0.29 (0.26, 0.33)	0.29 (0.21, 0.4)	0.29 (0.23, 0.36)

Note: Time to plasma glucose recovery were monitored at pre-dose, 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, and 45 minutes within 45 minute censoring time ° All p-values from log-rank test of dasiglucagon vs placebo are < 0.001; [*]Rescued: Number of subjects who received IV glucose within 45 minutes after dosing; [†]Censored: Number of subjects who were censored at 45 minute after

*dosing due to no recovery or having rescue IV glucose within 45 minutes after dosing; ††Maximum of recovery time for a rescued subject (censored at 45 min, but recovered at 30 min with rescue therapy) ‡By Sponsor using a discrete Cox Proportional Hazard model ⌗ By statistical reviewer using the survival time ratio from Parametric Survival Model, exp(coeff of treatment group) ** only for a reference due to violation of assumption of proportional hazards*
Source: Statistical reviewer's analysis

As additional information, the median time to recovery (95% CI) in the GlucaGen® group were similar to dasiglucagon group as 12 minutes [10,12] and 10 minutes [8,12] in Trial 16137 and Trial 17086, respectively. No formal testing was performed for dasiglucagon compared to the GlucaGen®.

In the pediatric study, Trial 17086, younger age group (6-11 years) and older age group (12-17 years) showed similar median time to recovery in dasiglucagon group (Table 8).

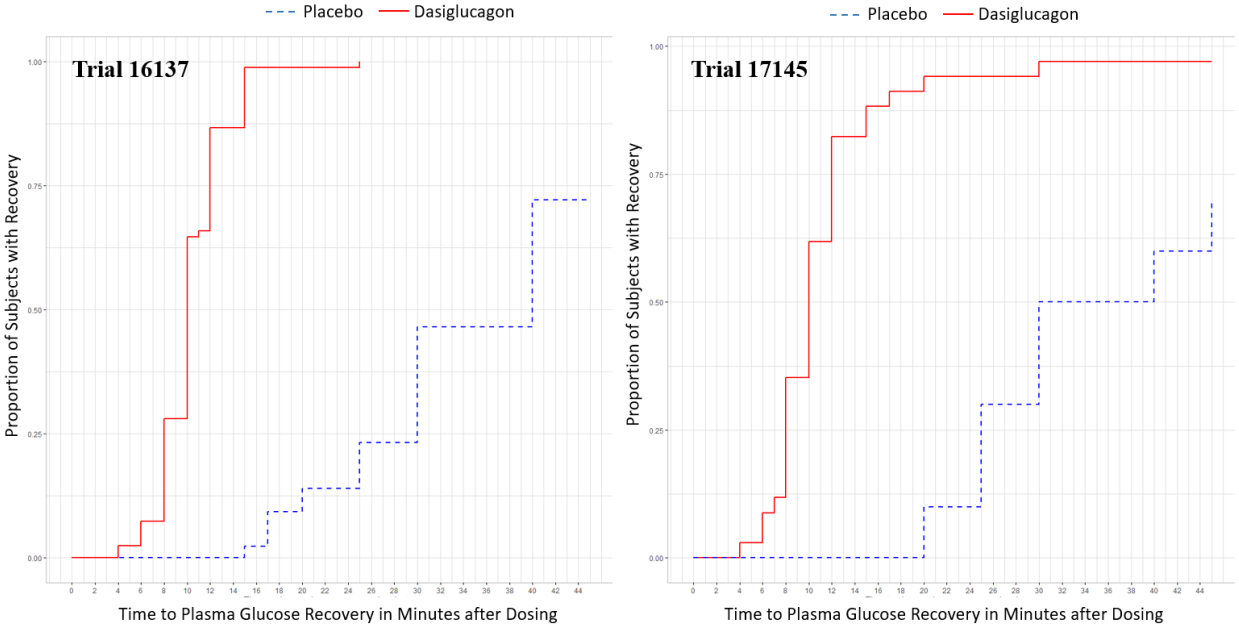
Table 8. Time to Plasma Glucose Recovery from Severe Hypoglycemia by Age Group in Trial 17086

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

*Note: Time to plasma glucose recovery were monitored at pre-dose, 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, and 45 minutes within 45 minute censoring time ° All p-values from log-rank test of dasiglucagon vs placebo are < 0.001; *Rescued: Number of subjects who received IV glucose within 45 minutes after dosing; †Censored: Number of subjects who were censored at 45 minute after dosing due to no recovery or having rescue IV glucose within 45 minutes after dosing;*
Source: Statistical reviewer's analysis

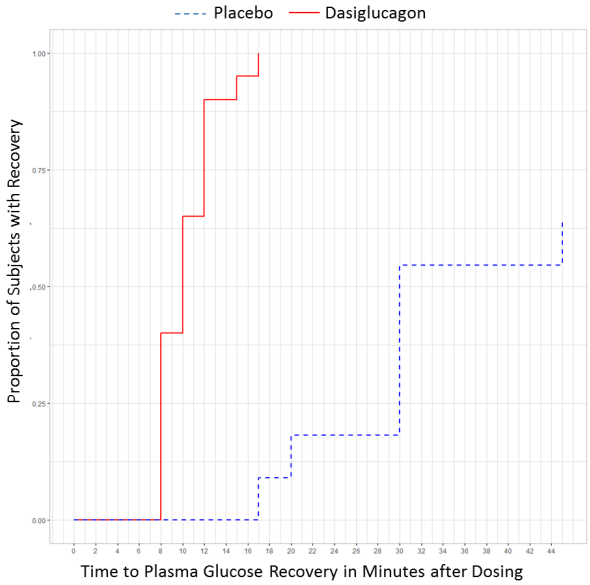
Figures 2 and 3 illustrated the cumulative proportions of subjects with recovery across time to recovery in minutes for dasiglucagon (red solid line) and placebo (blue dashed line) groups for adult studies (Trial 16137, 17145) and a pediatric study (Trial 17086) respectively. The curves in all three figures separated clearly and the red solid curves of dasiglucagon group showed earlier start of recovery and faster accumulation of proportions of subject with recovery compared to the blue dashed curves of the placebo group.

Figure 2. Cumulative Proportions of Subjects with Recovery for Trial 16137 & Trial 17145



Source: Statistical reviewer's analysis

Figure 3. Cumulative Proportions of Subjects with Recovery for Trial 17086



Source: Statistical reviewer's analysis

Because there was no missing data for the primary endpoint and very few subjects received the rescue IV glucose, all performed sensitivity analyses confirmed the robustness of superiority of efficacy in the dasiglucagon group in terms of the median time to recovery compared to placebo.

