PROTOCOL TITLE: An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism

NCT Number: NCT03941236

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Document History

Version	Date	Author	Description
1.0	03JUL2020	[redacted]	Initial Version
2.0	14OCT2021	[redacted]	Update as per protocol amendment
3.0	25FEB2022	[redacted]	Add CGM sensitivity analysis Add supportive analysis of CGM and gastric carbohydrates Include BOLUS in total dasiglucagon exposure calculation Specify rules for pancreatectomy censoring Specify analysis of PK/ADA unscheduled visits
4.0	31OCT2022	[redacted]	Pancreatectomy time-to event derivation made accurate Periods added to period derivation
5.0	19JUN2023	[redacted]	Added SMPG related efficacy endpoints as per new protocol version in sections 2.2.4, 8.3 Added handling of exposure records with regards to multiple regimens and missing times in section 6.1.8 Added CGM sensitivity analyses and description of data for main analysis in sections 8.1, 6.1.7 CGM assessment duration derivation rule added in section 6.1.7
6.0	03JUL2024	[redacted]	Added handling of pancreatectomy for SMPG endpoints the same way as for CGM and other efficacy endpoints

			Added imputation details for CGM endpoints Added information on additional PK/ADA interim analysis
7.0	11OCT2024	[redacted]	Added data imputation and analysis method description with LOCF method for oral and gastric/NG tube carbohydrate amounts that are administered for treating hypoglycemia Added related derived variables

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Zealand Pharma A/S protocol number ZP4207-17106 (An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism), dated 09-Apr-2024 Version 16.0 for all countries except UK and Germany, protocol dated 09-Apr-2024 Version 17.0 for Germany and protocol dated 02-Sep-2024 for UK. 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 ZP4207-17106.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety of dasiglucagon administered as subcutaneous (SC) infusion in children with CHI.

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the long-term efficacy of dasiglucagon in reducing hypoglycemia
- To evaluate the long-term efficacy of dasiglucagon in reducing glucose requirements
- To evaluate the long-term tolerability of dasiglucagon administered as SC infusion in children with CHI
- To investigate quality of life (QoL) and resource utilization

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint of this study is the incidence of adverse events.

2.2.2. Key Secondary Efficacy Endpoints

Key secondary efficacy endpoints of this study include the following:

- Total amount of gastric carbohydrates administered (nasogastric [NG] tube or gastrostomy) to treat hypoglycemia
- Time to removal of NG tube or gastrostomy
- Time to pancreatic surgery (sub-total or total pancreatectomy)
- Continuous glucose monitoring (CGM) percent time <70 mg/dL (3.9 mmol/L)
- Rate of CGM-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more
- Rate of clinically significant CGM-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more.

2.2.3. Secondary Efficacy Endpoints

- Number of gastric carbohydrates administrations (NG tube or gastrostomy) to treat hypoglycemia
- Number of nightly (midnight to 6 am) gastric carbohydrate administrations (NG tube or gastrostomy) to treat hypoglycemia
- Extent of hypoglycemia (Area over the glucose curve [$AOC_{glucose}$] below 70 mg/dL [3.9 mmol/L] as measured by CGM
- Extent of hypoglycemia (Area over the glucose curve [$AOC_{glucose}$] below 54 mg/dL [3.0 mmol/L] as measured by CGM
- Reduction in diazoxide dose (mg/kg body weight/day) from start of lead-in trial
- Reduction in somatostatin analog dose (µg/kg body weight/day) from start of lead-in trial
- Change in total amount of prescribed continuous gastric carbohydrate administrations from start of lead-in trial (g/day)
- Change in prescribed duration of infusion of continuous gastric carbohydrate administration from start of lead-in trial (h/day)
- Change in prescribed duration of infusion of nightly (8 pm – 8 am) continuous gastric carbohydrate administration from start of lead-in trial (h/day)

2.2.4. Other Efficacy Endpoints

- CGM percent time in range 70-180 mg/dL (3.9-10.0 mmol/L)
- CGM percent time > 180 mg/dL (10.0 mmol/L)

- CGM percent time < 54 mg/dL (3.0 mmol/L)
- Number of parent reported hypoglycemic events pr. week that required an intervention and with PG <70 mg/dL (3.9 mmol/L) as detected by self-monitored plasma glucose (SMPG) or CGM
- Number of SMPG-detected hypoglycemia episodes < 70 mg/dL (3.9 mmol/L) pr. week based on SMPG measurements as captured in patient device
- Number of clinically significant SMPG-detected hypoglycemia episodes < 54 mg/dL (3.0 mmol/L) pr. week based on SMPG measurements as captured in patient device
- Number of emergency department visits for hypoglycemia
- Number and length of hospitalizations caused by CHI or CHI-related events
- Number of outpatient visits to health care providers (family doctors, specialist, clinic visits not part of the mandatory scheduled ones) caused by CHI or CHI-related events
- Number of home-visits by paramedics due to hypoglycemia
- Quality-of-life (Pediatric Quality of Life Inventory |PedsQL] Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score] and CHI-Specific questionnaire).

2.2.5. Safety Endpoints

The safety endpoints of this study include the following:

- Changes in clinical evaluations:
  - Vital signs
  - Physical examination
  - 12-lead electrocardiogram (ECG)
- Changes for clinical laboratory assessments:
  - Hematology
  - Biochemistry
  - Antidrug antibodies (ADAs)

2.2.6. Pharmacokinetics

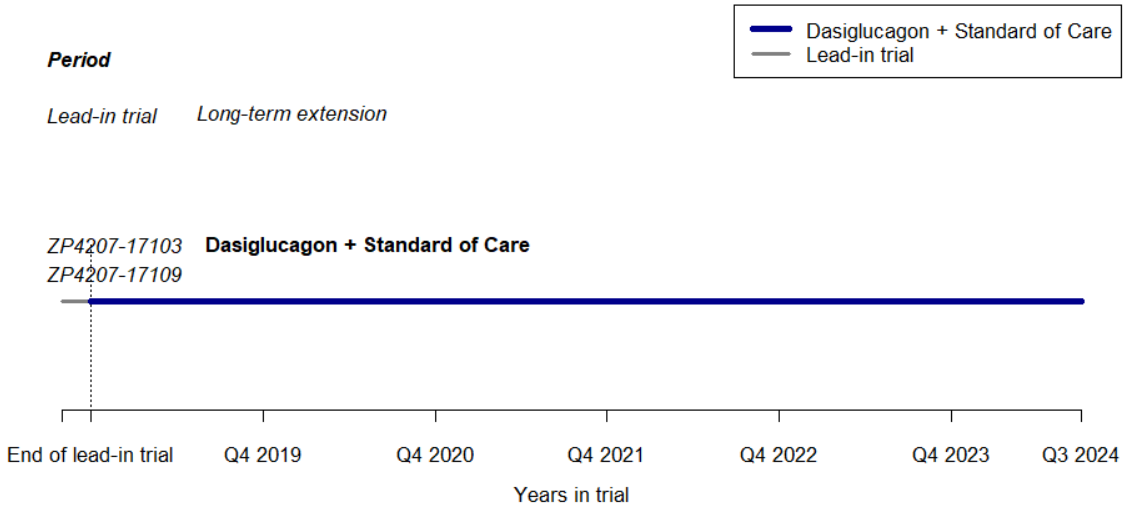
Blood samples will be collected at Month 3, Month 6, Month 12, every 6 months thereafter until End of Treatment and 12 weeks after the End of Treatment (Follow-up phase).

