PROTOCOL TITLE: A Two-Period, Open-label Trial Evaluating the Efficacy and Safety of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism

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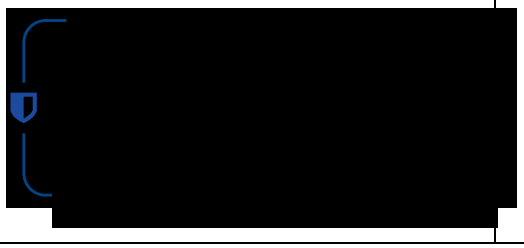
Zealand Pharma A/S Representative	Print Name: [redacted] Sign Name: 	13-nov-2020 | 01:26:24 PST

Document History

Version	Date	Author	Description
Final 1.0	13OCT2020	[redacted]	Initial Version
Final 2.0	12NOV2020	[redacted]	Restrict evaluation of endpoints related to gastric carbohydrates to the relevant subgroup and move the key secondary efficacy endpoint related to gastric carbohydrates to secondary efficacy endpoints. Update derivation of Extent of hypoglycemia to take into account duration of period. Remove one sentence on Interim analysis which is not applicable Update hypoglycemic event baseline derivation for subject 204501. Clarify fasting tolerance test derivation. Add sensitivity analysis on fasting tolerance test. Add imputation for non-event data missing not due to discontinuation
Final 3.0	13NOV2020	[redacted]	Remove reference to section 4.2.1 and explain DMC process Update PedsQL reference

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Zealand Pharma A/S protocol number ZP4207-17109 (A Two-Period, Open-label Trial Evaluating the Efficacy and Safety of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism), dated 12-Nov-2020 Version 13.0 for all countries except Germany, and protocol dated 12-Nov-2020 Version 14.0 for Germany. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to the trial master file prior to any unblinded inferential or descriptive analysis of data pertaining to Zealand Pharma A/S's study ZP4207-17109. For this study, only the continuous glucose monitoring (CGM) data will be blinded/masked.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of dasiglucagon administered as a subcutaneous (SC) infusion in reducing hypoglycemia in children with congenital hyperinsulinism (CHI).

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety and tolerability of dasiglucagon administered as an SC infusion in children with CHI
- To evaluate the efficacy of dasiglucagon in reducing glucose requirements
- To investigate quality of life and resource utilization

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is:

Treatment Period 1

- SMPG-detected hypoglycemia episode rate, defined as average weekly number of hypoglycemia episodes (plasma glucose [PG] <70 mg/dL or 3.9 mmol/L) during Weeks 2-4, as detected by self-monitored plasma glucose (SMPG).

2.2.1.2. Key Secondary Efficacy Endpoints

Key secondary efficacy endpoints of this study include the following:

Treatment Period 1

- Increase in fasting tolerance (time from beginning of meal to the beginning of the first continuous 15-minute CGM reading <70 mg/dL [3.9 mmol/L]).
- CGM percent time in range 70-180 mg/dL (3.9-10.0 mmol/L) during Weeks 2-4.
- Clinically significant SMPG-detected hypoglycemia episode rates, defined as average weekly number of episodes <54 mg/dL (3.0 mmol/L), as detected by SMPG during Weeks 2-4.

2.2.1.3. Secondary Efficacy Endpoints

Treatment Period 1

- Endpoints to be analyzed on the subgroup of patients having Gastrostomy or NG-tube at screening:
  - Total amount of gastric carbohydrates administered (via nasogastric [NG] tube or gastrostomy) per week to treat hypoglycemia during Weeks 2-4.
  - Rate of gastric carbohydrate administrations (NG tube or gastrostomy) per week to treat hypoglycemia during Weeks 2-4.
  - Amount of nightly (midnight to 6 am) gastric carbohydrates administered (NG tube or gastrostomy) per week during Weeks 2-4.
  - Total amount of gastric carbohydrates administered (NG tube or gastrostomy) per week during Weeks 2-4.

- Endpoints to be analyzed on whole population:
  - Extent of hypoglycemia (area over the glucose curve [$AOC_{glucose}$] below 70 mg/dL [3.9 mmol/L]) as measured by CGM during Weeks 2-4.
  - Extent of hypoglycemia (area over the glucose curve [$AOC_{glucose}$] below 54 mg/dL [3.9 mmol/L]) as measured by CGM during Weeks 2-4.

- CGM percent time in hypoglycemia (<70 mg/dL or 3.9 mmol/L) during Weeks 2-4.
- CGM-detected hypoglycemia episode rate, defined as number of episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more per week, as measured by CGM during Weeks 2-4.

Treatment Period 2

- Endpoints to be analyzed on the subgroup of patients having Gastrostomy or NG-tube at screening:
  - Rate of weekly number of gastric carbohydrate administrations (NG tube or gastrostomy) per week to treat hypoglycemia during Weeks 6-8.

- Endpoints to be analyzed on whole population:
  - CGM percent time in hypoglycemia (<70 mg/dL or 3.9 mmol/L) during Weeks 6-8.
  - SMPG-detected hypoglycemia episode rate, defined as number of episodes (PG <70 mg/dL or 3.9 mmol/L) per week during Weeks 6-8, as detected by SMPG.
  - Clinically significant CGM-detected hypoglycemia episode rate, defined as number of episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more per week, as measured by CGM during Weeks 6-8.

2.2.2.4 Other Efficacy Endpoints

- Number of intravenous (IV) glucose infusions to treat hypoglycemia per week during Weeks 2-4 of Treatment Period 1.
- Emergency department visits for hypoglycemia.
- Number and length of hospitalizations due to CHI or CHI-related events.
- Number of out-patient visits to health care providers (family doctors, specialist, etc.) caused by CHI or CHI-related events.
- Number of home visits by paramedics due to hypoglycemia.
- Quality of life endpoints (Pediatric Quality of Life Inventory™ [PedsQL] [Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score] and CHI-specific questionnaire).
- Rate of SMPG readings per week during Weeks 2-4 of Treatment Period 1.

2.2.2. Safety Endpoints

The safety endpoints of this study include the following:

- Adverse events (AEs)
- Changes in clinical evaluations:
  - Vital signs
  - Physical examination
  - 12-lead electrocardiogram (ECG)
- Changes for clinical laboratory assessments:

- Hematology
- Biochemistry
- Antidrug antibodies (ADAs)

2.2.3. Pharmacokinetics

Blood samples will be collected twice during the trial to measure for dasiglucagon levels at steady-state on Weeks 6 and 9.

3. Overall Study Design and Plan

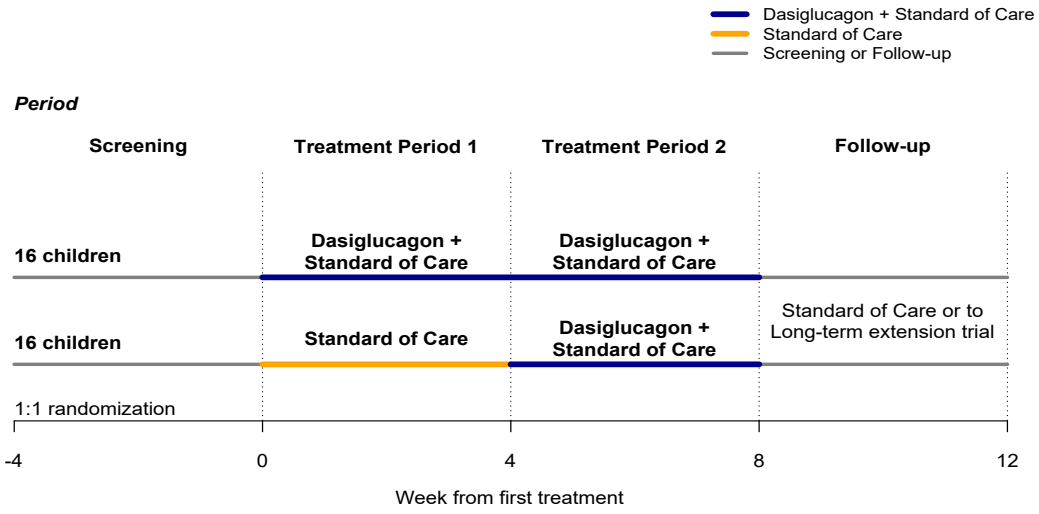
This is a phase 3, 2-period open-label study for the treatment of patients with CHI. The objective of this to evaluate the efficacy and safety of dasiglucagon in children between the ages of 3 months and 12 years who experience ≥3 hypoglycemia episode per week despite receiving standard of care (SOC). Approximately 32 patients will be included in this study. Patients meeting entry criteria into the study will have to complete a 2-week CGM period to establish plasma glucose baseline. Once this is complete, the patients are randomized in a 1:1 ratio to continue receiving SOC alone or dasiglucagon + SOC for 4 weeks in Treatment Period 1. In Treatment Period 2, all patients will receive dasiglucagon + SOC for 4 weeks.

All patients will be hospitalized for 1-2 days and trained in using CGM sensor and glucometer. Participants who are randomly assigned to dasiglucagon + SOC will have dasiglucagon infusion initiated and titrated and be trained with infusion pump. Patients who were assigned to SOC alone during Treatment Period 1 will be hospitalized for 1-2 days in Week 5 of Treatment Period 2 to have dasiglucagon infusion initiated and titrated.

No interim analysis is planned (see section 10 on changes from planned analysis).

The maximum study duration for each patient is approximately 16 weeks. The dasiglucagon treatment duration varies between 4 or 8 weeks for each patient. Figure 1 describes the study design. Patients completing the study will have choice to continue long-term trial for dasiglucagon treatment. If the patient chooses not to enter the extension trial, the study will end with a follow-up visit. The overall study design is expected to be 15 months. There will be screening which will last from 14-28 days followed by Treatment Period 1 for 4 weeks. This is followed by Treatment Period 2 and follow-up, each consisting of 4 weeks.

Figure 1: Study Design



3.1. Overall Design

3.2. Sample Size and Power

A total of up to 32 patients will be randomized if they have at least 3 events of hypoglycemia on average per week, as recorded in the diary during the 2 weeks prior to randomization. It is assumed that patients continuing on SOC will maintain a similar level through Treatment Period 1, with the number of hypoglycemia events (PG <70 mg/dL or 3.9 mmol/L) during Weeks 2-4, as detected by SMPG following a Poisson distribution with a mean of 9. The trial is powered to detect a treatment effect of 50%, hence, assuming that the number of hypoglycemia events reported for patients in the dasiglucagon group during Weeks 2-4 will follow a Poisson distribution with a mean of 4.5. At the final analysis, 32 patients will have 99% power testing at a 0.05 significance level. The overall alpha level is strongly controlled in this setting, remaining at or below 0.05.