3.2.4.2 Secondary endpoints

The number and proportion of subjects with plasma glucose recovery in each group within 30, 20, 15 and 10 minutes for all pivotal trials are tabularized in Table 9. Within 15 minutes, greater proportions of subjects (99%, 88%, and 95% in Trial 16137, 17145 and 17086, respectively) in dasiglucagon were recovered compared to one or none of subjects were recovered in the placebo group. All differences in the proportions between dasiglucagon and placebo within 30, 20, 15 and 10 minutes were significant with Fisher's exact p-values < 0.01.

Table 9. Secondary endpoint: Number and Proportion of Subjects, n(%) with Plasma Glucose Recovery within 30, 20, 15, and 10 minutes

	Trial 16137		***Trial 17145***		***Trial 17086***	
	Dasiglucagon N=82 n (%)	*Placebo N=43 n (%)*	*Dasiglucagon N=34 n (%)*	*Placebo N=10 n (%)*	*Dasiglucagon N=20 n (%)*	*Placebo N=11 n (%)*
≤ 30 minutes	82 (100%)	20 (47%)	33 (97%)	5 (50%)	20 (100%)	6 (54.5%)
≤ 20 minutes	81 (98.8)	6 (14%)	32 (94%)	1 (10%)	20 (100%)	2 (18.2%)
≤ 15 minutes	81 (98.8%)	1(2.3%)	30 (88.2%)	0	19 (95%)	0
≤ 10 minutes	53 (64.6%)	0	20 (58.8%)	0	13 (65%)	0

Source: Statistical reviewer's analysis

Plasma glucose change (mg/dL) in least squared (LS) mean and standard errors (SE) from ANCOVA model from baseline to 30, 20, 15 and 10 minutes for all three pivotal trials are summarized in Table 10. The mean of plasma glucose change is greater than 20 mg/dL at 10 minutes for dasiglucagon groups in all trials, meanwhile the mean of plasma glucose change is still less than 20 mg/dL at 30 minutes for placebo groups in all trials. All p-values of ANCOVA test for the treatment difference were significant (p value < 0.001).

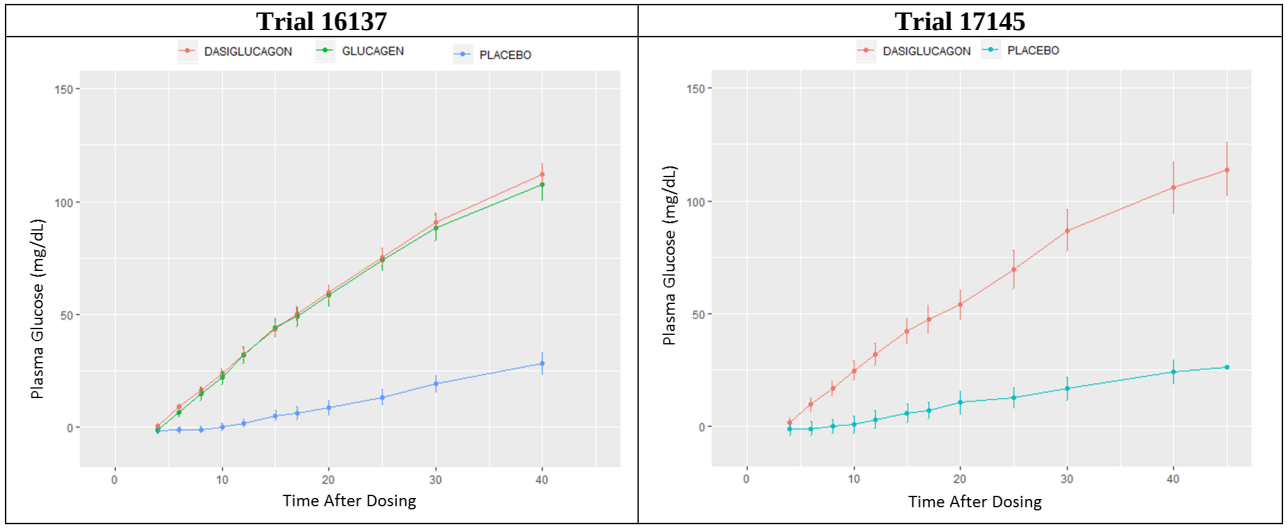
Table 10. Secondary endpoint: Plasma Glucose Change (LS mean (SE)) from baseline to 30, 20, 15, and 10 minutes

	Trial 16137		***Trial 17145***		***Trial 17086***	
	Dasiglucagon N=82 LS mean (SE)	*Placebo N=43 LS mean (SE)*	*Dasiglucagon N=34 LS mean (SE)*	*Placebo N=10 LS mean (SE)*	*Dasiglucagon N=20 LS mean (SE)*	*Placebo N=11 LS mean (SE)*
at 30 min	91.1 (1.9)	19.1(2.5)	85.4 (4.4)	15.6(8.1)	98.2(4.4)	17.3(4.7)
at 20 min	59.7(1.5)	8.7(2.1)	53 (3)	10 (5.6)	65.4(3.5)	7.3(4.0)
at 15 min	43.6 (1.2)	5.1 (1.7)	41.7 (2.6)	5.3(4.8)	45.3(3.4)	0.8 (3.4)
at 10 min	24.0 (0.9)	-0.14 (1.3)	24.6 (1.9)	0.7(3.6)	27.2 (3.1)	-3.4(2.4)

Source: Statistical reviewer's analysis

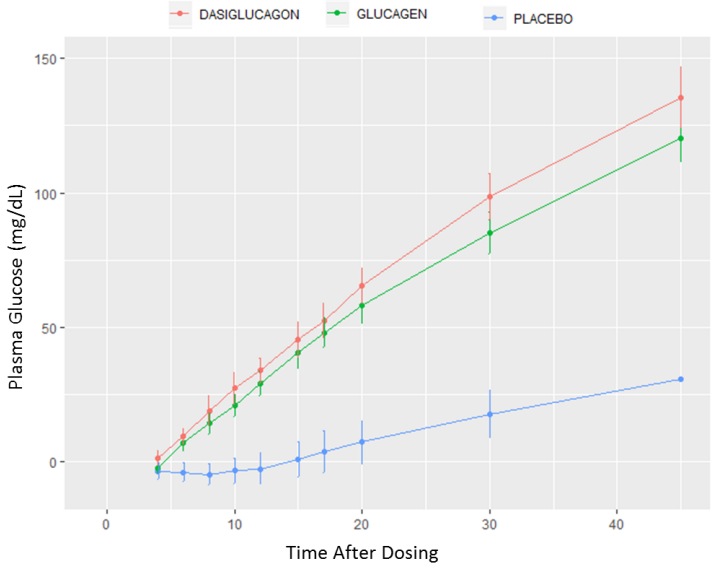
Figures 4 and 5 illustrated plasma glucose change (mg/dL) from baseline over time after dosing in Trials 16137, 17145 and 17086, respectively, for a descriptive visualization of slopes for a recovery to check in terms of the speed of recovery.