3. Overall Study Design and Plan

This is a phase 3, open-label, multinational, multicenter, long-term safety and efficacy extension trial in patients with CHI who completed either ZP4207-17103 or ZP4207-17109 (defined as a lead-in trial). The primary objective of this trial is to assess the long-term safety of dasiglucagon administered as SC infusion. Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with possible further dose adjustments to optimize treatment to each patient's needs.

The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial. Any post-treatment follow-up scheduled for patients in the lead-in trial will be redundant if they are enrolled in the present trial by the time of the scheduled Follow-up Visit.
Patients will be seen at the trial site at Months 1, 3, and 6, and every 3 months thereafter, and contacted by the investigator monthly by telephone in between site visits. Patients will be allowed to remain in the trial until approval and commercial availability of dasiglucagon in the country of participation or until approximately Q4 2022, whichever occurs first. Figure 1 depicts the trial design.

Figure 1: Study Design



3.1. Overall Design

3.2. Sample Size and Power

The sample size is based upon patients rolling over from the lead-in trials; no sample size calculation was performed.

3.3. Study Population

This trial pools patients with CHI from 2 lead-in trials, one in children ≥7 days and <3 months of age (Trial ZP4207-17103) and the other in children between 3 months and 12 years of age (Trial ZP4207-17109) and investigates safety and efficacy of dasiglucagon during extended exposure. Patients completing Trial ZP4207-17103 will generally have attained an age that is within the age span for Trial ZP4207-17109, and the pooling of the two trial populations for this extension trial is considered justified.

3.4. Treatments Administered

Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with an option to further titrate the dose to meet the needs of each individual patient. 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

Unblinded CGM will be used throughout the entire trial period to guide treatment decisions. Pauses are allowed; however, CGM must be used for the 30 days leading up each site visit.

3.5. Method of Assigning Patients to Treatment Groups

Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with an option to further titrate the dose to meet the needs of each individual patient.

3.6. Blinding and Unblinding

This is an open-label trial.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

	Trial Period									ADA Follow-up Period
Trial Period	**Last Visit in Previous Trial[a]**	**Treatment Period (Monthly Phone Calls between Visits[b])**							**Follow-up[d]**		**ADA Follow-up**
Visit Month	**As per protocol**	**M1**	**M3**	**M6**	**M9**	**M12**	**M...[c]**	**EoT**	**EoT + 4 weeks**	**EoT + 12 weeks**	**FU cont....[e]**
Day		**30**	**90**	**180**	**270**	**360**		**EoT**			
Time window (days)	**As per protocol**	**±3**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	**±7**	
Visit #	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7+...**	**EoT**	**FU1**	**FU2**	**ADA FU Visit**
General assessments											
Informed consent/assent	X										
Inclusion/exclusion criteria	X										
Demography	Transferred										
Body weight and length/height	X	X	X	X	X	X	X	X		X	
Medical history (including current illness)	Transferred										
Concomitant medication	X, and continuing medication transferred	X	X	X	X	X	X	X	X	X	
Safety assessment											
Electrocardiogram	X	X	X	X	X	X	X	X		X	
Echocardiography	X					X	X[f]			X	
Vital signs[g]	X	X	X	X	X	X	X	X		X	
Serum pregnancy test[h]	X		X	X	X	X	X	X		X	
Adverse events[i]	X, and ongoing events transferred	X	X	X	X	X	X	X	X	X	
Local tolerability	X	X	X	X	X	X	X	X			

	Trial Period									ADA Follow-up Period
Trial Period	**Last Visit in Previous Trial[a]**	**Treatment Period (Monthly Phone Calls between Visits[b])**							**Follow-up[d]**		**ADA Follow-up**
Visit Month	**As per protocol**	**M1**	**M3**	**M6**	**M9**	**M12**	**M...[c]**	**EoT**	**EoT + 4 weeks**	**EoT + 12 weeks**	**FU cont....[e]**
Day		**30**	**90**	**180**	**270**	**360**		**EoT**			
Time window (days)	**As per protocol**	**±3**	**±5**	**±7**	**±7**	**±7**	**±7**	**±7**	**±3**	**±7**	
Visit #	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7+...**	**EoT**	**FU1**	**FU2**	**ADA FU Visit**
Physical examination and neurological examination	X	X	X	X	X	X	X	X		X	
Laboratory											
Clinical laboratory tests[j]	X		X	X	X	X	X	X		X	
HbA1c		X		X		X	X[k]	X		X	
Antibodies[l]	X		X	X		X	X[k]	X	X	X	X
Pharmacokinetics/drug exposure	X		X	X		X	X[k]	X		X	
Efficacy											
CGM and daily self-monitored plasma glucose	Continuous										
Prescribed continuous gastric carbohydrates	X[m]			X		X		X			
Trial materials and reminders											
Dispense patient diary[n]	X	X	X	X	X	X	X				
Diary review[n]		X	X	X	X	X	X	X			
QoL questionnaires[o]	X	X	X	X	X	X	X	X		X	
Benefit/risk assessment[p]		X	X	X	X	X	X				
Dispensing of trial product	X	X	X	X	X	X	X				
Trial product return and accountability		X	X	X	X	X	X	X			

Abbreviations: ADA = antidrug antibodies; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CGM = continuous glucose monitoring; CHI = congenital hyperinsulinism; EoT = end of treatment; FU = follow-up; HbA1c = hemoglobin A1c; LAR = legally authorized representative; M = month; PK = pharmacokinetics; QoL = quality of life; SpO_2 = blood oxygen saturation level; V = visit