This sample size was calculated before cancellation of interim analysis, this is why it refers to interim analysis. Cancellation of interim analysis (see Section 10), does not imply new sample size calculation.

3.3. Study Population

The study population consists of male and female patients between the ages of 3 months and 12 years (inclusive) with established CHI and experiencing ≥3 events of hypoglycemia per week despite SOC medication. Patients are to have previously undergone sub-total pancreatectomy or being treated with a non-surgical approach, having been evaluated as not eligible for pancreatic surgery.

3.4. Treatments Administered

In Treatment Period 1, patients will receive SOC only or dasiglucagon + SOC for 4 weeks based on their treatment assignment. In Treatment Period 2, all patients will receive dasiglucagon + SOC for 4 weeks.

Dosing of dasiglucagon will approximate continuous infusion by delivering small doses at frequent intervals via the infusion pump.

The pump administers 0.000025 mL/dose ~ 0.1 µg/dose (4 mg/mL formulation):

- 10 µg/hour ~ 0.5 µg every 3 min
- 20 µg/hour ~ 1 µg every 3 min
- 30 µg/hour ~ 1.5 µg every 3 min
- 40 µg/hour ~ 2µg every 3 min
- 50 µg/hour ~ 2.5µg every 3 min
- 60 µg/hour ~ 3µg every 3 min
- 70 µg/hour ~ 3.5µg every 3 min

Dasiglucagon treatment will be initiated at 10 µg/hr (t=0). Every 2 hours (t=2, 4, 6, etc.), the dose will be increased by an additional 10 µg/hr until either:

1) The patient is weaned off entirely from gastric dextrose infusion and/or glucose-fortified feeds, or
2) PG during the last 2 hours was consistently above 120 mg/dL (6.7 mmol/L), or
3) The maximum trial drug product infusion rate of 70 µg/hr is reached, or
4) AEs emerge that are considered to be related to dasiglucagon (e.g., nausea and vomiting) and limit further dose escalation

The dose of dasiglucagon should not be escalated beyond reaching the treatment objectives of PG in the range of 70-120 mg/dL (3.9-6.7 mmol/L) while approaching a normal feeding regimen according to age.

The 2-hour dose-adjustment interval will allow plasma drug levels to approach approximately steady-state before the dose is further increased. Table 1 describes maximum dose a patient can be administered over 24 hour period.

The maximum dose of dasiglucagon should not exceed 70 µg/hr (1.68 mg/day) per day and the dose can be optimized based on each patient's treatment after the first 24 hours of dose administration.

Table 1: **Initial 24-hour Maximum Dose of Dasiglucagon**

Time (hours)	0	1	2	3	4	5	6	7	8	9	10	11
Dose (µg)	10	10	20	20	30	30	40	40	50	50	60	60
Cumulative dose (µg)	10	20	40	60	90	120	160	200	250	300	360	420

Time (hours)	12	13	14	15	16	17	18	19	20	21	22	23
Dose (µg)	70	70	70	70	70	70	70	70	70	70	70	70
Cumulative dose (µg)	490	560	630	700	770	840	910	980	1050	1120	1190	1260

3.5. Method of Assigning Patients to Treatment Groups

In Treatment Period 1, patients will be randomly assigned in a 1:1 ratio to receive either SOC only or dasiglucagon + SOC for 4 weeks using a block randomization scheme stratified by region United States (US)/non-US). In Treatment Period 2, all patients will receive dasiglucagon + SOC for 4 weeks. The stratification by region addresses the difference in practice of treatment for CHI, especially the prominent difference in frequency of sub-total pancreatectomy for diffuse CHI between US/non-US.

3.6. Blinding and Unblinding

This is an open-label trial. During parts of Screening, Treatment Period 1, and Treatment Period 2, patients will have CGM performed but the results will be masked.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 2.

Table 2: Schedule of Events

Trial Period	**Screening**	***Treatment Period 1***				***Treatment Period 2***				**Follow-up**
Week		**1[b]**	**Telephone Call[c]**	**2**	**4**	**5[d]**	**Telephone Call[c]**	**6**	**9**	**12**
Day		**1**		**8**	**22**	**29**		**36**	**57**	**85**
Time window (days)	**Day -28 to -14[a]**	**±2**		**±2**	**±2**	**±2**		**±2**	**±2**	**±5**
Visit #	**1**	**2**		**3**	**4**	**5**		**6**	**7[e]**	**8**
General assessments										
Informed consent/assent	X									
Inclusion/exclusion criteria	X	X								
Randomization criteria		X								
Demography	X									
Body weight and length/height[f]	X	X				X			X	X
Medical history (including current illness)	X									
Concomitant medication	X	X		X	X	X		X	X	X
Safety Assessment										
Electrocardiogram	X	X[r]		X		X[r]		X	X	X
Echocardiography	X[g]								X	X
Vital signs[h]	X	X[s]		X	X	X[s]		X	X	X
Serum Pregnancy test[i]	X								X	X
Adverse events		X	X	X	X	X	X	X	X	X
Local tolerability		X		X	X	X		X	X	
Physical examination and neurological examination	X	X		X	X	X		X	X	X
Laboratory Assessments										
Clinical laboratory test[j]	X			X		X		X	X	X
Antibodies[k]		X[l]				X			X	X[k]
Pharmacokinetics/drug exposure								X	X	

Trial Period	**Screening**	***Treatment Period 1***				***Treatment Period 2***				**Follow-up**
Week		**1[b]**	**Telephone Call[c]**	**2**	**4**	**5[d]**	**Telephone Call[c]**	**6**	**9**	**12**
Day		**1**		**8**	**22**	**29**		**36**	**57**	**85**
Time window (days)	**Day -28 to -14[a]**	**±2**		**±2**	**±2**	**±2**		**±2**	**±2**	**±5**
Visit #	**1**	**2**		**3**	**4**	**5**		**6**	**7[e]**	**8**
Efficacy										
Continuous glucose monitoring	X (for at least 14 days prior to randomization)	Continuous[m]								
Self-monitored plasma glucose	X (for at least 14 days prior to randomization)	X (at least 3 times daily)								
Fasting tolerance test[n]	X (during active CGM period)					X[o]				
Trial Materials and reminders										
Randomization		X								
Dispense patient diary	X[p]	X		X	X	X		X		
Diary review		X		X	X	X		X	X	
QoL questionnaires[q]		X				X			X	X
Dispensing of trial product		X		X	X	X		X		

Abbreviations: CGM = continuous glucose monitoring; PG = plasma glucose; QoL = quality of life; SMPG = self-monitoring of plasma glucose; SOC = standard of care; SpO_2 = blood oxygen saturation level; W = week

Note: An unscheduled visit can occur at any time if the investigator deems it necessary for patient safety.

a Screening must occur within a minimum of 14 days to allow for solid baseline assessment.
b At the beginning of Treatment Period 1 (Week 1), all patients will be hospitalized for 1-2 days. Patients assigned to SOC plus dasiglucagon treatment will be initiated and titrated on dasiglucagon, trained in the use of the infusion pump, and supervised. Patients are assigned to SOC alone will receive a similar degree of supervision alongside the training in the use of the infusion pump. This period can be extended for both treatment groups if dasiglucagon titration has not been finalized or if training of the family/caregivers has not been completed satisfactorily.
c Patients will be contacted by the investigator by telephone the day after discharge. The investigator will ask the parent(s)/guardian if they have any questions about the trial procedures and whether their child has experienced any AEs.
d In Treatment Period 2, patients who were assigned to SOC treatment only in Treatment Period 1 will be hospitalized for the first 1-2 days of Week 5.
e Visit 7 can be used as the first visit for Trial ZP4207 17106 (long-term extension trial) if the patient is continuing in long-term extension trial.
f Length/height will be measured at Screening only.
g An echocardiogram performed within 1 month of screening can be used.
h Vital signs include blood pressure, heart rate, respiratory rate, and SpO_2.
i A serum pregnancy test will be performed for girls of childbearing potential.
j Clinical laboratory tests include hematology and biochemistry.

k Any anti-dasiglucagon antibody-positive patient (treatment induced or treatment boosted) will be monitored at an additional follow-up visit, preferably 16 weeks after the last ADA-positive sample. Patients completing the trial before the ADA screening and confirmatory assays have been approved by the FDA and who do not continue treatment in the long-term extension trial will have this additional visit 16 weeks after the end of trial visit (Visit 8).
l The sample for ADAs should be taken prior to dosing of dasiglucagon in Treatment Period 1.
m Continuous glucose monitoring is required during Weeks 2-4 of Treatment Period 1 and Weeks 6-8 of Treatment Period 2.
n The fasting tolerance test will be stopped when PG is ≤60 mg/dL (3.3 mmol/L) and then ketones, insulin, and free fatty acids will be measured.
o The fasting tolerance test at Visit 5 should take place before initiation of dosing in Treatment Period 2 but while the patient is still on CGM.
p At screening, dispense diary and instruct patients' parent(s)/guardian in its use. At all other visits, the parent(s)/guardian will return the completed diary and obtain a new one.
q The PedsQL (parent-reported versions) and CHI disease-specific questionnaires should be the first assessments performed at each visit.
r ECG should be performed at the start of the visit and at 24 ± 4 hours after initiation of trial drug for patients initiating treatment.
s Vital signs should be measured at the start of the visit and at 6 ± 1, 12 ± 2, and 24 ± 4 hours after initiation of the trial drug for patients initiating treatment.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of patients (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of patients who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of patients in the study population for the within each treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of patients in the relevant study population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all testing of statistical significance will be 2-sided with a significance level of $\alpha = 0.05$ (see Section 10 Changes from Planned Analysis).

4.2. Interim Analysis and Data Monitoring

4.2.1. Interim Analysis

No interim analysis is planned.

4.2.2. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to conduct reviews of patient safety. It is expected that DMC meetings will occur 3 times a year during the course of the study. The reviews will monitor for issues that may justify modifying, suspending, or terminating the study.

The sponsor may request additional reviews, e.g., should any other findings/issues pertaining to safety or efficacy emerge requiring DMC review. Details of the operation of the DMC will be developed in conjunction with the members of the DMC before the first meeting and will be modified as required.

Although this is an open-label study with respect to treatment assignment, CGM data collected during the course of this study will be masked as well as randomized treatment group. The CGM data will be masked for preserving standard of care, not for treatment blinding.