Figure 4. Plasma Glucose Mean Changes from baseline (95%CI) over Time after Dosing by Each Treatment group in Trial 16137 & Trial 17145



Source: Statistical reviewer's analysis

Figure 5. Plasma Glucose Mean Changes from baseline (95%CI) over Time after Dosing by Each Treatment group in the Trial 17086



Source: Statistical reviewer's analysis

As additional information, average rates (mg/dL per minute) of difference in plasma glucose divided by time between assessed time points within 45 minutes were shown in Table 11. The recovery rates of dasiglucagon was greater than placebo and GlucaGen®.

Table 11. Average rates (mg/dL per minute) of Difference in Plasma Glucose divided by Time Between Assessed Time Points within 45 minutes in Trials 16137, 17145 and 17086

	dasiglucagon mg/dL/minute	***Placebo*** mg/dL/minute	***GlucaGen®*** mg/dL/minute
Trial 16137	3.2	0.6	3.1
Trial 17145	2.8	0.6	NA
Trial 17086	3.4	0.5	3.1

Source: Statistical reviewer's analysis

Figures A1, A2, and A3 in the Appendices are scatter plots of time to plasma glucose recovery with baseline plasma glucose for each trial. No other issues were identified regarding the speed of plasma glucose recovery and baseline plasma glucose impacts on time to plasma glucose recovery.

Time to first plasma glucose concentrations ≥ 70 mg/dL without administration of rescue IV glucose was also assessed as a PD endpoint in adult trials (Trials 16137 and 17145). In Trial 16137, median time to first plasma glucose concentrations ≥ 70 mg/dL without administration of rescue IV glucose were 8 minutes [95% CI: 6, 8] in dasiglucagon group and 25 minutes [95 % CI: 20, 30] in the placebo group. In Trial 17145, median time were 9 minutes [95% CI: 8, 10] in dasiglucagon and 27 minutes [95% CI: 12, 40] in the placebo group. In pediatric trial (Trial 17086), the targeted plasma glucose for insulin-induced hypoglycemia was between 54 and 80 mg/dL, and 70% of subjects had baseline plasma glucose ≥ 70 mg/dL. Thus, in pediatric trial, this PD endpoint was not informative.

3.2.4.3 Supportive Efficacy from Bridging Study of dasiglucagon Two Different Batches

Trial 17084 was a bridging study to show non-inferiority of the efficacy of a single SC dose of dasiglucagon Batch B (dual storage condition) relative to that of dasiglucagon Batch A (refrigerated condition).

There were no subjects who received the rescue IV glucose or censored at 45 minutes in either period. Neither period effect and nor sequence (carry-over) effect was detected (ANOVA 2-sided p-values= 0.62 (period); 0.24 (sequence)). The difference of Batch B versus Batch A was 0.4 minutes (95% CI: -0.08, 0.88) using PPS and linearly interpolated time points as the applicant's primary analysis in Table 11. This reviewer validated the results using FAS and observed time to recovery without interpolation. The difference was 0.58 minutes (95% CI:0.005, 1.17) with no period (p-value =0.63) and sequence (p-value= 0.15) effect.

Upper limits of mean difference in time to recovery are all within NI margin 2 minutes (0.88 minutes (53 second), 1.17 minutes (1 minute 10 seconds) and 1.25 minutes (1 minute 15 seconds)) in all analyses in Table 11. Non-inferiority of Batch B to Batch A was established.

Table 12. Time to Plasma Glucose Recovery and the Difference between Batch A and Batch B in Trial 17084

	Analysis Population	*Recovery Time*	*Batch A*	*Batch B*	*Difference in minutes (Batch B vs Batch A)*
			Mean (SD)	**Mean (SD)**	**Mean (95% CI)**
Sponsor'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 (0.005, 1.17)
Sponsor's sensitivity	PPS	Observed	10.10 (2.68)	10.70 (3.18)	0.64 (0.03, 1.25)

** 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: Statistical reviewer's analysis

Figure A4 in Appendices illustrated the mean of plasma glucose changes after dosing by Batch A and Batch B over time in minutes. Both curves from Batch A and Batch B overlapped almost identically.

3.2.4.4 Efficacy Evaluation Conclusion

All three pivotal efficacy trials (Trials 16137, 17145 and 17086) demonstrated the superiority of dasiglucagon compared to placebo for the primary endpoint, time to plasma glucose recovery from insulin-induced hypoglycemia. The median time to recovery in the dasiglucagon was significantly shorter than the one in the placebo group (10 minutes versus over 35 minutes). Key secondary endpoints also demonstrated the superiority of dasiglucagon with the greater proportions of recovered subjects within 10, 15, 20, and 30 minutes and with larger mean changes in plasma glucose compared to placebo starting at 10, 15, 20 and 30 minutes after dosing. The time to plasma glucose recovery with dasiglucagon was also supportive from results of two different batches in the supportive efficacy trial, Trial 17084 shown the mean time to recovery is 10.28 minutes in Batch A and 10.84 minutes in Batch B.

Overall, efficacy of dasiglucagon S.C 0.6mg demonstrated robust and strong benefit compared to placebo in both adults and pediatric studies to support a new indication for treatment of severe hypoglycemia in patients with diabetes aged 6 years and above.

3.3 Evaluation of Safety

The safety analysis set was defined as all randomized patients who received at least one dose of study treatment that is the same as FAS. Full safety evaluations for this submission were performed by the clinical reviewer, Dr. Kristen Pluchino. Refer to clinical review for more details regarding the safety findings of dasiglucagon.

In this review, three selected safety variables (nausea, vomiting, and hypoglycemia) were evaluated for pivotal efficacy trials (Trials 16137, 17145, and 17086). Two adult studies were pooled and the percentage of patients were adjusted using Cochran-Mantel-Haenzsel weighting method for different randomization ratio of each study. The results of GlucaGen® were also shown for a guide of other glucagon receptor agonist product.

There are 56.5% and 24.6% of subjects in the dasiglucagon group had nausea and vomiting, respectively; while 4.1% and 1.8% of subjects in the placebo group had nausea and vomiting, respectively, in the pooled adult studies (Table 12). Similar to dasigcluagon group proportions of subjects in the GlucaGen® had nausea (53%) and vomiting (21%) as adverse events, but these numbers came from Trial 16137 only because there was no active control arm in Trial 17145.