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

a The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial.
b Investigator-initiated monthly telephone calls in between visits to support the patient/parent(s)/guardian at home.
c After Visit 6, additional visits should be scheduled every 3 months until end of treatment.
d Any post-treatment Follow-up Visits will be redundant for the patients who are continuing treatment with dasiglucagon commercially or through an EAP, and they will end trial participation at their EoT Visit.
e After Trial Completion (Trial Period), patients who are ADA-positive will be invited to come for ADA FU Visits 1 to 3 times a year with a minimum of 4 months between the visits, until the ADA levels return to baseline or until 2 years after End of Trial, whichever occurs first. Baseline is defined as the ADA level prior to dasiglucagon dosing in the lead-in trial.
f Echocardiography will be done every 12 months throughout the Treatment Period.
g Vital signs include blood pressure, heart rate, respiratory rate, and SpO_2.
h A serum pregnancy test will be performed every 3 months in females of child-bearing potential
i The investigator should ask the patient and their caregiver(s), about any possible signs and symptoms of seizures, as described in Appendix D
j Clinical laboratory tests include hematology and biochemistry.
k HbA1c, ADA, and PK/drug exposure sampling will be performed at intervals of 6 months after Visit 6.
l Any treatment-induced or treatment-boosted ADA-positive patients will be monitored until the ADA levels return to baseline
m Data related to the start of the lead in trial should also be collected at V1 (ZP4207-17103: Start of the trial is defined as the 7 days prior to the run-in period and for ZP4207-17109: Start of the trial is defined as the 7 days prior to randomization).
n Diaries should be handed out and collected at each visit. Patients' parent(s)/guardian and patient, as appropriate, will be reminded how to use the diary and obtain a new one at each visit.
o The PedsQL (parent-reported versions) and CHI disease-specific questionnaires should be the first assessments performed at each visit.
p Investigators will be required to reaffirm and document a positive benefit/risk assessment of continued treatment with dasiglucagon at each site visit, in close collaboration with the parent(s)/LAR to ensure that patients are not unnecessarily exposed to the trial product.

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, 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 (i.e., 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 $\alpha = 0.05$.

4.2. Interim Analysis and Data Monitoring

4.2.1. Interim Analysis

Interim evaluation will be performed on all endpoints to support regulatory filing. No adjustment for multiplicity will be done, since evaluation of endpoints are not confirmatory.

An additional partial Interim Analysis will be performed only for PK/ADA data to support regulatory filing.

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.

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 trial drug during the extension trial or lead-in trials. This population will be used to provide descriptive summaries of safety data.
- **Full Analysis Set (FAS):** The FAS includes all patients in the Safety Set who complete at least 1 day of trial drug. This population will be used to analyze efficacy data.
- **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.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For total carbohydrates administered to treat hypoglycemia, baseline is defined as the average weekly value during the last 2-weeks of the lead-in trial.
For CGM percent time below 70 mg/dL baseline is defined as the CGM percent time below 70mg/dL during the last 2 weeks of the lead-in trial.
For clinically significant CGM-detected episodes of hypoglycemia, baseline is defined as the average weekly value of hypoglycemic rate (CGM) during the last 2 weeks of the lead-in trial.
For quality of life questionnaire, they are assessed at entry in lead-in study.
For all other efficacy and safety endpoints, baseline is defined as the End of Treatment Visit time point value from lead-in trials ZP4207-17103 or ZP4207-17109.
For endpoints related to concomitant medication (diazoxide, somatostatin), start of lead-in trial refers to the concomitant medication recorded on the day of first exposure to treatment (or randomization date for standard of care only group) in lead-in trial.
For the three secondary endpoints, related to change of prescribed continuous gastric carbohydrate administrations, start of lead-in trial is defined as:

- 7-days prior to run-in for ZP4207-17103 trial

- 7-days prior to randomization for ZP4207-17109 trial

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

All statistical tests performed for key secondary endpoints are exploratory in nature so no adjustment for multiple comparisons will be performed.

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

6.1.4.2. Imputation of Missing CGM Data

CGM-based efficacy parameters will be imputed as per the following rules:

6.1.4.2.1 Parameters to be imputed

The following CGM parameters will be imputed:

- CGM Percent Time in Range (%)
- CGM Percent Time in Hypoglycemia < 70 mg/dL (%)
- Rate of Hypoglycemic Episodes (CGM) (per week)
- Rate of Clinically Significant Hypoglycemia Episodes (CGM) (per week)
- CGM Percent Time in Clinically Significant Hypoglycemia < 54 mg/dL (%)

6.1.4.2.2 Reason for imputation

In the main trial analysis CGM parameters were analyzed by trial time period (Month 1, Month 2 to Month 3, Month 4 to Month 6, etc.), so the relevant period for imputation is each trial time period (the CGM devices are only able to store data points for 30 days' worth of data and data outside the 30 days were therefore not available for upload to the trial database at the clinic visits). According to Battelino et al (2023), a paper recommended by the FDA in this context, the aim should be to collect at least 14 consecutive days of CGM data with at least 70% of data during that time period. This was not always met for all of the trial time periods during the trial so some imputation will be implemented.

For calculation of the % of missing data in a time period, it is assumed that CGM readings should be recorded every 5 minutes, so complete data would be 288 CGM readings in a 24 h period, and missing data is defined as anything less than 288 readings per 24 h, with the % of missing data in a 24 h period calculated as the difference in the number of observed readings from 288 and using 288 as the denominator. Although trial time periods are often considerably longer than 14 days (most of them have a duration of 3 or 6 months), a trial time period will be considered to have adequate data as long as there is at least one period of consecutive CGM

recording of at least 14 days with 70% data completeness during that period.

6.1.4.2.3 Evaluation of data to be imputed

Data will be imputed only for those trial time periods in which the patient is still on trial treatment.

Time periods for efficacy evaluation are described in Section 8 and under derivations, Section 6.1.7, time periods used for imputation refer to the same periods: Month 1, Month 2-3, Month 4-6, Month 7-9, Month 10-12, Month 13-18, Month 19-24, Month 24-30 and every 6 months until end of treatment period.

If a patient has already permanently discontinued treatment before the start of a time period, no data will be imputed. If a patient discontinues part way through a time period, then the following rules will apply:

- If a patient has observed data during the time period, and the data meet the criteria of at least 14 consecutive days for data with 70% data completeness during that time period, then the data will be used as is and no imputation is necessary
- If a patient has any amount of observed data during the time period that does not meet the above criteria, then observed data will be disregarded and data will be imputed for the time period
- If a patient has no observed data at all during the time period, then data will be imputed for the time period irrespective of how long the patient remains in the time period before permanent discontinuation of trial treatment.

We will therefore create derived variables for each trial time period, and impute data at the trial time period level if data are missing or inadequate. For this purpose, any trial time period with less than 14 consecutive days of data collection or with less than 70% data completion during the longest consecutive recording period will be considered inadequate. Partial data from inadequate trial time periods will be discarded and completely replaced by imputation. This will avoid the potential bias if the observed data at time periods with partial data is not representative of the time period as a whole (for example, if data were collected only in the daytime and not at night).

6.1.4.2.4 Aim of imputation

The analysis of the trial is mostly descriptive, so the aim of imputation is simply to provide appropriate estimates for what missing values might have looked like, and not to estimate the imputation variance. Only a single imputation will therefore be done for each missing value, rather than multiple imputation.

6.1.4.2.5 Method of imputation

The imputation is planned fitting a mixed model for repeated measures to the entire dataset at once, in which missing values would be imputed based on predicted values for a model including all timepoints simultaneously in the model and treating them as repeated measures with random patient effects and first order autoregressive effects for the correlation within patients.