The DMC analysis will be performed by an independent statistician who is not the author of this plan. The independent statistician has the real randomization available and will receive the unmasked CGM data from the vendor and scramble the results for the blinded team, thus maintaining the mask. The blinded statistician will prepare the outputs for the DMC reports based on dummy randomization and masked CGM data. He will provide SAS programs for the independent statistician to use. The independent statistician will prepare the aggregate outputs based upon unmasked CGM data and real randomization list. He will provide the outputs to DMC members.

. The study team (excluding the project statistician and programming team) will see only DMC summary tables aggregated over all patients (i.e., not split by treatment) until the final database lock.

4.2.3. Zealand Pharma Safety Committee

An internal Zealand Safety Committee is constituted to perform ongoing safety surveillance of clinical trials with dasiglucagon, including this trial.

If safety signals or concerns are observed, whether based on reported serious AEs (SAEs), review of all AEs and laboratory parameters reported, or any other notification of significant findings, the Safety Committee will respond appropriately to protect the safety of the patients. The Safety Committee meets quarterly and additionally on an ad hoc basis as needed.

The data package will be delivered based on Appendix 6 of the Pharmacovigilance Agreement; the shells for the data package will be provided in a separate document.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Set (SAF):** The Safety Set is defined as all patients administered with any randomized treatment. All patients randomized to “Standard of Care Only” group will be included in Safety Set. This population will be used to provide descriptive summaries of safety data. Patients will be summarized by treatment period according to treatment received.
- **Full Analysis Set (FAS):** The FAS includes all patients in the Safety Set who have a valid (non-missing) baseline primary efficacy assessment (i.e., baseline SMPG-detected hypoglycemia episode rate). This population will be used to analyze efficacy data. Patients will be analyzed by treatment period according to planned treatment.
- **Per Protocol (PP) Analysis Set**: The PP Set will include all patients in the FAS without any major protocol deviations. This population will be used to analyze primary and key secondary endpoints as a supportive analysis. Patients will be analyzed according to planned treatment for the first treatment period only.
- **Pharmacokinetic (PK) Analysis Set:** The PK Set will include all patients in the Safety Set who have at least 1 measurement with quantifiable plasma concentration of dasiglucagon. This population will be used to provide descriptive summaries of PK data. Patients will be summarized according to treatment received.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For efficacy endpoints involving external CGM data, baseline is defined as the average weekly value over 14 days (non necessarily consecutive) before randomization.

One subject (#204501) did not meet Randomisation Criteria #3, due to wrong procedure for measuring SMPG in the two weeks prior to randomisation (SMPG measures had been taken following meals and not pre-meal as required by protocol). Correct procedure was used in the. first 2 weeks of the screening period and in that period the patient met the randomization criteria. During the data review meeting, it has been decided to use the first two weeks of the screening period of SMPG-detected hypoglycemic episodes to define baseline value for this subject.

For efficacy endpoints involving a rate or count (specifically for the primary and key secondary endpoints; e.g., SMPG-detected hypoglycemia episode rate, total amount of gastric carbohydrates administered), baseline is defined as the average weekly value during the 2-week baseline period. Otherwise, the last non-missing assessment recorded before date of randomization will be used as the baseline observation for all calculations of change from baseline. For anti-drug antibodies (ADA), baseline is last assessment recorded before first dasiglucagon dosing.

6.1.2. Adjustments for Covariates

Where statistical modelling is performed, the baseline value of that assessment will be used as a covariate.

6.1.3. Multiple Comparisons

This section details the null hypotheses for this study, which are presented in the form H_{ij}, where i = treatment period (i = 1) and j = hypothesis number (j = 1, 2, 3, 4).

The hypothesis relating to the primary endpoint is:

H_{11}: SMPG-detected hypoglycemia episode rate $_{\text{dasiglucagon}}$ = SMPG-detected hypoglycemia episode rate $_{\text{SOC only}}$

The hypotheses relating to the key secondary endpoints are:

H_{12}: Increase in fasting tolerance $_{\text{dasiglucagon}}$ = increase in fasting tolerance $_{\text{SOC only}}$

H_{13}: CGM percent time in range $_{\text{dasiglucagon}}$ = CGM percent time in range $_{\text{SOC only}}$

H_{14}: Clinically significant SMPG-detected hypoglycemia episode rate $_{\text{dasiglucagon}}$ = clinically significant SMPG-detected hypoglycemia episode rate $_{\text{SOC only}}$

A fixed-sequence statistical strategy will test the primary (Section 2.2.1.1) and 3 key secondary endpoints of Treatment Period 1 (Section 2.2.1.2) in a pre-defined order, all at the same significance level ($\alpha = 0.05$ for the final analysis) to maintain an overall Type I error rate of at maximum $\alpha = 0.05$, moving to a second endpoint only after a success on the previous endpoint. Failure at any stage in the sequence implies automatic failure at all subsequent stages. All *P* values for each comparison without adjustments will be provided in the summary tables for informational purposes.

The test hierarchy is:

Treatment Period 1

- H_{11}: SMPG-detected hypoglycemia episode rate during Weeks 2-4 of the treatment period (primary endpoint)
- H_{12}: Increase in fasting tolerance (i.e., time from meal to PG <70 mg/dL) from baseline to Weeks 2-4 of the treatment period (key secondary endpoint)
- H_{13}: CGM percent time in range 70-180 mg/dL (3.9-10.0 mmol/L) during Weeks 2-4 of the treatment period (key secondary endpoint)
- H_{14}: Clinically significant SMPG-detected hypoglycemia episode rate, defined as average weekly number of episodes <54 mg/dL (3.0 mmol/L) during Weeks 2-4 of the treatment period (key secondary endpoint)

6.1.4. Handling of Dropouts or Missing Data

6.1.4.1. Premature Withdrawal from Study

Patients who withdraw from the study prematurely will not be replaced. If a substantial number of patients withdraw prematurely, the sponsor will evaluate the need for developing replacement criteria.

Randomized patients who subsequently withdraw from the trial may not re-enter. The patient number from a withdrawn patient will not be reassigned to another patient.

6.1.4.2. Imputation of Missing Event Data

For analysis of primary endpoint and key secondary endpoint of clinically significant hypoglycemia events, a jump-to-control (J2C) multiple imputation (MI) method, using SAS procedures PROC GENMOD, PROC GLMMOD, PROC SCORE, and PROC MIANALYZE, will be performed to handle missing data; note that missing count data following a negative binomial distribution cannot be analyzed in PROC MI, so additional steps must be taken to impute the missing data. Due to the expectation of rapid metabolism and excretion of trial drug, it is expected that efficacy would be similar to the control group in cases of premature treatment discontinuation; thus, the J2C method is appropriate to handle missing values in this situation (considered missing not at random [MNAR]). Since the primary endpoint is an event, it is possible that the event will not occur before discontinuation of study drug or end of Treatment Period 1; in that case, the number of events will be considered as 0.

The analysis will have 3 broad components: i) the MI process for the SOC-only data; ii) the MI process for the dasiglucagon + SOC patients' data; and iii) the analysis model that will be used to draw inference regarding the primary causal estimand, along with the method for combining the

results across the multiply-imputed datasets. These will be carried out in 6 steps, as outlined below. The seed to be used in the analysis is 12255070. The algorithm will use 20 burn-in iterations before each imputation, and 1000 imputed datasets will be created for the analysis for each of components i and ii. The methodology for imputing missing count data is based off of work by Keene et al.[4]

1. All observed data will be fitted using a Bayesian negative binomial model with a log link using PROC GENMOD using treatment and region as fixed effects (and class variables) and baseline event rate as a covariate. A thinning rate of 20, number of burn-ins of 20, number of iterations after burn-in of 20000, and a seed of 12255070 will be used in the analysis. Since the thinning parameter selects every 20th of the 20000 iterations, 1000 imputations are performed. The sampled posterior parameter estimates will be output; that dataset will be used in a later step, when PROC SCORE is utilized.
2. Design matrices will need to be created for each subject that displays their parameterization for the model. To create the design matrices, a dataset will need to be created that has records representing: (1) the observed total number of hypoglycemia events per patient in Treatment Period 1, from Day 1 through the end of Treatment Period 1 or trial discontinuation, whichever is earlier; (2) the data that will be used to model event rate before trial discontinuation; and (3) the data that will be used to model the event rate after trial discontinuation (this will be the same as the data in 1, however, the treatment will be set to the SOC-only arm). The design matrices will be created using PROC GLMMOD, using the same model as was used in PROC GENMOD previously,.
3. Generate the predicted number of events from the pre-discontinuation dataset without taking time-in-study into account. This will be done by using PROC SCORE to multiply design matrix corresponding with dataset (2) from Step 2 above with the parameter estimates from the Bayesian posterior model in Step 1. Note that the dataset described in Step 2 has been merged with study exposure time in Treatment Period 1, log of study exposure time in Treatment Period 1, treatment, region, baseline number of events, and observed post-baseline number of events. Similarly, generate the predicted number of events from the post-discontinuation dataset without taking time-in-study into account, by using PROC SCORE to multiply the design matrix corresponding with dataset (3) from Step 2 with the parameter estimate from the Bayesian posterior model in Step 1.
4. To complete the imputation, merge the two scored datasets together by sequential record number. For cases where predicted values from the pre-withdrawal and post-withdrawal datasets are known, derive the following parameters:
    a. Inversion of dispersion parameter: $k = 1/dispersion$
    b. Predicted number of events accounting for length of time in Treatment Period 1 before withdrawal:

$$\hat{y}_1 = e^{Predicted\ Y,pre-wd} \times time\ in\ Treatment\ Period\ 1$$

    c. Predicted number of events accounting for length of time in Treatment Period 1 after withdrawal:

$$\hat{y}_2 = e^{Predicted\ Y,post-wd} \times \max(28 - time\ in\ Treatment\ Period\ 1, 0)$$

d. Conditional probability: $p_{cond} = \frac{k+\hat{y}_1}{k+\hat{y}_1+\hat{y}_2}$

Then impute the counts as follows:

i. If patient completed Treatment Period 1 or the event is impossible or unlikely (i.e., $p_{cond} > 0.999999$), then $\text{count}_{\text{impute0}} = \text{count}_{\text{observed}}$.

ii. If patient discontinued before the end of Treatment Period 1 but k is large (i.e., dispersion is close to zero; $k > 1 \times 10^{20}$) then $\text{count}_{\text{impute0}} = \text{rand('Poisson', } \hat{y}_2)$.

iii. If patient discontinued before the end of Treatment Period 1 and k is not large then $\text{count}_{\text{impute0}} = \text{rand('NEGATIVEBINOMIAL',}p_{cond}\text{,k+count}_{\text{observed}})$.