Table 13. Selected Adverse Events for Placebo-Controlled Pool for Adult Trials (16137 & 17145)

	dasiglucagon (N=116) n* (%) E**	***Placebo (N=53) n* (%) E*****	***GlucaGen® (N=43) n* (%) E*****
Nausea	66 (56.5) 67	2 (4.1) 2	23 (53.5) 23
Vomiting	29 (24.6) 36	1 (1.8) 1	9 (20.9) 11

**n: number of subjects; **E; number of episodes of adverse events*
Source: statistical reviewer's analysis

In the pediatric study (Trial 17086), 65% of subjects in the dasiglucagon group had nausea while no subjects had nausea in the placebo group (Table 13). 50% of subjects in the dasiglucagon group had vomiting while no subjects had vomiting in the placebo group. Most of subjects had nausea (11 out of 13) or vomiting (8 out of 10) were between 12 and 17 years old in the dasiglucagon group.

Table 14. Selected Adverse Events for Pediatric Trial (17086)

	dasiglucagon (N=20) n* (%) E**	***Placebo (N=11) n* (%) E*****	***GlucaGen® (N=10) n* (%) E*****
Nausea	13 (65) 14	0	3 (30) 4
Vomiting	10 (50) 13	0	1 (10) 1

**n: number of subjects; **E; number of episodes of adverse events*
Source: statistical reviewer's analysis

Hypoglycemic episodes after dosing study treatment per arm per trial as adverse events of counting during entire observation period and of counting within 12 hours of dosing are presented in Table 14. All hypoglycemic episodes were mild or moderate in severity except only one episode determined as severe hypoglycemia in the dasiglucagon group in Trial 17145 timed at 5 minutes after dosing. In Trial 16137, higher proportions of subjects had hypoglycemic episodes during entire observation period in the dasiglucagon group compared to the placebo group and the GlucaGen group. In two other trials, proportions of subjects who had hypoglycemic episodes during entire observation period in the dasiglucagon group were comparable or lower than placebo.

Table 15. Hypoglycemia Episodes in Three Pivotal Trials

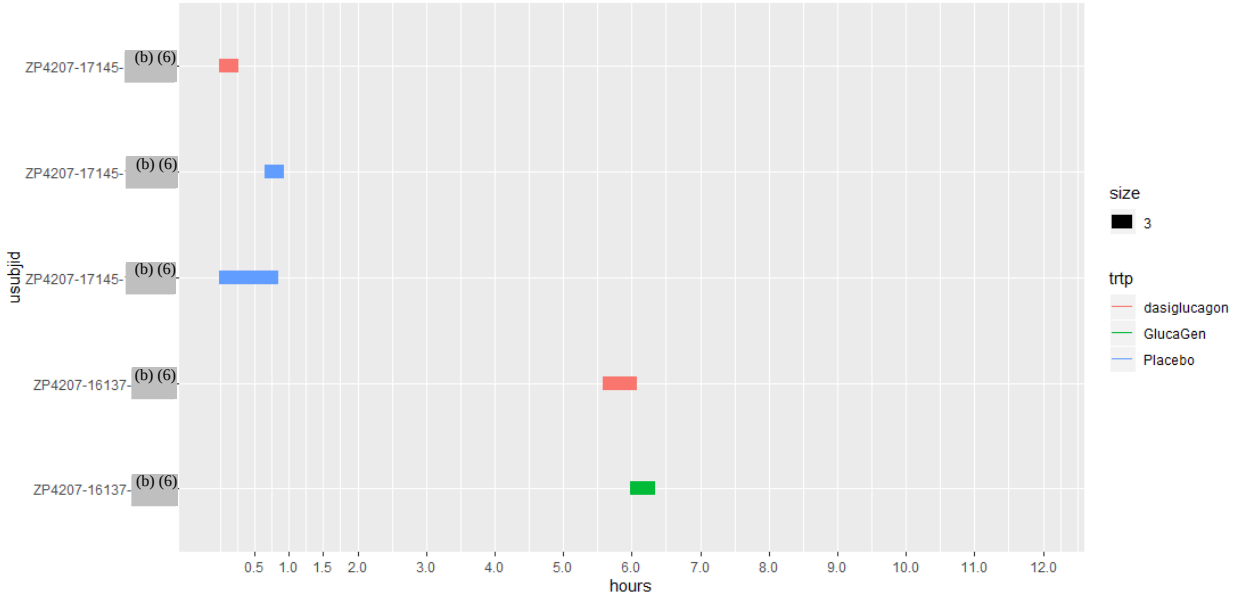
	dasiglucagon n* (%) E**	***Placebo n* (%) E*****	***GlucaGen® n* (%) E*****
16137			
Safety Analysis Set	82	43	43
Entire observation period	23 (28.0) 39	5 (11.6) 6	9 (20.9) 10

Within 12 hours of dosing	1 (1.2) 1	0	1 (2.3) 1
17145			
Safety Analysis Set	34	10	0
Entire observation period	6 (17.6) 29	2 (20) 3	NA
Within 12 hours of dosing	1 (2.9) 1	2 (20) 2	NA
17086			
Safety Analysis Set	20	11	10
Entire observation period	2 (10) 2	4 (36.4) 16	2 (20) 2
Within 12 hours of dosing	0	1 (10) 1	0

[*]n: number of subjects; [**]E; number of episodes of adverse events
Source: statistical reviewer's analysis

Hypoglycemic episodes within 12 hours of dosing were occurred in five subjects (3 in Trial 17145 and 2 in Trial 16137) with no notable pattern related to study drug. Figure 4 illustrated the start time of hypoglycemia with resolution time of five subjects (red: dasiglucagon group, green: GlucaGen, blue: placebo). Three subjects (1 in the dasiglucagon (red bar), 2 in the placebo (blue bar)) in the Trial 17145 received a rescue IV glucose within 1 hour after dosing.

Figure 6. Hypoglycemic Episodes Within 12 Hours With Resolution Time



Source: statistical reviewer's analysis

Safety Conclusion

For nausea and vomiting, proportions of events were higher in the dasiglucagon group compared to the placebo group. However, clinical reviewer confirmed that these adverse events were known to be common side-effects for glucagon-receptor agonist. Furthermore, these adverse events were considered relatively mild symptoms compared to potential fatality due to delay of the recovery from severe hypoglycemia. Most hypoglycemic episodes were mild and moderate severity. Overall, no new safety concern was raised in this review.