The imputed values will be the point estimate of the predicted values from the regression model.

A linear regression model (proc mixed) will be used for the % time in range, a generalized linear regression model (proc glimmix) with a normal distribution and a log link function will be used for % time in hypoglycaemia (by each definition), and a negative binomial regression model for count outcomes.

Each model will be a mixed model for repeated measures with a random patient effect and a first-order autoregressive structure assumed for the covariance between repeated measures in the same patient.

For the count outcomes, the count of events during each trial time period will be treated as the dependent variable, and the log of the duration of the data collection period (in weeks) will be used as the offset variable. The duration will be taken as the number of weeks in which CGM data were recorded. For values being imputed where CGM data are available but are disregarded because they did not meet the minimum data quality standard, the actual number of weeks for which CGM data were recorded will be taken as the duration, and for values being imputed where no data are available at all, a 1 week duration will be assumed and data imputed for a 1 week period. To calculate imputed rates per week, the number of events in the period will be divided by the duration of CGM measurement during the period in weeks.

For GLIMMIX models for % time in hypoglycaemia (by each definition), and a negative binomial regression model for count outcomes, random intercept is added at the subject level to take account of the differences among subjects.

6.1.4.2.6 Procedure details

The procedure for analysis will be as follows.

Table 2: Imputation procedure

Step No	Brief description	Details
1	Set incomplete values to missing	Set individual values to missing if the amount of observed data is below the threshold for imputation (< 14 consecutive days of data collection or < 70% data completion during the longest consecutive period of data collection).
2	Mixed model for repeated measures to impute missing data.	A mixed model for repeated measures will be run for the entire dataset, including trial time period and region as fixed effects and patient as a random effect . In addition a first-order autoregressive effect will be included for the correlation between timepoints within patients. An offset will also be included for count variables as described in section 6.1.4.2.5. Values will be imputed based on the predicted values of the model. No imputation will be done for trial time periods after the patient permanently discontinues treatment. Appropriate constraints will be applied to imputed values (% values cannot be <0 or > 100).

Step No	Brief description	Details
3	Run analysis on imputed data	The imputed data will be used to calculate descriptive statistics for the parameters as in the original trial.

6.1.4.3. Imputation of Missing/Not Answered Gastric/ NG Tube Carbohydrate and Oral Carbohydrate Treating Hypoglycemia Data

If there are Hypoglycemic Events recorded, with intervention, and intervention details (amount of carbohydrates given) are not available, then imputation will be performed as per the following for

- Recordings of hypoglycemia with oral intervention with missing oral carbs
- Recordings of hypoglycemia with gastric intervention with missing gastric carbs

Rationale behind imputing data: Some carbohydrates have been administered as per diary source to treat hypoglycemia; it is only amount that is not known.

If amount of carbohydrates is not answered and recorded as such as per source data, amount will be imputed using LOCF (last observation carried forward) method, taking the latest value captured before the date of the administration of Not Answered amount.

Rationale behind decision on LOCF: as feedings vary in great extent among subjects (in some cases breastfed, in others usual fluid/food taken), using subjects' own data from other feeding occasion is deemed to be appropriate.

If there are hypoglycemic events with oral/gastric carbohydrate interventions recorded, but there are no carbohydrate administrations treating hypoglycemia with non-missing carbohydrate amount in the entire treatment period, patient will be not included in the analysis of endpoints related to carbohydrate administration treating hypoglycemia.

6.1.5. Analysis Visit Windows

For analyses involving shift table from baseline to maximum/minimum values, unscheduled measurements will be taken into account.

For all other 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
Month 1	30	27	33
Month 3	90	85	95
Month 6	180	173	187
Month 9	270	263	277
Month 12	360	353	367
Every 3 Months until EoT		-7 days	+7 days
End of Treatment	EoT	-7 days	+7 days
Follow-up + 4 weeks	FU1	-3 days	+3 days
Follow-up + 12 weeks	FU2	-7 days	+7 days

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 / Baseline visit** = The End of Treatment visit from lead-in trial (ZP4207-17103 or ZP4207-17109).

- **Last 2 weeks of Lead-in trial :** Defined as Week 7 and Week 8 from ZP4207-17109 study definition and Week 3 and Week 4 from ZP4207-17103 study definition.

- **Time-period**: time period will be defined as Month1, Month2-Month3, 3-month for first year and 6-month for subsequent years. CGM, Exposure, Adverse events, Gastric carbohydrates, CHI related hospitalization are mapped according to those time periods. Mapping is done as per below instructions:

  "Month 1" start date = day 1, end date = Min(start date + 29 days, date of trial discontinuation)
  "Month 2 - Month 3" start date = month 1 end date + 1, end date = Min(start date + 59 days, date of trial discontinuation)
  "Month 4 - Month 6" start date = month 2-3 end date + 1, end date = Min(start date + 89 days, date of trial discontinuation)
  "Month 7 - Month 9" start date = month 4-6 end date + 1, end date = Min(start date + 89 days, date of trial discontinuation)
  "Month 10 - Month 12" start date = month 7-9 end date + 1, end date = Min(start date + 89 days, date of trial discontinuation)

"Month 13 - Month 18" start date = month 12 end date + 1, end date = Min(start date + 179 days, date of trial discontinuation)
"Month 19 - Month 24" start date = month 13-18 end date + 1, end date = Min(start date + 179 days, date of trial discontinuation)
"Month 25 - Month 30" start date = month 19-24 end date + 1, end date = Min(start date + 179 days, date of trial discontinuation)
"Month 31 - Month 36" start date = month 25-30 end date + 1, end date = Min(start date + 179 days, date of trial discontinuation)
"Month 36 - Month 42" start date = month 31-36 end date + 1, end date = Min(start date + 179 days, date of trial discontinuation)

Same rules for further time periods.

- **Event Rate =** average of the weekly number (sum) of events/episodes, based on the number of weeks in the relevant period (Month1, Month2-Month3, 3-month or 6-month). Number of weeks is defined using start and end dates defined above in time period definition. Events include clinically significant CGM-detected hypoglycemia, and gastric carbohydrate administrations. For gastric carbohydrate and nightly gastric carbohydrate administrations treating hypoglycemia, all administrations are considered, those observed and imputed by LOCF method.

- **CGM event rate by CGM assessment duration: =** average of the weekly number (sum) of events/episodes, based on the number of weeks in the relevant period when CGM device has been worn (Month1, Month2-Month3, 3-month or 6-month).
- **CGM assessment duration =** for each phase, duration in weeks is calculated for the specific analysis based on analysis and backfill flags: total CGM assessment duration for the period for CGM assessments meeting the analysis criterion is summed, assuming each CGM assessment last 5 minutes.

- **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 =** A treatment-emergent AE is defined as an AE with an onset at the time of or following the start of treatment with the trial drug through the 12-weeks Follow-up Visit or Early Termination Visit, whichever occurs first. For patients who discontinued treatment but continues in the trial, TEAE will be defined up until 12 weeks after treatment termination.