Note that the number of events before discontinuation must be added and the number of events in Week 1 must be subtracted, since the primary endpoint is number of events in Weeks 2-4.

If patient discontinued after Week 1 then the number of events in Week 1 is based on the observed data, using the study weeks as outlined in Section 6.1.7.

For case i. $\text{count}_{\text{impute}} = \text{count}_{\text{impute0}}$ - # events in Week 1

For case ii. and iii. $\text{count}_{\text{impute}} = \text{count}_{\text{observed}} + \text{count}_{\text{impute0}}$ - # events in Week 1

If patient discontinued during Week 1, then

$$\text{count}_{\text{impute}} = ceil[\text{count}_{\text{impute0}} \times (1 - \frac{7 - time\ in\ Treatment\ Period\ 1}{28 - time\ in\ Treatment\ Period\ 1})].$$

5. The analysis model will be a negative binomial regression with number of hypoglycemia episodes during Weeks 2-4 as the dependent variable, and all covariates from the primary analysis model. The causal estimand will be estimated using the difference in the least squares means between the 2 treatment groups in each of the 1000 imputed datasets.
6. The negative binomial regression results from the multiply-imputed datasets will be combined using the usual Rubin's rules for multiple imputation[5] and will be done in SAS using PROC MIANALYZE. A significance test of the treatment difference will be tested at the 2 sided α level (α = 0.05), and corresponding CIs (based on the respective α values) will be calculated.

6.1.4.3. Imputation of Missing Non-Event Data

For analysis of key secondary endpoints of fasting tolerance, and CGM percent time in range, a J2C MI method, with SAS procedures PROC MI and PROC MIANALYZE, will be performed to impute missing data for patients who have discontinued treatment. Any missing values occurring before the patient discontinues/completes treatment will be imputed during the monotone step based on the data from the same treatment group (considered missing at random [MAR]).

The analysis will have 3 broad components:

i) the MI process for the non-monotone data;
ii) ii) the MI process for the monotone data
   a. J2C MI method for missing data for patients who discontinue treatment

b. Monotone regression [MAR] for missing values occuring before the patient discontinues/completes treatment

iii) iii) the analysis model that will be used to draw inference regarding the primary causal estimand, along with the method for combining the results across the multiply-imputed datasets.

The seed to be used in the analysis is 12255070. The algorithm will use 20 burn-in iterations before each imputation, and 1000 imputed datasets will be created for the analysis for each of steps i and ii

- Step i) description:

Imputation of non-monotone data (missing data at intermediate visits) using PROC MI based on Markov Chain Monte Carlo (MCMC) methodology (considering MAR and using impute=monotone options to impute only the non-monotone data). Variables treatment, baseline region and weekly values will be included in this model. .

This first imputation step will produce 1000 datasets with a monotone missing pattern.

- Step ii)

a- analysis for missing data for subjects who discontinue treatment:

Missing post-withdrawal monotone data will be imputed in a sequential manner, using a method proposed by Ratitch and O'Kelly, 2011[7]. Due to the expectation of rapid metabolism and excretion of trial drug, it is expected that efficacy would be similar to the control group in cases of premature treatment discontinuation; thus, the J2C method is appropriate to handle imputation of monotone data (missing data after premature treatment discontinuation, considered MNAR – control-based pattern imputation).

A sequential regression approach will be used to implement the imputation of each of the monotone missing datasets. Imputation process will be break into a sequence of multiple calls to PROC MI, where each call is intended to impute missing values at one time-point only:

- For time-point X : Monotone missing pattern dataset will be divided in two datasets: one with all SOC only subjects and those with Dasiglucagon + SOC missing data at time-point X with observed post-baseline measurements in the Dasiglucagon + SOC group set to missing to comply with the J2C assumption (A) and the other ones with subjects not having missing data for Dasiglucagon + SOC at time-point X (B). The imputation of dataset will be carried out in SAS PROC MI using the monotone method with a regression model approach[6]. The method then repeats the operation multiple times to iterate to a stable solution. Variables baseline, region, value at Week X, Values at Week X-1, etc…. will be included in the model:
  - This will be repeated for Week1, Week2, Week3, and Week4.
  - Note that the fasting tolerance test only occurs at one point in Treatment Period 1 in Week 4, so Weeks 1-3 are not included in the model for that endpoint.
  - If the model does not converge, first region will be removed and the procedure rerun; if it still does not converge, then weekly outcome results will be removed from the model starting with Week 1 (when imputing other weeks).

b- analysis for missing data occurring before the patient discontinues/completes

treatment:
SAS PROC MI will be used to impute missing values by each treatment group separately utilizing the monotone reg option, including baseline, region, value at Week X, Values at Week X-1, etc…. in the model:.

- Step iii) description:

The analysis model then applied will be an ANCOVA with outcome during Weeks 2-4 as the dependent variable (CGM percent time in range) or end of Treatment Period 1 (fasting tolerance), and all covariates from the primary analysis model. The causal estimand will be estimated using the difference in the least squares means between the 2 treatment groups for each of the 1000 imputed datasets. The ANCOVA results from the multiply-imputed datasets will be combined using the usual Rubin's rules for multiple imputation[5] and will be done in SAS using PROC MIANALYZE. A significance test of the treatment difference will be tested at the 2-sided α level (α = 0.05), and corresponding CIs (based on the respective α values) will be calculated.

6.1.5. Analysis Visit Windows

For all analyses, unscheduled and/or repeated measurements will only be included if a scheduled measurement is not available and the unscheduled/repeated measurement falls within the analysis visit windows as described in Table 3. Otherwise, visits will be analyzed as scheduled, and unscheduled/repeated measurements falling outside of the visit windows will be excluded from analysis.

Table 3: Analysis Visit Windows

Analysis Visit	Target Day	Lower Limit	Upper Limit
Baseline		-28	-14
Week 1	1	1	--
Week 2	8	4	12
Week 4	22	18	26
Week 5	29	25	33
Week 6	36	32	40
Week 9	57	53	61

6.1.6. Pooling of Sites

Not applicable; sites are pooled into regions as part of randomization stratification.

6.1.7. Derived Variables

- **Day 1** = first day of Treatment Period 1, where either dasiglucagon is first initiated (dasiglucagon + SOC treatment group) or date of randomization (SOC only treatment group). Study day will be calculated with respect to Day 1.

- **Study Week =** a 7- or 21-day period derived for displays of events related to CGM and/or SMPG results, gastric carbohydrate administrations, health care outcomes, and other assessments that may occur between clinic visits where a defined study week is needed. The study weeks will be derived as follows:

Study Week	Planned Days	Analysis Start Date	Analysis Stop Date
Baseline	Days -14 – -1	Analysis Stop Date – 13 days	Day 1 visit date – 1 day
Week 1 *	Days 1 – 7	Day 1 visit date	Week 5 visit date – 22 days
Week 2	Days 8 – 14	Analysis Stop Date – 6 days	Week 5 visit date – 15 days
Week 3	Day 15 – 21	Analysis Stop Date – 6 days	Week 5 visit date – 8 days
Week 4	Days 22 – 28	Analysis Stop Date – 6 days	Week 5 visit date – 1 day
Weeks 2-4	Days 8 – 28	Same as Week 2 Analysis Start Date	Week 5 visit date – 1 day
Week 5 *	Days 29 – 35	Week 5 visit date	Week 9 visit date – 22 days
Week 6	Days 36 – 42	Analysis Stop Date – 6 days	Week 9 visit date – 15 days
Week 7	Days 43 – 49	Analysis Stop Date – 6 days	Week 9 visit date – 8 days
Week 8	Days 50 – 56	Analysis Stop Date – 6 days	Week 9 visit date – 1 day
Weeks 6-8	Days 36 – 56	Same as Week 6 Analysis Start Date	Week 9 visit date – 1 day

Study Week	Planned Days	Analysis Start Date	Analysis Stop Date

* This might end up being more or less than 7 days if the Week 5 visit day is not exactly at Day 29 or if the Week 9 visit day is not exactly at Day 57; both Week 5 and Week 9 visits have a ± 2 day visit window.

No overlap in days between study weeks is allowed, except in cases where a multiple-week period is indicated. If there is overlap, the earlier week is favored. In case of early termination before a subject reached the end of the respective period (Week 5 or Week 9), the derivation for the weeks will be based on the planned day up to date of discontinuation (where any week after date of discontinuation will be set to missing), as follows:

Study Week	Planned Days	Analysis Start Date	Analysis Stop Date
If subject discontinues trial before reaching Week 5:			
Week 1	Days 1 – 7	Day 1 date	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation
Week 2	Days 8 – 14	Date 1 date + 7 days	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation
Week 3	Day 15 – 21	Date 1 date + 14 days	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation
Week 4	Days 22 – 28	Date 1 date + 21 days	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation
Weeks 2-4	Days 8 – 28	Same as Week 2 Analysis Start Date	Same as latest of Week 2, Week 3, or Week 4 Analysis Stop Date
If subject discontinues trial before reaching Week 9:			
Week 5	Days 29 – 35	Week 5 date	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation
Week 6	Days 36 – 42	Week 5 date + 7 days	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation

Study Week	Planned Days	Analysis Start Date	Analysis Stop Date
Week 7	Days 43 – 49	Week 5 date + 14 days	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation
Week 8	Days 50 – 56	Week 5 date + 21 days	Earliest of Analysis Start Date + 6 days, or date of trial discontinuation
Weeks 6-8	Days 36 – 56	Same as Week 6 Analysis Start Date	Same as latest of Week 6, Week 7, or Week 8 Analysis Stop Date

- **Study Visit =** in-clinic visit as per the schedule of events, to be used for assessments that can only occur during a clinic visits (e.g., PedsQL, safety assessments like clinical laboratory assessments and vital signs).

- **Change from baseline =** value at current time point – value at baseline.

- **TEAE =** an AE with an onset at the time of or following the start of treatment with the trial drug (dasiglucagon + SOC arm) or date/time of randomization (SOC only arm) through the Follow-up visit or Early Termination visit, whichever occurs first.

- **PK Clearance:**

$$CL/f\ (L/h) = R0/Css$$

where R0= infusion rate (pmol/h) and Css = concentration at steady state (pmol/L), weight (1µg/kg/hr = 295.7 nmol/kg/h)

- **SMPG-detected Hypoglycemia episode =** PG <70 mg/dL or 3.9 mmol/L, as detected by SMPG and reported in the eCRF. A single hypoglycemia episode is defined as up until 60 minutes from the start of the episode even if normoglycemia (>70 mg/dL) is not reached within this time. A new episode of hypoglycemia is to be reported when the next PG value below 70 mg/dL (3.9 mmol/L) is measured. Episodes are defined as the ones entered in the eCRF, no statistical programming will be done to define an episode.