3.4 Benefit-Risk Assessment

This statistical evaluation confirmed that three pivotal efficacy trials demonstrated a robust and significant superiority benefit of dasiglucagon compared to placebo in time to recovery from severe hypoglycemia. Despite the higher proportions of common adverse events with dasiglucagon, clinically meaningful benefit of dasiglucagon to reduce time to recovery outweighs the risk of common adverse events.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For subgroup analysis of efficacy, the applicant pooled the data from a phase II dose-finding study, Trial 15126 (dasiglucagon 0.6 mg arm only), and the data from a phase III bridging study, Trial 17084 (Batch A arm only) with the data from two pivotal phase III adult studies (Trials 16137 and 17145). At the pre-NDA meeting (IND127,866) on December 19, 2019, Agency recommended using the placebo-controlled trials only for pooling the data for the subgroup analysis. Also, no additional information were added to the small sample sized subgroups (white or ≥ 65 years old group) and placebo groups using a dose-finding study and a bridging study. In this review, two pivotal placebo-controlled adult studies (Trials 16137 and 17145) were pooled and used for the subgroup analysis.

Subgroup analyses using the primary efficacy analysis (i.e., Kaplan-Meier estimates for median time to recovery and 95% CI, log-rank test) were performed. Subgroups are defined by sex (Female vs. Male), age (≥ 65 vs. < 65), race (White, African American, and Others), ethnicity (Hispanic/Latino, Non-Hispanic/Latino), geographic region (US, outside of US), injection site (Abdominal, Buttock, Deltoid, and Thigh) and BMI (<25, 25-30, 30-35, ≥35) for adult studies or weight (20-40 kg, ≥ 40kg) for a pediatric study in this review. In adult studies, because majority of population were whites and younger than 65 years old given relatively small sample size, there were insufficient number of subjects in the subgroup of older than 65 years of age, and other races except white. In pediatric study with limited sample size (20 subjects in the dasiglucagon versus 11 subjects in the placebo), all subjects except 1 subject were white. Thus, the subgroup analysis of race in pediatric study was not performed.

The applicant used the log-rank test stratified by the subgroup using the pooled data from the dasiglucagon group only without the placebo group for checking the subgroup effects within dasiglucagon group. Because the purpose of subgroup analyses was to check for the heterogeneity of treatment effect (dasiglucagon versus placebo) across subgroups, this reviewer used Cox regression model including the interaction term between treatment group and subgroup stratified by injection site and study. No interaction test between any subgroup and treatment group was significant (all p-values for interaction terms from cox regression model are > 0.1).

In the integrated summary of efficacy report from the applicant, the applicant did not illustrate the placebo group results in the forest plot. The applicant showed the efficacy results, median time to plasma recovery with 95% confidence interval, only for the dasiglucagon group. Because efficacy of dasiglucagon is established by showing the superiority compared to the placebo,

results from both groups should be presented for the subgroup analysis. To visualize the efficacy results by subgroups overall, this reviewer used recovery time ratio (see Section 3.2.2) of dasiglucagon over placebo and 95 % CI in the forest plot.

4.1 Gender, Race, Age, and Geographic Region

Consistent superiority of dasiglucagon compared to placebo across subgroups was found within the range of 10 minutes to 15 minutes in median time to recovery in the dasiglucagon group versus within the range of 20 minutes to 40 minutes in median time to recovery in the placebo group for the pooled adult trials (Table 15). This table of subgroup results will be published in Drug Trials Snapshot[2] if dasiglucagon is approved.

Table 16. Time to Plasma Glucose Recovery from Severe Hypoglycemia by Subgroups (Pooled Pivotal Placebo-Controlled Adult Trials – Trial 16137 and Trial 17145)

DEMOGRAPHIC PARAMETERS	DASIGLUCAGON S.C 0.6 MG		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, ∞)
Female	50 (49)	10 minutes [8, 10]	17 (15)	30 minutes [20, 40]
Age				
Below 65 years	111 (110)	10 minutes [10, 10]	52 (37)	40 minutes [30, 40]
65 years and above	5 (5)	15 minutes [15, ∞)	1 (1)	30 minutes [0, ∞)
Race				
White	110 (109)	10 minutes [10, 10]	46 (35)	35 minutes [30, 40]
African American	1 (1)	12 minutes [0, ∞)	2 (2)	37.5 minutes [30, ∞)
Others	5 (5)	10 minutes [8, ∞)	5 (1)	20 minutes [0, ∞)
Geographic Region				
US	34 (33)	10 minutes [8, 12]	10 (7)	35 minutes [20, ∞)
Outside of US	82 (82)	10 minutes [10, 10]	43 (31)	40 minutes [30, 40]
Ethnicity				
Hispanic or Latino	6 (6)	10 minutes [8, ∞)	5(4)	30 minutes [25, ∞)
Not Hispanic or Latino	116 (115)	10 minutes [10, 10]	53 (38)	40 minutes [30, 40]

*Note: Time to plasma glucose recovery were monitored at pre-dose, 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, and 45 minutes within 45 minute censoring time *N: number of subject in the subgroup; **n: number of subjects who recovered within 45 minutes after dosing without a rescue IV glucose administration;*
Source: statistical reviewer's analysis

Consistent superiority of dasiglucagon compared to placebo across was found within the range of 8 minutes to 12 minutes in median time to recovery in the dasiglucagon group versus within the range of 25 minutes to 45 minutes in median time to recovery in the placebo group for the pediatric trial, Trial 17846 (Table 16).

[2] Dasiglucagon is NME that is made of new molecular structures that have not been approved by the Agency before. Drug Trials Snapshots provide demographic data information with efficacy subgroup analysis results.

Table 17. Time to Plasma Glucose Recovery from Severe Hypoglycemia by Subgroups (Pediatric Trial – Trial 17086)