- **Serious Adverse Events Associated with Devices (SADEs):** those are defined as TEAE serious with AE related to a study device or a device procedure item answered “Possible” or “Probable” for the German population or with serious AE not related to study but related to other reason which is study device for the non-German population.

- **PK Clearance:**

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

- where R0= infusion rate (pmol/h) and Css = concentration at steady state (pmol/L), conversion factor for infusion rate (1µg/hr = 295.72 nmol/h)

- **Hypoglycemic CGM-detected episode =** PG <70 mg/dL (3.9 mmol/L) for 15 minutes or more within 60 minutes, as measured by CGM. The 15 minutes do not need to be consecutive. 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 after the 60 minutes time frame. Episode will be defined by programming using external CGM data.(External data is not captured in EDC but transferred directly from vendor in data file as per data transfer agreement).

- **Clinically significant hypoglycemia CGM-detected episode** = PG <54 mg/dL or 3.0 mmol/L for 15 minutes or more within 60 minutes, as detected by CGM. The 15 minutes do not need to be consecutive. 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 after the 60 minutes time frame. Episode will be defined by programming using external CGM data.

- **Hypoglycemic SMPG-detected episode =** PG <70 mg/dL (3.9 mmol/L) for 15 minutes or more within 60 minutes, as measured by SMPG. The 15 minutes do not need to be consecutive. 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 after the 60 minutes time frame. Episode will be defined by programming using external (Vitalograph SMPG) data (External data is not captured in EDC but transferred directly from vendor in data file as per data transfer agreement).

- **Clinically significant hypoglycemia SMPG-detected episode** = PG <54 mg/dL or 3.0 mmol/L for 15 minutes or more within 60 minutes, as detected by SMPG. The 15 minutes do not need to be consecutive. 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 after the 60 minutes time frame. Episode will be defined by programming using external (Vitalograph SMPG) data.

- **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)
  - **Hyperglycemia:** PG >180 mg/dL (10 mmol/L)
  - **Clinically significant hypoglycemia:** PG <54 mg/dL (3.0 mmol/L)

- **Time to removal of NG tube or gastrostomy =** time from day 1 to removal of NG tube or gastrostomy as reported in medical history at entry in extension study and in the Healthcare Encounters eCRF form during extension study. In case of study withdrawal, patient will be censored to end of study day. Time will be calculated in months. This analysis will be performed on the subgroup of patients with an NG tube or gastrostomy at entry in extension trial. As from Healthcare Encounters time is given in date/time format, in case time is missing it will be set to 00:00. Day 1 time will be set to 00:00.

- **Time to pancreatic surgery =** time from day 1 to pancreatic surgery (>= 95% removal) as reported in healthcare encounters. In case of study withdrawal, patient will be censored to end of study day. Time will be calculated in months. This analysis will be performed on the subgroup of patients without pancreatic surgery at entry in extension trial. This subgroup of patients is the group of patients without any recordings in medical history with preferred term “Pancreatectomy” and percentage greater than or equal to 95%.

- **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-months treatment period. When k = 0, t_k is set to 0 and PG_k is the PG value corresponding to the start of the 3-month 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 measured 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 threshold 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 time period.

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}.

- **Nightly gastric carbohydrates** = amount of gastric carbohydrates (g) given between midnight and 6 am, inclusive. All values added, those observed and imputed by LOCF method.

- **Number of Gastric Carb Administrations with Not Answered Amount**= count of gastric carbohydrates (g) with Not Answered amount administered throughout a period.

- **Number of Oral Carb Administrations with Not Answered Amount**= count of oral carbohydrates (g) with Not Answered amount administered throughout a period.

- **PedsQL scoring for each scale and summary score[4]:**

    - 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).

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 or missing.

If partial event (AE or concomitant medication) dates occur, the convention for replacing

missing dates for the purposes of calculating derived variables is as follows:

For partial event start dates:

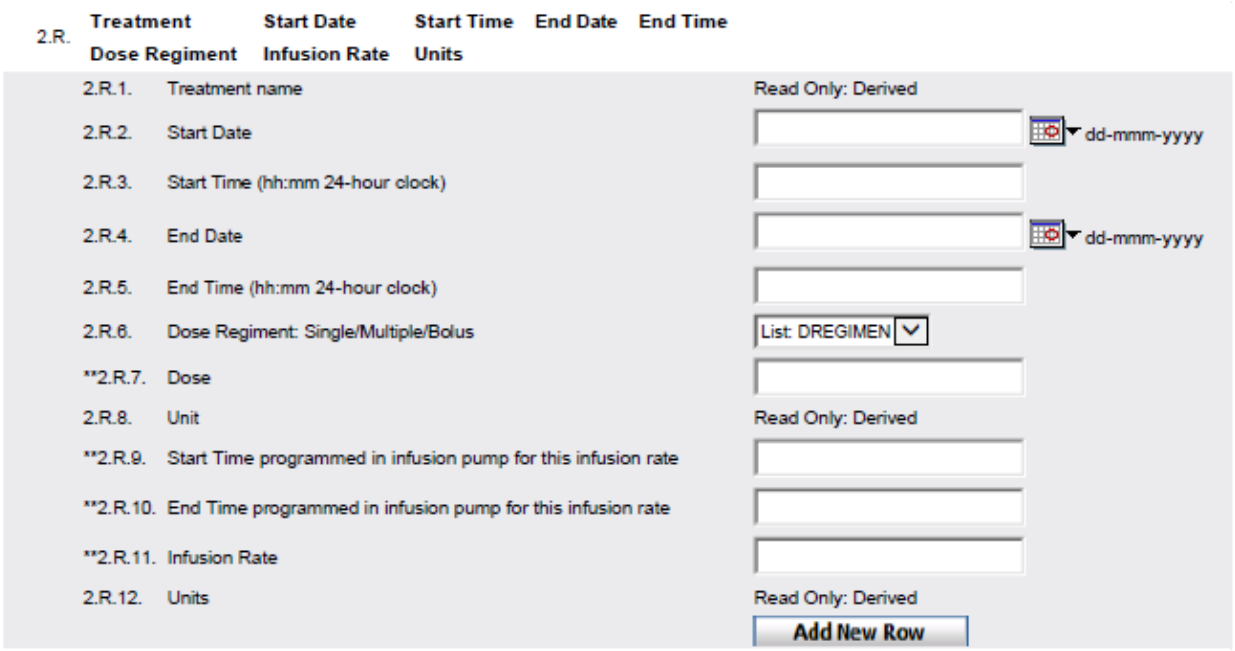
- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, or event is ongoing, then impute as the month and day of the first dose date.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

For partial event 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.