- **Clinically significant SMPG-detected hypoglycemia episode = defined as SMPG-detected Hypoglycemia episode with any** PG <54 mg/dL during the episode, (value reported in the hypoglycemic event form)..

- **CGM-detected hypoglycemia episode =** PG <70 mg/dL (3.9 mmol/L) for 15 minutes or more, as measured by CGM. A single hypoglycemia episode is defined as up until 60 minutes from the start of the episode even if normoglycemia (>70 mg/dL) is not reached within this time. A new episode of hypoglycemia is to be reported when the next PG

value below 70 mg/dL (3.9 mmol/L) is measured. Episodes are defined by programming using external CGM data.

- **Clinically significant CGM-detected hypoglycemia episode** = PG <54 mg/dL or 3.0 mmol/L for 15 minutes or more, as detected by CGM. A single clinically significant hypoglycemia episode is defined as up until 60 minutes from the start of the episode even if normoglycemia (>54 mg/dL) is not reached within this time. A new episode of clinically significant hypoglycemia is to be reported when the next PG value below 54 mg/dL (3.0 mmol/L) is measured. Episodes are defined by programming using external CGM data.

- **Event rate** = average of the weekly number (sum) of events/episodes, based on the number of weeks in the relevant period (Baseline, Week 2-4, or Week 6-8). Events include hypoglycemia, clinically significant hypoglycemia, gastric carbohydrate administrations, and SMPG readings.

- **Number of weeks** = number of days in a relevant period (Baseline, Treatment Period 1, Week 2-4, Treatment Period 2, or Week 6-8) divided by 7. If a subject discontinues during a week, then a partial week will be calculated.

- **Percent time (CGM)** = (number of minutes where PG at a pre-defined level / total number of minutes patient is wearing CGM) * 100%. For this calculation, one assessment of CGM will be considered having a 5 minutes duration. The possible levels are:

  - **In range:** PG between 70-180 mg/dL (3.9-10.0 mmol/L), inclusive
  - **Hypoglycemia:** PG <70 mg/dL (3.09 mmol/L)
  - **Clinically significant hypoglycemia:** PG <54 mg/dL (3.0 mmol/L)

- **Time to hypoglycemia** = time from beginning of meal to the beginning of the first continuous 15-minute CGM reading of PG <70 mg/dL.

- **Extent of hypoglycemia ($AOC_{glucose}$)** =

$$\sum_{k=0}^{X-1} \frac{(UL - PG_k) + (UL - PG_{k+1})}{2} \times (t_{k+1} - t_k)$$

where *UL* is the upper limit for the hypoglycemia definition (70 mg/dL or 54 mg/dL); *k* is the k^{th} time point that glucose is measured using CGM; PG_k is the PG value in mg/dL on the k^{th} time point; and *X* is the end time point of the 3-week treatment period (Weeks 2-4). When $k = 0$, t_k is set to 0 and PG_k is the PG value corresponding to the start of the 3-week treatment period. Only PG values less than UL will be included in the calculation. If PG ≥ UL at the k^{th} time point and PG < UL at the k^{th}+1 time point, then the extent of hypoglycemia for that interval will be determined as follows:

1. Estimate time point on x-axis where PG = UL – 0.01 (for values measures in mmol/L), as if a straight line were drawn between time points by using the following formula:

$$\hat{k} = \frac{(UL - 0.01) - b}{m}$$

Where b = y-intercept of line created by the coordinates (k^{th} time point,PG_k) and (k^{th}+1 time point,PG_{k+1}) and m = slope of that line.

2. Substituting PG_k with UL and t_k with $t_{\hat{k}}$, the formula for the estimated interval below UL is as follows:

$$\frac{(UL - UL) + (UL - PG_{k+1})}{2} \times (t_{k+1} - t_{\hat{k}})$$

Similar methodology would be utilized if PG < UL at the k^{th} time point and PG ≥ UL at the k^{th}+1 time point, with the estimate of the time point where PG crosses the UL threshhold being estimated for $t_{\hat{k}+1}$.

If the time period between two timepoints is greater than 1 hour then no area will be calculated over this timeperiod.

If PG results from the k^{th} time point are missing, then *k-1* scores will be used and the weight will be t_{k+1}-t_{k-1}.

The extent of hypoglycemia calculated as above will then be divided by the total duration of CGM assessments calculating as summing all $t_{k+1} - t_k$ duration used in previous formulae. Time points for which PG>UL will be included in the total duration. This variable will then be used the endpoint evaluation.

- **Nightly gastric carbohydrates =** amount of gastric carbohydrates (g) given between midnight and 6 am, inclusive.

- **Amount of [variable] =** average of the weekly amount of [variable] in the relevant period (Baseline, Week 2-4, and/or Week 6-8). Variables include total amount of gastric carbohydrates administered (via NG tube or gastrostomy) to treat hypoglycemia, nightly gastric carbohydrates administered, total amount of gastric carbohydrates administered, and number of IV glucose infusions to treat hypoglycemia.

- **PedsQL scoring for each scale and summary score[8]:**

    - Step 1: Transform score - items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0 so that higher scores indicate better health-related quality of life (QoL) (less negative impact).

    - Step 2: Calculate scores - computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed.

- **PedsQL Physical Functioning scale score** = average of transformed physical functioning scale items; up to 6 items for infants (1-12 months), 9 items for infants (13-24 months), and 8 items for toddlers, young children, children, and teens.

- **PedsQL Emotional Functioning scale score** = average of the transformed emotional functioning scale items; up to 12 items for infants (1-12 months) and infants (13-24 months) and 5 items for toddlers, young children, children, and teens.

- **PedsQL Social Functioning scale score** = average of the transformed social functioning scale items; up to 4 items for infants (1-12 months) and 5 items for infants (13-24 months), toddlers, young children, children, and teens.

- **PedsQL School Functioning scale score** = average of the transformed school functioning scale items; up to 3 items for toddler and 5 items for young children, children, and teens. This scale was not collected for infants (1-12 months) or infants (13-24 months).

- **PedsQL Physical Symptoms scale score** = average of the transformed physical symptoms scale items; up to 10 items for infants (1-12 months) and infants (13-24 months). This scale was not collected for toddlers, young children, children, or teens.

- **PedsQL Cognitive Functioning scale score** = average of the transformed cognitive functioning scale items; up to 4 items for infants (1-12 months) and 9 items for infants (13-24 months). This scale was not collected for toddlers, young children, children, or teens.

- **PedsQL Physical Health summary score** = average of the transformed physical functioning scale items and physical symptoms scale items (infants [1-12 months] and infants [13-24 months] only).

- **PedsQL Psychosocial Health summary score** = average of the transformed emotional functioning scale items, social functioning scale items, school functioning scale items (toddlers, young children, children, and teens only), and cognitive functioning scale items (infants [1-12 months] and infants [13-24 months] only).

- **PedsQL Total scale score** = average of the transformed physical functioning scale items, emotional functioning scale items, social functioning scale items, school functioning scale items (toddlers, young children, children, and teens only), physical symptoms scale items (infants [1-12 months] and infants [13-24 months] only), and cognitive functioning scale items (infants [1-12 months] and infants [13-24 months] only).

- **Fasting Tolerance start and end dates**

Fasting Tolerance start date/time is defined as per e-CRF fields: Meal start date, start time

Fasting Tolerance end date/time is defined as the earliest between:

-e-CRF end date, end time

- first continuous 15-minute CGM reading of <70 mg/dL (3.9 mmol/L) from external CGM data. As CGM assessment is not exactly done every 5 minutes it will require at least 2 CGM evaluation < 70mg/dL no separated more than 10 minutes and no CGM value > 70mg/dL during this 15 minutes time period.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (eg, 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events (AE) will be coded using the MedDRA version 21.1 thesaurus.

A treatment-related AE is any AE with a relationship to the study drug of possible or probable.

Missing AE dates will not be imputed. The AE CRF does not allow the study investigators to report partial start and end dates, so partial AE date imputation is not required

If partial medication dates occur, the convention for replacing missing dates for the purposes of calculating derived variables is as follows:

For partial medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then:
  - If the year matches the year of first dose date and the end date (if present) is after first dose date, or medication is ongoing, then impute as the month and day of the first dose date. If this produces a date after the medication end date, assign 01 January.
  - Otherwise, assign 01 January.
- If the day is unknown, then:
  - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date. If this produces a date after the medication end date, assign 01.
  - Otherwise, assign 01.

For partial medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the month is unknown, then assign December.

- If the day is unknown, then assign the last day of the month.

7. Study Patients and Demographics

7.1. Disposition of Patients and Withdrawals

The numbers of patients enrolled, randomized, completing, and withdrawing from treatment and the trial, along with reasons for withdrawal for treatment and trial, respectively, will be tabulated overall and by randomized treatment group. The number of patients in each analysis set will be reported, as well as the number of patients at each visit. A CONSORT diagram showing patient disposition will be provided.

All disposition information will be listed.

7.2. Protocol Violations and Deviations

Protocol deviations will be provided in a listing.

7.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, child-bearing potential, race, ethnicity, weight, weight z-scores, length/height, and length/height z-scores) will be summarized using descriptive statistics for patients in FAS by randomized treatment group. Z-scores (based on the World Health Organization [WHO] growth charts) will be derived using a patient's age and sex. Gastrostomy and Pancreatectomy will be described at baseline.

Gastrostomy is defined from medical history form. For programming purpose select following preferred terms: Gastrostomy (not including the tube removal), Gastrointestinal tube insertion, insertion of nasogastric tube, nasogastric tube for feeding or similar.

Pancreatectomy is defined from medical history. For programming purpose select following preferred terms: Pancreatectomy. Near total is defined as > 95% as specified in medical history.

No formal statistical analyses will be performed.

7.4. Exposure and Compliance

Study drug administration will be summarized separately for total dasiglucagon exposure (µg/kg) and total duration of exposure (days), respectively, for each treatment period. The total dasiglucagon exposure will also be described by study week. Additionally, the infusion rate, defined as the average hourly weight-adjusted infusion rate over the last 7 days of the respective treatment period (i.e., µg/kg/hr and µg/hr), will be summarized for each treatment period and each study week.