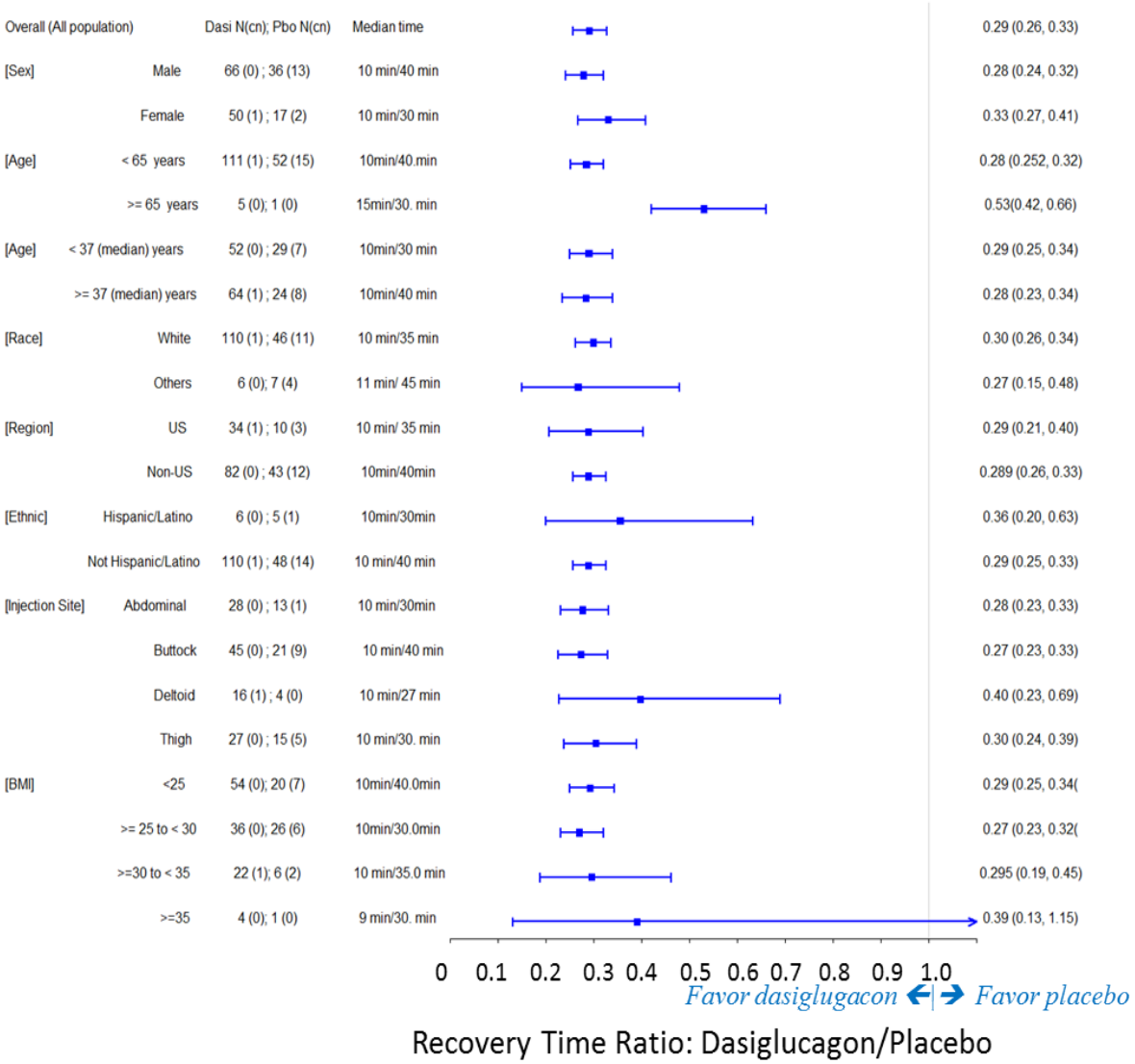
DEMOGRAPHIC PARAMETERS	DASIGLUCAGON S.C 0.6 MG		PLACEBO	
	N* (n**)	Median Time to Plasma Glucose Recovery (95% CI)	N* (n**)	Median Time to Plasma Glucose Recovery (95% CI)
Overall				
	20 (20)	10 minutes [8, 12]	11 (7)	30 minutes [20, ∞)
Sex				
Male	10 (10)	10 minutes [8, 12]	5 (3)	45 minutes [30, ∞)
Female	10 (10)	9 minutes [8, 12]	6 (4)	30 minutes [17, ∞)
Age				
6-11 years	8 (8)	9 minutes [8, 12]	4 (3)	25 minutes [17, ∞)
12-17 years	12 (12)	10 minutes [8,12]	7 (4)	45 minutes [30, ∞)
Geographic Region				
US	13 (13)	10 minutes [8, 12]	9 (7)	30 minutes [17, ∞)
Outside of US	7 (7)	8 minutes [8, 12]	2 (0)	NA***
Ethnicity				
Hispanic or Latino	4 (4)	12 minutes [8, 17]	2 (1)	30 minutes [30, ∞)
Not Hispanic or Latino	16 (16)	10 minutes [8, 10]	8 (5)	37.5 minutes [20, ∞)

*Note: Time to plasma glucose recovery were monitored at pre-dose, 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, and 45 minutes within 45 minute censoring time *N: number of subject in the subgroup; **n: number of subjects who recovered within 45 minutes after dosing without a rescue IV glucose administration; *** NA: No subjects were recovered.*
Source: statistical reviewer's analysis

Figure 5 illustrated the forest plot of recovery time ratio with 95 % CI to compare overall efficacy results across subgroups for adult studies. The recovery time ratio for overall population from the pooled placebo-controlled adult trials was 0.29 (0.26, 0.33). The recovery time ratio of each subgroup was within the range of 0.27 to 0.53, consistently showing less time to recovery in the dasiglucagon group compared to time to recovery in the placebo group (i.e., the recovery time ratio is less than 1 (grey vertical line in Figure 5)).

The geriatric group (≥ 65 years of old) showed the larger recovery time ratio (0.53) than the overall population (0.29). The highest BMI group (≥ 35) showed the larger CI including 1 for the recovery time ratio. Because these two groups have insufficient number of subjects (less than 5), the results of these subgroups cannot be concluded reliably.

Figure 7. Forest Plot of Recovery Time Ratio by Subgroups (Pooled Pivotal Placebo-controlled Adult Trials)



** N(cn): sample size (censored subjects);The last column of the forest plot is survival time ratio (95% CI) in each subgroup.*
Source: statistical reviewer's analysis

4.2 Other Special/Subgroup Populations

No major difference of treatment effects of dasiglucagon compared to placebo were found in the subgroups by injection site (Abdominal, Buttock, Deltoid, and Thigh) and BMI (<25, 25-30, 30-35, ≥35) for adult studies (Figure 5) or weight (20-40 kg, ≥ 40kg) for a pediatric study (data not shown).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There was no major statistical issue regarding efficacy evaluation of dasiglucagon supported by the statistical findings in Section 5.2. Collective Evidence. Minor statistical issues of presentation of subgroup analysis results and presentation of figure in the labeling were addressed in Section 5.4 Labeling Recommendations.