Handling of exposure data will be done as per the following:

For Dasiglucagon infusion exposure records, where multiple regimens are recorded in CRF (as per CRF Dose Regiment=Multiple), observations are to be divided to have consecutive exposure observations. This is done taking the start and end date/time of the infusion (Start date/Start time and End date/End time in CRF respectively) and taking the programmed start/end time of the infusion pump (Start Time/End time programmed in infusion pump for this infusion rate). If start time is not recorded and dates are the same, then the previous end time is used as start time for the regimen. If end time is not recorded and dates are the same, then the next start time is used as end time for the regimen. If this was not possible due to both previous end and next start having not been recorded, then change in regimen time is assumed to be midnight: 00:00 for start times and 23:59 for end times.



7. Study Patients and Demographics

7.1. Disposition of Patients and Withdrawals

The numbers of patients enrolled in extension study, completing, and withdrawing from treatment and the trial, along with reasons for withdrawal from treatment and trial, respectively, will be tabulated overall. 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 overall and by region (US, Non-US). Z-scores (based on the World Health Organization [WHO] growth charts) will be derived using a patient's age and sex. 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 time period (Month 1, Month 2-3,

Month 4-6, Month 7-9, Month 10-12, Month 13-18, Month 19-24, Month 24-30 and every 6 months until end of treatment period). The total dasiglucagon exposure will also be described weekly for the first three months and then monthly for the first year. As some subjects have received Dasiglucagon bolus during the study, those bolus will be added to total dasiglucagon exposure (µg/kg) calculation. Additionally, the infusion rate, defined as the average hourly weight-adjusted infusion rate (i.e., µg/kg/hr) over the last 7 days of each time period will be calculated. It will be summarized for each time period (Month 1, Month 2-3, Month 4-6, Month 7-9, Month 10-12, Month 13-18, Month 19-24, Month 24-30 and every 6 months until end of treatment period), weekly for the first three months and then monthly for first year. The same description will be performed for infusion rate as per eCRF in µg/hr.

8. Efficacy Analysis

Efficacy Procedures

Continuous Glucose Monitoring: CGM will be used to guide treatment decisions and to evaluate efficacy.

During the study, if patient needs a pancreatectomy to remove all or part of the pancreas (all kind of pancreatectomy taken into account, no percentage threshold), the evaluation of efficacy endpoints will then be impacted by pancreatectomy. To be able to assess only treatment effect as primary analysis the following rules will be applied:

- Carbohydrates administrated, CGM-detected episode (hypoglycemia and CS hypoglycemia), CGM percent time endpoint, extent of hypoglycemia, and reduction of diazoxide/somatostatin dose, SMPG-detected episode (hypoglycemia and CS hypoglycemia) will be set to missing after pancreatectomy.

- Time to removal of NG-tube of gastrostomy will be censored at time of pancreatectomy

For all efficacy analysis, all available data in the form of actual measurements until end of treatment ('Treatment completion/treatment discontinuation date' from Treatment Termination CRF page) will be included in the analysis, irrespective of adherence to treatment) or use of subsequent therapy. Data recorded during Follow-up period will not be used as those are not systematically collected, those will only be listed. Efficacy analysis will be performed on FAS population.

For all endpoints, each time period is defined as Month 1, Month 2-3, Month 4-6, Month 7-9, Month 10-12, Month 13-18, Month 19-24, Month 24-30 and every 6 months until end of treatment period.

8.1. Key Secondary Efficacy Analysis

Note on CGM data that is used for main analysis:

All CGM within 30 days upload and non-backfilled any time. Data after pancreatectomy excluded. The CGM device can store CGM measurements corresponding to 30 days of full recording. For this study, visits and therefore data uploads are more than 30 days apart data outside this window of 30 days are expected to be overwritten. However, a special category of

backfilled data has been observed not to be overwritten. In order to avoid bias from backfilled data outside the 30 days window the data included for the analyses are all CGM measurements within 30 days of upload and non-backfilled at any time.

8.1.1. Total amount of gastric carbohydrates administered to treat hypoglycemia

Total amount of gastric carbohydrates includes amounts imputed by LOCF method as described in section 6.1.4.3.

Descriptive statistics for observed and change from baseline in the average weekly total amount of gastric carbohydrates administered (g) to treat hypoglycemia will be summarized for each time period overall and by region.

Total amount of gastric carbohydrates administered (g) to treat hypoglycemia (nasogastric tube or gastrostomy) will be analyzed by using a mixed-model for repeated measures using restricted maximum likelihood (REML). The repeated measures will be the average weekly values of total amount of gastric carbohydrates administered to treat hypoglycemia obtained over each time period described above. The model will include time period, region as fixed effects, baseline average weekly carbohydrates administered to treat hypoglycemia as covariate and patient as random effect. Denominator degrees of freedom will be calculated according to Kenward-Roger method. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the autoregressive structure will be used. Least-square means and 95% confidence intervals will be provided for each time period.

The same analysis will be performed on the subgroup of patient with gastrostomy or NG-tube at entry in extension trial.

8.1.2. Time to removal of NG tube or gastrostomy

Time to removal of NG tube or gastrostomy is defined as time from Day 1 to removal of NG tube or gastrostomy as described in the Healthcare Encounters form of the e-CRF. Time will be calculated in months.
Patients withdrawal from study will be censored at the last time in the study according to study completion form. Kaplan-Meier estimates will be presented. This analysis will be performed on the subgroup of patients from FAS with an NG tube or gastrostomy at the time of entry into the extension study.

8.1.3. Time to pancreatic surgery

Time to pancreatic surgery (sub-total or total pancreatectomy- cutoff 95% or more) is defined as time from Day 1 to pancreatic surgery as described in the Healthcare Encounters form of the e-CRF. Time will be calculated in months and described overall and by region (US, Non-US).
Patient's withdrawal from study will be censored at the last time in the study according to study completion form. Kaplan-Meier estimates will be presented, stratification by region will be performed. This analysis will be performed on the subgroup of patients from FAS without any pancreatic surgery at the time of entry into the extension study.

8.1.4. CGM percent time below 70mg/dL

Percent time below 70 mg/dL [3.9 mmol], as measured by CGM, where percent time is calculated as described in Section 6.1.7, will be analyzed by using a mixed-model for repeated measures using REML. The repeated measures will be the CGM percent time below 70mg/dL obtained over each time period described above. The model will include time period, region as fixed effects, baseline CGM percent time below 70mg/dL as covariate and patient as random effect. Denominator degrees of freedom will be calculated according to Kenward Roger method. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the autoregressive structure will be used. Least-square means and 95% confidence intervals will be provided for each time period. Descriptive statistics for observed CGM percent time in range will be summarized for each time period.