8. Efficacy Analysis

The FAS and PP Set will be used to summarize efficacy data. The PP Set will be used only as supportive analysis. Patients will be analyzed by treatment period according to the planned treatment group (SOC and dasiglucagon + SOC for Treatment Period 1 and dasiglucagon + SOC for Treatment Period 2).

The efficacy analysis will be separated into 3 categories:

1. Treatment Period 1, FAS
2. Treatment Period 1, PP (primary and key secondary endpoints only)
3. Treatment Period 2, FAS

Efficacy Procedures

Plasma Glucose Monitoring: During the study, SMPG assessments will be performed regularly (at least 3 times daily, preferably before meals) to evaluate efficacy. At each visit, the investigator will check for patient compliance in number of daily SMPG measurements and that hypoglycemia episodes are recorded in the diary.

Continuous Glucose Monitoring: CGM will be used in a blinded manner to evaluate efficacy in terms of hypoglycemia episodes. The CGM is required for the 2 weeks up to randomization, during Week 2-4 of Treatment Period 1, and during Week 6-8 of Treatment Period 2. However, short pauses of 1-3 days due to skin irritation or discomfort are allowed after consultation with the investigator.

Fasting Tolerance: During the screening period and at the end of Treatment Period 1, all patients will undergo a fasting tolerance test. This test must be performed when the CGM is active, and not the first day of CGM sensor, e.g., the day before randomization. The test will commence after the patient's normal meal (t=0 will be the beginning of the meal). The meals have to be the same for both tests for the same individual. This test is planned to last for 12 hours but will be stopped when PG is ≤60 mg/dL (3.3 mmol/L) and then ketones, insulin, and free fatty acids will be measured. The child will then be fed. If this value has not been reached at 12 hours, the test should be extended until it is reached. The duration of fasting tolerance will be measured from the beginning of the normal meal until the beginning of the first continuous 15-minute CGM reading of <70 mg/dL (3.9 mmol/L) or the time the test ended if a continuous 15-minute CGM reading <70 has not been reached.

8.1. Primary Efficacy Analysis

8.1.1. Primary Analysis for the Primary Endpoint

The primary efficacy endpoint is the SMPG-detected hypoglycemia episode rate during Weeks 2-4 of Treatment Period 1. A hypoglycemia episode is defined as PG <70 mg/dL or 3.9 mmol/L, as detected by SMPG. The analysis will be based on the hypoglycemia episodes reported in the eCRF. Baseline SMPG-detected hypoglycemia episode rate is defined as the average weekly number of hypoglycemia episodes during the 2-week baseline period. Hypoglycemia episode rate in Weeks 2-4 of Treatment Period 1 is defined as the average weekly number of hypoglycemia episodes across the last 3 weeks of the treatment period. The hypothesis:

H_{11}: SMPG-detected hypoglycemia episode rate $_{dasiglucagon}$ = SMPG-detected hypoglycemia episode rate $_{SOC\ only}$

will be analyzed by using negative binomial regression, with region and treatment group as fixed effects, baseline hypoglycemia rate as a covariate and number of hypoglycemia episodes during weeks 2-4 as dependent variable. The log-transformed number of weeks in Weeks 2-4 of Treatment Period 1, after accounting for imputation (i.e., log(3) for subjects with imputed data, or number of weeks in Weeks 2-4 otherwise), will be used as an offset variable. The null hypothesis is that there is no difference in the incidence of average weekly number of hypoglycemia events between the 2 treatment groups, which will be tested at the significance level of α=0.05.

The primary analysis will estimate the treatment effect based on the de facto (treatment policy) estimand. All available data in the form of actual measurements will therefore be included in the analysis, irrespective of adherence to treatment or use of subsequent therapy. Missing data will be imputed using the MI methodology as described in Section 6.1.4.2. In case of no missing data, primary analysis will be run without multiple imputation.

Descriptive statistics for observed and change from baseline in incidence of average weekly number of hypoglycemia events between the 2 randomized treatment groups will be presented. The study weeks presented will be Baseline, Week 1, Week 2, Week 3, Week 4, and Week 2-4. No imputation of missing data will be performed for descriptive statistics.

A graph will be provided showing the mean number of weekly hypoglycemia events for each treatment group.

This analysis will be conducted on patients in the FAS.

8.1.2. Sensitivity and Supportive Analyses for the Primary Endpoint

As a sensitivity analysis, the primary endpoint will also be analyzed without imputation of missing data; however, this analysis will not be included in the fixed-sequence hierarchical testing strategy. The log-transformed number of weeks in Weeks 2-4 of Treatment Period 1 will be used as an offset variable. In case of no missing data, this sensitivity analysis will not be run.

As a supportive analysis, the primary endpoint analysis will be repeated on the PP Set; this includes the negative binomial regression both with and without imputation (with an offset variable used for without imputation inference), summary statistics for observed and change from baseline.These analyses will not be included in the fixed-sequence hierarchical testing strategy. In case of no missing data, the supportive analysis with imputation will not be run.

The primary endpoint may be analyzed excluding post-baseline data collected after trial drug discontinuation/completion; however, this will be performed on an *ad hoc* basis.

8.2. Key Secondary Efficacy Analysis

8.2.1. Primary Analyses for the Key Secondary Endpoints

Treatment Period 1

For all key secondary endpoints (except for fasting tolerance), baseline outcome is defined as the

mean weekly value during the 2-week baseline period; Weeks 2-4 of Treatment Period 1 outcome is defined as the mean weekly value across the last 3 weeks of the treatment period. Missing data will be imputed using the MI methodology as described in Sections 6.1.4.2 (event data) and 6.1.4.3 (non-event data) for statistical inference only (i.e., not descriptive statistics or graphs). These analyses will be conducted on patients in the FAS.

Fasting Tolerance

Increase in fasting tolerance (i.e., change from baseline in time from meal to PG <70 mg/dL) will be analyzed using an ANCOVA, with treatment group and region as fixed effects and baseline fasting tolerance as a covariate. Kaplan-Meier curves for time from beginning of meal to PG <70 mg/dL between each treatment group in Treatment Period 1 will be provided.

CGM Percent Time in Range

Percent time in range (i.e., the percent time between 70 mg/dL [3.9 mmol] and 180 mg/dL [10.0 mmol], inclusive, as measured by CGM, where percent time is calculated as described in Section 6.1.7, will be analyzed by using an ANCOVA, with treatment group and region as fixed effects and baseline time in range as a covariate. Descriptive statistics for observed CGM percent time in range will be summarized for each study week (Baseline, Week 1, Week 2, Week 3, Week 4, and Week 2-4) by randomized treatment group. A graph will be provided showing the mean weekly percent time in range for each treatment group.

Clinically Significant Hypoglycemia Events

SMPG-detected clinically significant hypoglycemia (<54 mg/dL [3.0 mmol/L]) episode rate. The analysis will be based on the hypoglycemia episodes reported in the eCRF with at least one SMPG measurement <54 mg/dL. The endpoint will be analyzed using a negative binomial regression, with treatment group and region as fixed effects and baseline hypoglycemia rate as a covariate. Descriptive statistics for observed and change from baseline in the number of SMPG-detected clinically significant hypoglycemia episodes will be summarized for each study week (Baseline, Week 1, Week 2, Week 3, Week 4, and Week 2-4) by treatment group. A graph will be provided showing the mean weekly number of clinically significant hypoglycemia episodes for each treatment group.

A forest plot will be produced with the results of the main analysis of the primary endpoint and the main analysis of the key secondary endpoints.

8.2.2. Sensitivity and Supportive Analyses for the Key Secondary Endpoints

Inferential analyses will be repeated without imputation of missing data (with the inclusion of an offset variable for negative binomial regression); as with the primary endpoint, these analyses will not be included in the fixed-sequence hierarchical testing strategy. Additionally, all inferential analyses will be repeated on the PP Set (including with and without imputation of missing data), as well as descriptive statistics.

For fasting tolerance test a sensitivity analysis will be done not including patients with fasting tolerance protocol deviation as defined during the data review meeting.

8.3. Secondary Efficacy Analysis

The secondary efficacy analysis for this study includes the below summaries. These are continuous endpoints and will be summarized using descriptive statistics by study visit, treatment group, and treatment period (where applicable). No inference will be performed and missing data will not be imputed.

Analysis to be performed on subgroup of patients having gastrostomy or NG-tube at screening:

- Rate of gastric carbohydrate administrations (NG tube or gastrostomy) per week to treat hypoglycemia during Weeks 2-4 (Treatment Period 1) and Weeks 6-8 (Treatment Period 2)
- Total amount of gastric carbohydrates administered (g) (Gastrostomy or NG-tube) to treat hypoglycemia per week during Weeks 2-4 (Treatment Period 1). A graphic will be produced.
- Total amount of gastric carbohydrates administered (NG tube or gastrostomy) per week during Weeks 2-4 (Treatment Period 1).
- Amount of nightly (midnight to 6 am) gastric carbohydrates administered (NG tube or gastrostomy) per week during Weeks 2-4 (Treatment Period 1).

Analysis to be performed on whole population:

- CGM percent time in hypoglycemia (<70 mg/dL or 3.9 mmol/L) during Weeks 2-4 (Treatment Period 1) and Weeks 6-8 (Treatment Period 2).
- CGM-detected hypoglycemia episode rate, defined as number of episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more per week, during Weeks 2-4 (Treatment Period 1). A single CGM episode will be defined as up until 60 minutes from the start of the episode even if normoglycemia (>70 mg/dL) is not reached within this time. A new episode of hypoglycemia is to be reported when the next PG value below 70 mg/dL (3.9 mmol/L) is measured. Episodes will be derived by programming.
- SMPG-detected hypoglycemia episode rate, defined as number of episodes <70 mg/dL (3.9 mmol/L), during Weeks 6-8 (Treatment Period 2). A single SMPG episode will be defined as up until 60 minutes from the start of the episode even if normoglycemia (>70 mg/dL) is not reached within this time. A new episode of hypoglycemia is to be reported when the next PG value below 70 mg/dL (3.9 mmol/L) is measured, this will reported in the corresponding CRF form. The analysis will be based on the hypoglycemia episodes reported in the eCRF.
- CGM-detected clinically significant hypoglycemia episodes, defined as number of episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more per week, during Weeks 6-8 (Treatment Period 2).

For the above endpoints, observed and change from baseline values will be presented. Study weeks are as defined in Section 6.1.7.

- Extent of hypoglycemia ($AOC_{glucose}$ below 70 mg/dL [3.9 mmol/L]) as measured by CGM during Weeks 2-4 of Treatment Period 1.
- Extent of hypoglycemia ($AOC_{glucose}$ below 54 mg/dL [3.9 mmol/L]) as measured by CGM during Weeks 2-4 of Treatment Period 1.