5.2 Collective Evidence

- **Robustness of superiority in time to plasma glucose recovery from insulin-induced hypoglycemia:** All three pivotal efficacy trials (Trials 16137, 17145 and 17086) demonstrated the superiority of dasiglucagon compared to placebo in time to plasma glucose recovery from insulin-induced hypoglycemia. The primary analysis results for primary endpoint as well as key secondary endpoints established the strong and robust evidence to support the superiority of dasiglucagon compared to placebo (**Tables 7, 8, 9 and 10**). The median time to recovery in the dasiglucagon was significantly shorter than one in the placebo group (10 minutes versus over 35 minutes). The time to plasma glucose recovery with dasiglucagon was also supportive from results in the supportive efficacy trial, Trial 17084 shown the mean time to recovery is 10.28 minutes (**Table 11**).

- **Subgroup analysis results and a presentation in Drug Trials Snapshot**: Consistent superiority of dasiglucagon compared to placebo in time to plasma glucose recovery was found across subgroups (**Tables 15 and 16; Figure 5**). For a presentation of subgroup analysis results, both results from the dasiglucagon group and the placebo group were tabularized in a table format. If dasiglucagon is approved, then these tables for the pooled adult studies and for the pediatric study will be published in Drug Trials Snapshot that is required by all NME approvals.

- **Cumulative proportions of subjects with recovery over time:** Two distinct curves of cumulative proportions of subjects with recovery over time for both dasiglucagon and placebo groups were visualized explicitly the difference between two groups with information of the starting recovery time and the accumulative proportions of subjects with recovery across time after dosing (**Figures 2 and 3**). These figures helped to confirm the superiority of dasiglucagon for earlier and fast time in recovery after dosing. These figures were more informative to compare two groups than the applicant's figure of a single cumulative recovery curve for the dasiglucagon group only without the one for the placebo group in the proposed labeling.

- **Benefit-risk results:** There were higher frequency of nausea and vomiting in the dasiglucagon group compared to placebo. However, these adverse events were common side-effects for glucagon-receptor agonist and were considered relatively mild symptoms

compared to potential fatality caused from delay of the recovery from severe hypoglycemia (**Section 3.3 and 3.4**). Most of hypoglycemic episodes were mild and moderate severity without any issue of resolution (**Figure 4**). Despite the higher proportions of common adverse events with dasiglucagon, clinically meaningful efficacy benefit of dasiglucagon to reduce time to recovery outweighs the risk of common adverse events in this review.

5.3 Conclusions and Recommendations

Robust and strong evidence for superiority of dasiglucagon S.C. 0.6 mg was demonstrated in adequate and well-controlled two clinical trials for adults and one clinical trial for children of 6 years and above. There were no notable safety signal or risk outweighed benefits of dasiglucagon compared to placebo.

In conclusion, all three pivotal efficacy trials support the superiority of dasiglucagon 0.6 mg in time to plasma glucose recovery compared to placebo. This reviewer recommends approval of a new indication and adding information in CLINICAL STUDIES section in the label. However, figures in the proposed labeling need to be revised. Recommendations for labeling are following in Section 5.4.

5.4 Labeling Recommendations

In the proposed labeling from the sponsor, this reviewer agrees to add a new indication for treatment of severe hypoglycemia in patients with diabetes aged 6 years and above and clinical trial information of pivotal efficacy trials in Section 14 with some revisions. This reviewer recommends adding the curve from the placebo groups in the figures of cumulative proportions of subjects with recovery over time for the placebo-controlled adult and pediatric studies.

In Section 8.5, the applicant proposed the geriatric use including following language:

(b) (6)

Because there were insufficient number of patients 65 year of age and older in placebo-controlled clinical trials, this reviewer suggests using the language from the guidance[3] as following:

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

In Drug Trials Snapshot if dasiglucagon is approved, this reviewer recommends using Tables 15 and 16 to present the subgroup analysis results to compare dasigcluagon with placebo.

[3] Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry, ***Draft Guidance for Industry,*** September 2020

APPENDICES

Figure A 1. Time to Plasma Glucose Recovery versus Baseline Plasma Glucose in the Trial 16137

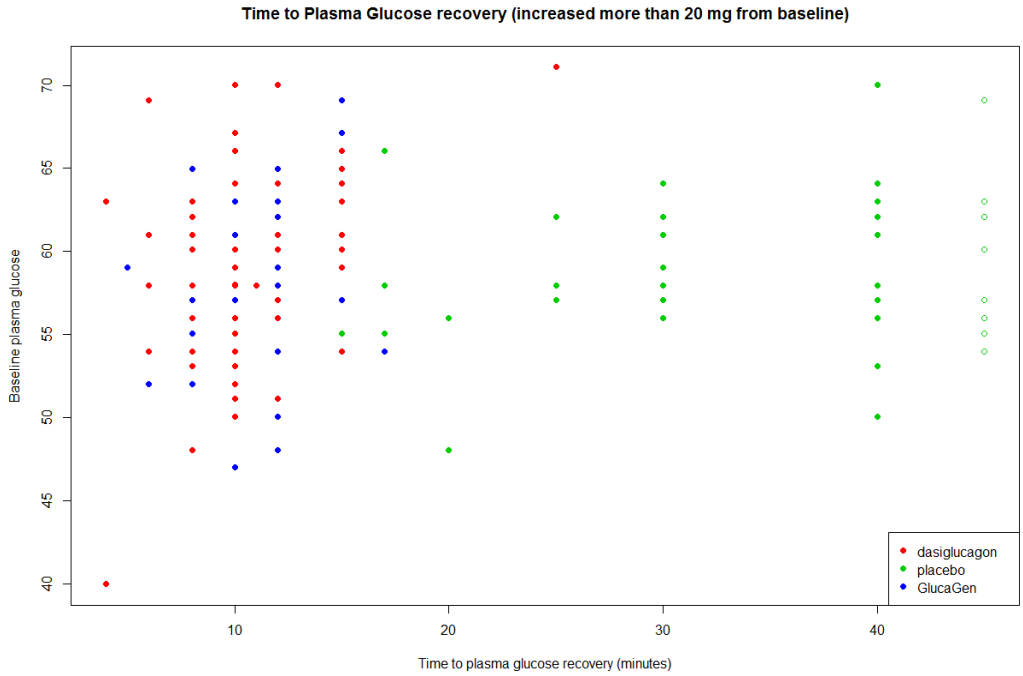


Figure A 2. Time to Plasma Glucose Recovery versus Baseline Plasma Glucose in the Trial 17145