8.1.5. CGM-detected episodes of hypoglycemia

Hypoglycemia (<70 mg/dL [3.9 mmol/L] for 15 minutes or more) CGM-detected event rates will be based on the hypoglycemia events reported in the external CGM data from Cenduit. Event rates will be averaged weekly and reported over the time periods. The average CGM-detected episodes of hypoglycemia will be analyzed by a generalized linear mixed-model (GLMM) regression approach, with time period and region as fixed effects and patient as a random effect; this model will adopt a log-link function, assuming a negative binomial distribution and include baseline hypoglycemic rate as a covariate. Denominator degrees of freedom will be calculated according to Kenward Roger method. The log-transformed number of weeks in time period will be used as an offset variable. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the autoregressive structure will be used. Least-square means and 95% confidence intervals will be provided for each time period. Descriptive statistics for observed and change from baseline in the number of averaged weekly hypoglycemia CGM-detected events will be summarized for each time period.

8.1.6. Clinically significant CGM-detected episodes of hypoglycemia

Same analysis will be performed as the one described in section 8.1.5 but including clinically significant CGM-detected episodes of hypoglycemia defined as < 54 mg/dL [3.0 mmol/L].

8.1.7. Sensitivity Analyses for the Key Secondary Endpoints

In addition, a sensitivity analysis will be performed for all Key secondary endpoints not applying any missing rule when pancreatectomy is performed. Time to pancreatic surgery will not be included in this sensitivity analysis as not impacted by missing rules.

For main CGM analysis all CGM within 30 days upload and non-backfilled any time. Data after pancreatectomy excluded. For CGM related key secondary endpoints, following sensitivity analyses will be run on a subset of data:

- CGM measurements sensitivity: Per patient, periods of assessments will be included in analysis if:
    - there is at least 7 days of at least 200 CGM assessment per day during Month1,

Month 2-3, and 3-months periods. Those 7 days does not need to be consecutive.
  - if there is at least 14 days of at least 200 CGM assessments per day during the remaining 6-months periods. Those 14 days does not need to be consecutive.
- Paracetamol sensitivity: For G5 Dexcom users, any CGM data during the use of paracetamol from start of paracetamol until 4 hours after the end, are not included
- All CGM sensitivity: analysis including backfill data outside 30 days before data upload.
- Sensitivity with CGM within last 30 days before upload: sensitivity analysis including only CGM within 30 days before upload
- Sensitivity based on number of CGM measurements per day: Including non-backfilled GGM values within last 30 days before uploads and non-backfilled CGM values outside last 30 days before uploads from days that have at least 72 non-backfilled measurements.

8.2. 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 time period for patients in the FAS.

For all endpoints, each time period is defined as Month 1, Month 2-3, Month 4-6, Month 7-9, Month 10-12, Month 13-18, Month 19-24, Month 24-30 and every 6 months until end of treatment period.

No inference will be performed, and missing data will not be imputed for the below detailed secondary efficacy endpoints.

If amount is Not Answered in case of carbohydrates, it is considered in the number of administrations treating hypoglycemia.

- Number of gastric carbohydrate administrations (NG tube or gastrostomy) to treat hypoglycemia. This endpoint will be described overall and by region and also on the subgroup of patient having gastrostomy or Ng-tube at entry in extension study.
- Number of nightly (midnight to 6 am) gastric carbohydrate administrations (NG tube or gastrostomy) to treat hypoglycemia. This endpoint will be described overall and by region and also on the subgroup of patient having gastrostomy or Ng-tube at entry in extension study.
- Extent of hypoglycemia (area over the glucose curve [$AOC_{glucose}$] below 70 mg/dL [3.9 mmol/L] as measured by CGM. Extent of hypoglycemia will be described in mmol/L and in mg/dL.
- Extent of hypoglycemia (area over the glucose curve [$AOC_{glucose}$] below 54 mg/dL [3.0 mmol/L] as measured by CGM. Extent of hypoglycemia will be described in mmol/L and in mg/dL.
- Reduction in diazoxide dose from start of lead-in trial. This analysis will be performed on patients with diazoxide dose at start of lead-in trial. Start of lead-in trial is defined as first exposure to treatment or randomization date for standard of care only group. This analysis will be performed for each planned visit (Baseline, Month 1, Month 3, Month 6, and each 6-months visits). The dose on the day of the visit will be used for assessment.

- Reduction in somatostatin analog dose from start of lead-in trial. This analysis will be performed on patients with somatostatin analog dose at start of lead-in trial. Start of lead-in trial is defined as first exposure to treatment or randomization date for standard of care only group. This analysis will be performed for each planned visit (Baseline, Month 1, Month 3, Month 6, and each 6-months visits). The dose on the day of the visit will be used for assessment.
- Change in total amount of prescribed continuous gastric carbohydrate administrations during the 7 days leading up to the visit from start of lead-in trial (g/day)
- Change in prescribed duration of infusion of continuous gastric carbohydrate administration during the 7 days leading up to the visit from start of lead-in trial (h/day)
- Change in prescribed duration of infusion of nightly (8 pm – 8 am) continuous gastric carbohydrate administration during the 7 days leading up to the visit from start of lead-in trial (h/day)

For exploratory purposes, reduction in diazoxide/somatostatin analog dose will also be analyzed from the start of extension trial on patients with diazoxide/somatostatin dose at start of extension trial. As start of extension trial, we will consider the end of treatment visit date from lead-in trial as reference.

Diazoxide dose will be derived from concomitant medication form using the ATC level 4 code = V03AH. Somatostatin dose will be derived from concomitant medication form using the ATC level 4 code = H01CB.

8.3. Other Efficacy Analysis

8.3.1. CGM percent time

Below mentioned are continuous endpoints which will summarized using descriptive statistics (observed and change from baseline) by time period for patients in the FAS.

- CGM percent time in range 70-180 mg/dL (3.9-10.0 mmol/L)
- CGM percent time > 180 mg/dL (10.0 mmol/L)
- CGM percent time < 54 mg/dL (3.0 mmol/L)

8.3.2. Reported hypoglycemic events

Number of parent reported hypoglycemic events pr. week that required an intervention and with PG <70 mg/dL (3.9 mmol/L) as detected by self-monitored plasma glucose (SMPG) or CGM. Those data comes from the eCRF forms Hypoglycemia Episodes.

8.3.3. SMPG-detected episodes of hypoglycemia

Hypoglycemia (<70 mg/dL [3.9 mmol/L] for 15 minutes or more) SMPG-detected event rates will be derived based on the hypoglycemia events collected in the external SMPG data from Vitalograph.

8.3.4. Clinically significant SMPG-detected episodes of hypoglycemia

Hypoglycemia (<54 mg/dL [3.0 mmol/L] for 15 minutes or more) SMPG-detected event rates will be based on the hypoglycemia events reported in the external SMPG data from Vitalograph.

8.3.5. Supportive analysis of SMPG

- Number of SMPG measurements will be described by Time Period

8.3.6. Supportive analysis of CGM and gastric carbohydrates

- Number of CGM measurements will be described by Time Period
- As oral gastric carbohydrates to treat hypoglycemia are also reported in the eCRF those will be described by Time Period. Total gastric carbohydrates to treat hypoglycemia including Ng-tube, Gastrostomy and Oral ones will also be described by Time Period. Total amount of oral/gastric carbohydrates includes amounts imputed by LOCF method as described in section 6.1.4.3
- Number of Not Answered oral and also gastric carbohydrate administrations will be described by Time Period.