For the above endpoint, $AOC_{glucose}$ at Baseline and Weeks 2-4 (Treatment Period 1) will be summarized.

8.4. Other Efficacy Analysis

8.4.1. Glucose Infusions and SMPG readings

Below mentioned are continuous endpoints which will summarized using descriptive statistics (observed and change from baseline) by study week and planned treatment for patients in the FAS. Study weeks are the same as specified in Section 6.1.7.

- Number of IV glucose infusions to treat hypoglycemia per week during Weeks 2-4 (Treatment Period 1).
- Rate of SMPG readings per week during Weeks 2-4 from external Vitalograph data source (Treatment Period 1).

8.4.2. Quality of Life

Quality of life will be assessed by the PedsQL and additional CHI disease-specific QoL questions (parent-reported versions) according to the Schedule of Events (Table 2).

PedsQL

The PedsQL consists of forms for children ages 1-12 months (infant), 13-24 months (infant), 2-4 (toddler), 5-7 (young children), 8-12 years (children), and 13-18 years (teens). For each item of the PedsQL instrument (parent), a 5-point response scale is used (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always).

The PedsQL consists of the following subscales: Physical Functioning, Physical Symptoms (only applicable for infants, 1-24 months), Emotional Functioning, Social Functioning, Cognitive Functioning (only applicable for infants, 1-24 months), and School Functioning (only applicable for children, 2-18 years). Physical Health summary, Psychosocial Health summary, and Total scale scores can be derived from the PedsQL subscales. Scoring of the scales and derivation of the summary and total scores are specified in Section 6.1.7.

Change from baseline for PedsQL for each of the scales (Physical Functioning, Physical Symptoms, Emotional Functioning, Social Functioning, School Functioning, and Cognitive Functioning) and summary scores (Total scale score, Physical Health summary score, and Psychosocial Health summary score) will be summarized using descriptive statistics at each study visit by treatment group for each treatment period for the patients in FAS. As number of subjects is not sufficient, for this to be meaningful, results for each age group will not be summarized separately.

CHI Disease-Specific Questionnaire

Answers to each question on the CHI disease-specific questionnaire will be summarized using frequencies and percentages at each study visit by treatment group for each treatment period.

8.4.3. CHI Related Hospitalization

The frequencies and percentage of patients with admissions/emergency department visits for hypoglycemia, hospitalizations due to CHI or CHI-related events, visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and need for home visits by paramedics due to hypoglycemia will be summarized by treatment group at each study week (as defined in Section 6.1.7) for each treatment period.

Additionally, number and length (in days) of hospitalizations due to CHI, number of visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and number of home visits by paramedics due to hypoglycemia will be summarized descriptively by study week and treatment group for the patients in FAS based on treatment period.

9. Safety and Tolerability Analysis

Safety assessments will include the evaluation of AEs, clinical laboratory assessments (hematology, biochemistry, and ADAs), vital signs, physical examinations; electrocardiograms (ECGs), echocardiography, and local tolerability issues. No formal inferential analyses will be conducted for safety variables, unless otherwise specified. All safety analyses will be summarized by treatment received within treatment period and also by active treatment (Dasiglucagon pooling data of treatment period 1 and 2) and by study visit, if applicable.

9.1. Adverse Events

An AE is any untoward medical occurrence in a clinical trial patient administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not related to the product. Adverse events that begin after the first dose of dasiglucagon (dasiglucagon + SOC treatment group) or randomization (SOC only treatment group) will be defined as treatment emergent (TEAE).

The causal relationship of the AE to the study drug is determined by the investigator as Not Related, Unlikely, Possible, and Probable. These will be mapped to Unrelated (*Not Related* or *Unlikely*) and Related *(Possible* or *Probable*) for summarization purposes. Relationship for patients on SOC only is expected to be “Not related” according to data entry guidelines. If it is missing for a patient in this period it should be mapped to “Not related” other missing data will be mapped to “Related”.

Adverse event severity grades are reported as mild, moderate, or severe.

Each patient will be counted only once within each summation level system organ class (SOC) and preferred term (PT). If a patient experiences more than 1 TEAE within each summation level only, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be

included in the summaries of relationship and severity. The summary will be presented in descending order of frequency of SOC and then PT within SOC based on dasiglucagon arm of period 1, then by standard of care only in period 1 and then by period 2.

The incidence of TEAEs will be summarized with frequencies and percentages for patients in Safety Set (including number of TEAEs occurring, as well as rate of events), by treatment group within treatment period and the following:

- SOC and PT
- SOC, PT, and severity
- SOC, PT, and relationship to study drug
- SAEs by SOC and PT

Rate of events will be described as Exposure-adjusted TEAE rate calculated by summing all events and dividing by total exposure time. For Standard of Care only the total exposure time will be calculated from randomization to day before first intake in treatment period 2.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rate (frequencies and percentages) of TEAEs leading to discontinuation of study drug, by treatment group within treatment period, SOC, and PT will be prepared for patients in Safety Set. No inferential statistical tests will be performed.

A data listing of TEAEs leading to discontinuation of study drug will also be provided displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious TEAEs (and Related Serious TEAEs will be listed and also tabulated by SOC and PT and presented by treatment group within treatment period and overall.

9.1.3. Other Significant Adverse Events

Four types of AEs of special interest (AESI) are collected in this study. They are risk of liver injury, neurological events, suspicion of necrolytic migratory erythema, and Post-Dose Hemodynamic Changes. All Treatment Emergent AESI types occurring in at least 1 patient will be presented.

Incidence of Treatment Emergent AESI will be summarized by frequencies and percentages by treatment group within treatment period and overall for patients in Safety Set by the following:

- AESI type, SOC, PT
- AESI type, SOC, PT, and relationship to the study drug

Additional information describing each AESI type, captured separately from date in the AE CRF, will be listed.

9.2. Clinical Laboratory Evaluations

Samples for hematology and chemistry will be collected at the Screening and Weeks 2, 5, 6, 9, and 12. Standard of care blood samples can be used as screening samples if they were collected within 1 week of screening.

Descriptive summaries of observed and changes from baseline values will be presented for clinical laboratory values by study visit and treatment group within treatment period.

Shifts from baseline for clinical laboratory values below, within, or above the normal range will be provided for hematology and chemistry results. Minimum/Maximum post-baseline values will also be included in those shift tables, including values from unscheduled visits.

Frequencies of clinically significant abnormal laboratory values for hematology and chemistry results will be presented by treatment group within treatment period at each study visit.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

Serum pregnancy test results and antidrug antibodies will be listed.

Immunogenicity data will be analyzed descriptively. No statistical tests are planned. Baseline ADA-positive patients will be calculated as a percentage of the total number of patients whose baseline samples were tested for ADA. Overall ADA incidence, the combined results of treatment induced, and treatment boosted ADA-positive patients, will be calculated as a percentage of the total number of evaluable patients, excluding baseline positive patients without any samples available after drug administration. Titers will be reported as median and interquartile range.

9.3. Vital Signs

Vital signs will be collected at Screening, Day 1, and Weeks 2, 4, 5, 6, 9, and 12. Moreover, for patients enrolled under version 9 of protocol and later, vital signs are also measured on Day 1 and Day 29 at the start of the visit and at 6 ± 1, 12 ± 2, and 24 ± 4 hours after initiation of the trial drug for patients initiating treatment. Those data will be included in descriptive analysis.

Descriptive summaries of observed and change from baseline values will be calculated for systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and oxygen saturation (SpO_2) by study visit and treatment group within treatment period for patients in Safety Set.

Frequencies and percentages of vital sign interpretation results (normal, abnormal clinically significant, and abnormal not clinically significant) will be summarized by treatment group within treatment period and study visit.

Shifts from baseline for vital sign values normal, abnormal not clinically significant and abnormal clinically significant will be provided for each parameter by treatment group within treatment period and study visit.

9.4. Electrocardiograms

An ECG will be performed at Screening and Weeks 2, 5, 6, 9, and 12. Moreover, for patients enrolled under version 9 of protocol and later, ECG is also measured at the start of the visit and at 24 ± 4 hours after initiation of trial drug for patients initiating treatment. Those data will be included in descriptive analysis.

Descriptive summaries of observed and change from baseline values will be presented for continuous ECG measures of heart rate, PQ interval, QRS duration, QT interval, and QTcF interval by study visit and treatment group within treatment period.

Frequencies and percentage of patients of investigator interpretation of ECG results (normal, abnormal clinically significant, and abnormal not clinically significant) will be summarized for patients in Safety Set by each treatment group within treatment period and study visit.

Additionally, frequencies and percentage of patients with observed QTcF >450, >480, and >500 msec, as well as change from baseline in QTcF >30, >50, and >60 msec, will be summarized for patients in the Safety Set by each treatment group within treatment period and study visit.

9.5. Echocardiography

An echocardiogram will be performed at Screening and Weeks 9 and 12.

Frequencies and percentage of echocardiography interpretation results (normal, abnormal clinically significant, and abnormal not clinically significant) will be summarized by patients in Safety Set by study visit, overall.

9.6. Physical Examination

A complete physical examination of body systems (excluding breast and genitourinary examinations) according to standard of care and a neurological examination (including cranial nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait, all as applicable for the patient's age) will be performed at Screening, Day 1, and Weeks 2, 4, 5, 6, 9, and 12.

Frequencies and percentages of physical examination interpretation results (normal, abnormal clinically significant, and abnormal not clinically significant) will be summarized by treatment group within treatment period and study visit for each body system on patients in the Safety Set.

In addition, physical examination results will be summarized in listing.

9.7. Local Tolerability

Local tolerability data will be collected separately from AEs at Day 1 and Weeks 2, 4, 5, 6, and 9. Data will be collected on the nature of any reaction (including spontaneous pain, pain on palpitation, itching, redness, edema, induration/infiltration, and other type of reaction; other type of reaction will be coded using MedDRA, same version as for AEs), if reaction at injection site, the severity (i.e., mild, moderate, or severe), and any action taken (i.e., no action, interruption of infusion, and other). The likely cause of the reaction will also be collected (i.e., insertion site,

drug, adhesive dressing, or other).

The frequencies and percentages of patients with local tolerability findings collected separately from AEs, will be summarized within treatment period and study visit. Description will be performed only on the Dasiglucagon group.

9.8. Concomitant Medication

Concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) (Version September 01, 2018 or later) thesaurus.