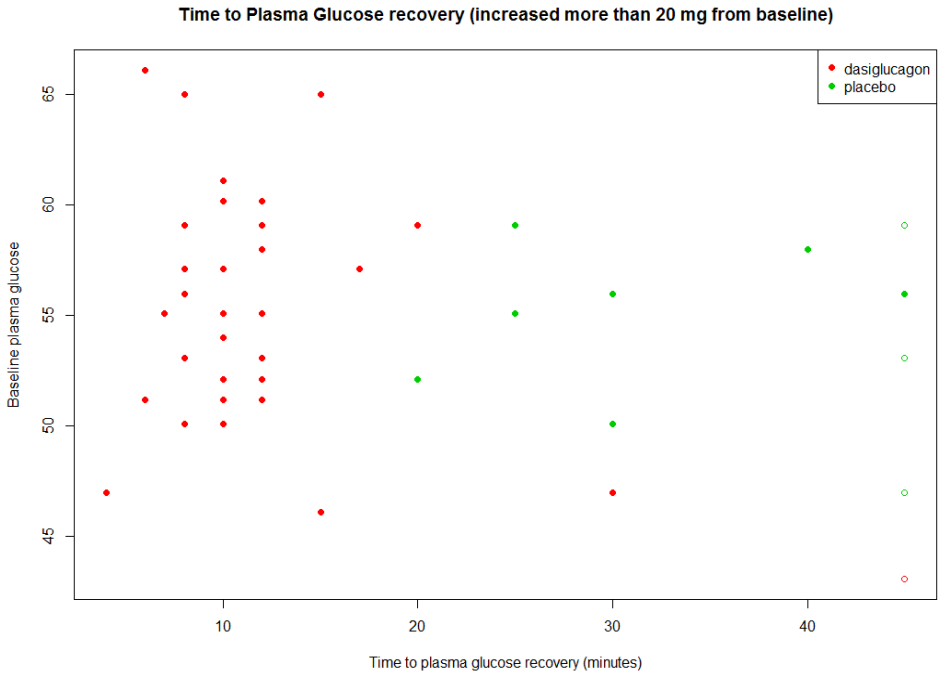


Figure A 3. Time to Plasma Glucose Recovery versus Baseline Plasma Glucose in the Trial 17086

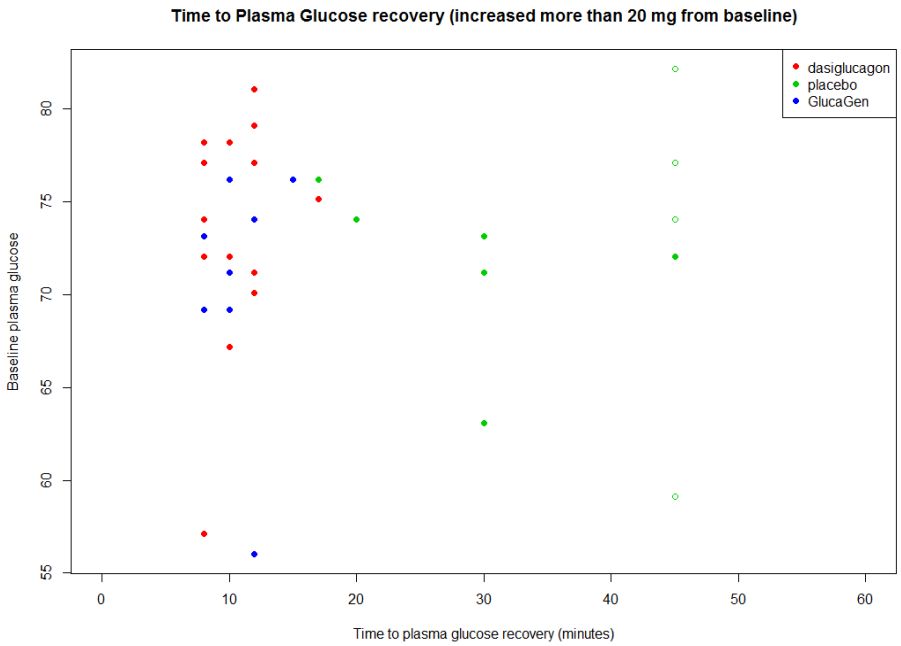
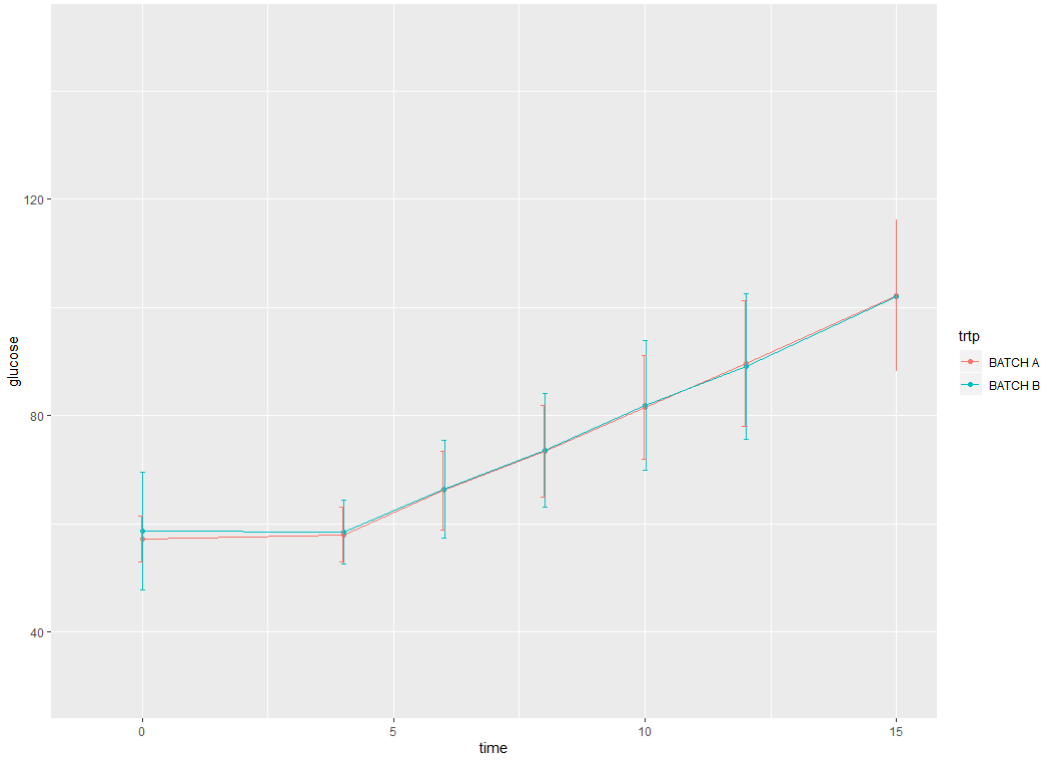


Figure A 4. Plasma Glucose (mg/dL) Levels and Time to Recovery by Batch in Trial 17084



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/s/

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