Medications that started before first dose of dasiglucagon (dasiglucagon + SOC treatment group) or randomization (SOC only treatment group) will be considered prior medications if they were stopped before first dose of dasiglucagon/randomization. Any medications ongoing at start of trial will be considered to be concomitant medication ongoing at start. If a medication starts during the trial it will be considered as medication starting during the trial.

Concomitant Medication are described on the FAS according to randomized treatment.

Frequencies and percentages will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and Preferred Name, if applicable, by overall patients and treatment group within treatment period. The summary will be presented in descending order of frequency of ATC and then Preferred Name within ATC based on overall patients.

10. Changes from Planned Analysis

- The protocol mentioned how to handle analyses involving trial site; however, since randomization is stratified by region (US vs non-US), region will be included in the analyses (it is not included in the protocol). Thus no analyses will be performed by trial site.
- The Full Analysis Set definition was clarified to indicate that the primary endpoint baseline assessment needs to be non-missing for a patient to be included in the set.
- A PK Set was added to support summaries of PK data.
- In the protocol a common methodology for the imputation of missing data for primary and key secondary endpoints was described. This has been split into appropriate methods for imputing missing event data based on the negative binomial model and non-event data based on the MCMC method for non-monotone missing data and sequential regression for monotone missing data.
- Baseline for endpoints related to external CGM data will be defined taking into account data from 14 days before randomization, those days will not necessary by consecutive, this is different from baseline definition of the other endpoints.
- For the calculation of Extent of Exposure, regarding interpolation analysis any assessment more than 60 minutes apart will not be taken into account and this parameter has to be calculated taking the duration of CGM measurements into account. This is done by dividing AOC by duration of CGM measurements.
- Consistent wording of hypoglycemia episodes for all Zealand studies. Those endpoints are written SMPG-detected hypoglycemia episode and CGM-detected hypoglycemia episode.
- Add analysis assessment of COVID-19 impact

- While preparing for the blinded data review meeting for the ZP4207-17109 trial, the review identified that only 24 of 32 patients had a gastrostomy or NG tube at baseline. Patients without gastrostomy or NG tube cannot have any intake of gastric carbohydrates during the trial. Endpoints related to the use of gastric carbohydrates are therefore only applicable to the subgroup of patients with gastrostomy or NG tube. This zero-inflated distribution of the change in gastric carbohydrate use within the total trial population violates the assumption (that all enrolled patients could be receiving gastric carbohydtrates) behind the planned statistical evaluation. As a consequence, the key secondary efficacy endpoint addressing total amount of gastric carbohydrates to treat hypoglycemia will be removed from the key secondary efficacy endpoints, since it is not applicable to the entire trial population. All the secondary efficacy endpoints related to the use of gastric carbohydrates (now including "Total amount of gastric carbohydrates administered (via nasogastric [NG] tube or gastrostomy) per week to treat hypoglycemia during Weeks 2-4" removed from the key secondary endpoints) will be evaluated descriptively only in the subgroup of patients with gastrostomy or NG tube at screening.
- One subject (#204501) did not meet Randomisation Criteria #3, due to wrong procedure for measuring SMPG in the two weeks prior to randomisation (SMPG measures had been taken following meals and not pre-meal as required by protocol) Correct procedure was used in the first 2 weeks of the screening period and in that period the patient met the randomization criteria. During the blind data review meeting it has been decided to use the first two weeks of the screening period of SMPG-detected hypoglycemic episodes to define baseline value for this subject.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

Plasma concentrations are collected on week 6 and week 9 as per Schedule of Events Table 2.Descriptive summaries will be presented for plasma PK concentrations by study visit and infusion rate (in µg/kg/hr) at the end of Treatment Period 2, as described in Section 7.4. Information pertaining to PK data collection will be listed.

PK analysis is performed using PK population according to actual treatment received.

11.2. COVID-19 Assessment Analysis

As some patient were still in the study during the COVID-19 pandemic, we have assessed the impact on trial participants as well as the resulting measures taken to address the COVID-19 pandemic.
This assessment was made with blinded data and split in several sections.

- First section was about investigational product and trial withdrawal due to COVID-19. The conclusion was that COVID-19 did not impact the use of investigational drug, and there were no study withdrawals due to COVID-19.
- Secondly we have made an assessment on adverse events. No adverse events were related to COVID-19.
- Then we have made an assessment on Efficacy and Safety:

- Regarding efficacy, we just have one missing fasting tolerance test due to COVID-19. This missing assessment will be handled using the prespecified MI analysis stated in section 8.2. No other efficacy endpoint is affected by COVID-19.
  Regarding safety, as some visits were done remotely, we have some safety data which are missing for laboratory, vital signs, ECG, Echocardiography, Physical Examination, Local Tolerability. By visit, no more than 10% of subjects had any missing safety assessments. No specific analysis will be done on safety related to COVID-19 as impact is limited.
- As the impact of COVID-19 related to efficacy analysis/endpoints is limited, it has been decided to present a summary table of patients/visits impacted by COVID-19 as well as a listing describing data impacted for each impacted subject .

12. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

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3. The Royal Statistical Society: Code of Conduct, 2014.

4. Keene, O.N., J. H. Roger, B. F. Hartley, and M. G. Kenward (2014). "Missing data sensitivity analysis for recurrent event data using controlled imputation." *Pharmaceut Statist* **13**: 258–264.

5. Little, R. and D. Rubin (1987). Statistical Analysis with Missing Data, New York: Wiley.

6. Carpenter, J. R., and M. G. Kenward (2013). Multiple Imputation and its Application (Statistics in Practice), Wiley.

7. Ratitch, B. and M. O'Kelly (2011). "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures." PharmaSUG. Available at http://www.pharmasug.org/proceedings/2011/SP/PharmaSUG-2011-SP04.pdf

8. The PedsQL Measurement Model for the Pediatric Quality of Life Inventory – Scoring Instructions (www.pedsql.org).

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize the presentation with common notations.

General Reporting Conventions

- All tables and data listings will be developed in landscape orientation.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used on a table, figure, or data listing.
- Adverse events with missing MedDRA coding will have their system organ class and/or preferred term presented as “Not Coded” in the tables. The “Not Coded” frequencies will be sorted to the end of the tables. This will only be applicable for any deliveries sent before database lock (e.g., for dry runs).
- Programming notes may be inserted into the shells, these notes will not appear in the final output.

Population Summary Conventions

- Population sizes may be presented for each classification factor as totals in the column header as (N=xx), where appropriate.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed; however, counts and percentages of missing values may be needed.
- All population summaries for continuous variables will include: n, mean, SD, median, minimum, and maximum. Other summaries (e.g., number missing, geometric mean, median, quartiles, 95% CIs, and coefficient of variation [CV] or % CV) may be used as appropriate. The precision of the maximum and minimum will match the maximum precision in the data. The mean and median will have 1 additional decimal place. The SD will have 2 additional decimal places.
- All percentages are rounded and reported to a single decimal point (xx.x%).

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AD	associated documents
ADR	adverse drug reactions
AE	adverse event
AERLI	adverse event risk of liver injury
AESI	adverse events special interest
AESINE	adverse event neurological events
AESINME	adverse event suspicion of necrolytic migratory erythema
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLQ	beneath limit of quantification
BMI	body mass index
BRD	business requirements document
BSL	biostatistician lead
CCGs	CRF completion guidelines
CD	compact disc
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CGM	continuous glucose monitoring

Abbreviation	Definition
CHI	congenital hyperinsulinism
CI	confidence intervals
CIOMS	council for international organizations of medical sciences
CIP	clinical investigational plan
CM	clinical manager
CMP	clinical monitoring plan
COV	close out visit
COVID-19	COronaVIrus Disease 2019
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSM	clinical supply manager
CSR	clinical study report
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DBP	diastolic blood pressure
DCRF	data change request form

Abbreviation	Definition
DDE	drug dispensing error form
DEA	drug enforcement administration
DIA	drug information association
DIS	data integration specification
DLT	dose limiting toxicity
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DML	data management lead
DMP	data management plan
DNA	deoxyribonucleic acid
DOB	date of birth
DS	document specialist
DSG	drug safety group
DSM	drug supply management (drug distributor)
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
DTS	data transfer specification
DVD	digital video disk
EC	ethics committee

Abbreviation	Definition
ECD	edit check and derivation specifications
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European medicines agency
eTMF	electronic trial master file
EU	European Union
FA	full analysis
FDA	food and drug administration
FMP	file management plan
FPFV	first patient first visit
FPI	first patient in
GCP	good clinical practice
GMP	good manufacturing practices
GPV	global pharmacovigilance
HR	heart rate
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization
ID	identification
IDM	independent drug monitoring

Abbreviation	Definition
IEC	independent ethics committee
IM	investigator meeting
IMV	interim monitoring visit
IND	investigational new drug
INDSR	investigational new drug safety reports
IP	investigational product
IRB	institutional review board
IRF	inventory release file
IRR	infusion related reactions
IRT	interactive response technology
ISF	investigator site file
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
IxRS	interactive voice/web response system
J2C	jump-to-control
KPI	key performance indicator
LAN	local area network
LDM	lead data manager
LMS	learning management system
LLOQ	lower limit of quantification

Abbreviation	Definition
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MAAP	medical affairs and pharmacovigilance teams
MAH	marketing authorization holder
MAR	missing at random
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
MNAR	missing not at random
MTD	maximum tolerated dose
MVR	monitoring visit report
N	number
NA	not applicable
NCS	non-clinically significant
NF	non-functional
PD	protocol deviation
PDGP	protocol deviation guidance plan
PE	physical examination

Abbreviation	Definition
PG	plasma glucose
PI	principal investigator
PIN	personal identification number
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol
PRIMS	Premier Research information management system
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life
ROT	record of training
RR	respiratory rate or relative rate
RSM	regional site monitor
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SC	study coordinator
SCR	software change request
SD	standard deviation
SDS	study design specifications
SDTM	study data tabulation model
SDV	source data verification
SECC	self-evident correction conventions
SECP	self-evident correction plan
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SLA	service level agreement
SMP	safety management plan
SMPG	self-monitored plasma glucose
SOC	system organ class
SOP	standard operating procedure
SOW	statement of work
SQV	site qualification visit
SUA	start-up associate

Abbreviation	Definition
SUSAR	suspected, unexpected, serious adverse (drug) reaction
TA	trial assistant
TEAE	treatment-emergent adverse event
TMF	trial master file
TOM	task ownership matrix
UAT	user acceptance testing
USA	United States of America
UTC	universal coordinated time
WAN	wide area network
WAR	work at risk
WG	working guideline
WHO	world health organization
WHO-DD	world health organization drug dictionary