8.3.7. Quality of Life

Quality of life will be assessed by the PedsQL and additional CHI disease-specific QoL questions (parent-reported versions) at Baseline (entry lead-in study), Month 1, Month 3, Month 6, Month 9, Month 12 and every 3 month until end of treatment period.

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 for the patients in FAS.

CHI Disease-Specific Questionnaire

8.3.8. Answers to each question on the CHI disease-specific questionnaire will be

summarized using frequencies and percentages at each study visit.CHI Related Hospitalization

Time period for CHI Related Hospitalization are defined as Month 1, Month 2-3, Month 4-6, Month 7-9, Month 10-12, Month 13-18, Month 19-24, Month 24-30 and every 6 month until end of treatment period.

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 time 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, number of emergency visits for hypoglycemia and number of home visits by paramedics due to hypoglycemia will be summarized descriptively by time period.

These descriptions will be performed for the patients in FAS.

9. Safety and Tolerability Analysis

Safety assessments will include the evaluation of AEs, Serious Adverse Events associated with Device (SADE), clinical laboratory assessments (hematology, biochemistry, and ADAs), vital signs, physical examinations; electrocardiograms (ECGs), echocardiography, and local tolerability. No formal inferential analyses will be conducted for safety variables, unless otherwise specified. All safety analyses will be summarized by time period or study visits depending on the endpoints.

9.1. Adverse Events

Time period for adverse events reporting are defined as Month 1, Month 2-3, Month 4-6, Month 7-9, Month 10-12, Month 13-18, Month 19-24, Month 24-30 and every 6 month until end of treatment period.

Adverse events that begin on or after the first dose of dasiglucagon during extension study and no longer than 12 weeks after treatment discontinuation will be defined as treatment emergent. All summary tables will present treatment-emergent AEs. 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. Missing data will be mapped to “Related”.

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

The summary will be presented in descending order of frequency of SOC and then PT within SOC based on overall patients.

The incidence of AEs will be summarized with frequencies and percentages for patients in Safety Set (including number of AEs occurring, as well as person-year rate of events [number of events / years of exposure in each time period]), by time period and overall and the following:

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

Denominator for percentages will be the number of subjects in the corresponding time period.

SADE will be presented by SOC and PT.

9.1.1. Adverse Events Leading to Withdrawal

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

A data listing of AEs leading to discontinuation of study drug will also be provided displaying details of the event(s) captured on the CRF. SADE leading discontinuation of trial/treatment will be listed.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study will be listed.

Serious Aes, SADE, and Related Serious AEs (SAEs) will be listed and also tabulated by SOC and PT and presented by time period and overall.

9.1.3. Adverse Events of Special Interest

Four types of AEs of special interest (AESI) are collected in this study. They are suspicion of necrolytic migratory erythema; the risk of liver injury (defined as ALT or AST >3x ULN AND total bilirubin >2x ULN, where no alternative etiology exists); neurological events specified as loss of consciousness, partial and generalized seizures; and clinically significant changes in blood pressure and heart rate. All AESI types occurring in at least 1 patient will be presented.

Incidence of AESI will be summarized by frequencies and percentages by time 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.

9.1.4. Other Important Events

A listing of other important events will be provided.

9.2. Clinical Laboratory Evaluations

Samples for hematology and biochemistry will be collected at Baseline, Months 3, 6, 9, 12, every 3 months thereafter until the End of Treatment, at End of Treatment, 12 weeks after the End of Treatment (Follow-up visit).

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

Shifts from baseline to worst value 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.

Frequencies of clinically significant abnormal laboratory values for hematology and chemistry results will be presented by study visit.

Laboratory values that are outside the normal range will also be listed. 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. Any unscheduled assessment will be included in the tables according to the visit they have been reported, they will also be listed.

9.3. Vital Signs

Vital signs will be collected at Baseline, Months 3, 6, 9, 12, every 3 months thereafter until the End of Treatment, at End of Treatment, 12 weeks after the End of Treatment (Follow-up visit). 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 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 study visit.

Shifts from baseline to worst value for vital sign interpretation results will be provided.

9.4. Electrocardiograms

An ECG will be performed at Baseline, Months 3, 6, 9, 12, every 3 months thereafter until the End of Treatment, at End of Treatment, 12 weeks after the End of Treatment (Follow-up visit)..

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.

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 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 study visit.

9.5. Echocardiography

An echocardiogram will be performed at Baseline and every 12 months throughout the treatment period and on Follow-up (End of Treatment + 12 weeks).

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.

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 Baseline, Months 3, 6, 9, 12, every 3 months thereafter until the End of Treatment, at End of Treatment, 12 weeks after the End of Treatment (Follow-up visit).

Frequencies and percentages of physical examination interpretation results (normal, abnormal clinically significant, and abnormal not clinically significant) will be summarized by 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 Baseline, Months 3, 6, 9, 12, every 3 months thereafter until the End of Treatment, at End of Treatment, and 12 weeks after the End of Treatment (Follow-up visit). 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 at least one reaction, for each type of reaction will be summarized overall. Action taken and likely cause of the reaction will be summarized overall by type of reaction.

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 in ZP4207-17106 trial will be considered prior medications if they were stopped before first dose of dasiglucagon in ZP4207-17106 trial. Any medications ongoing at start of ZP4207-17106 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.

Frequencies and percentages will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and Preferred Name, if applicable, by overall patients. 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 in Protocol

- Supportive analysis of CGM and gastric carbohydrates data has been added.
- Extent of hypoglycemia will be described in mmol/L but as well in mg/dL.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

Plasma drug concentrations are collected at Baseline, Month 3, Month 6 and then every 6 month until end of treatment, End of treatment, and finally on Follow-up (End of treatment + 12 weeks). Descriptive summaries will be presented for plasma PK concentrations by study visit and quintiles of infusion rate (in µg/kg/hr), as described in Section 7.4. Information pertaining to PK data collection will be listed.

Any PK data from unscheduled visits will only be listed not included in tables.

PK analysis is performed using PK population.

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.
2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
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. The PedsQL Measurement Model for the Pediatric Quality of Life Inventory – Scoring Instructions (www.pedsql.org).
6. Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, Buckingham BA, Carroll J, Ceriello A, Chow E, Choudhary P. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. The Lancet Diabetes & Endocrinology. 2023:11:42–57. doi: 10.1016/S2213-8587(22)00319-9

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: Library of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse events special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
CGM	continuous glucose monitoring
CHI	congenital hyperinsulinism
CI	confidence intervals
CRF	case report form
CSR	clinical study report
DSMB	data safety monitoring board
eCRF	electronic case report form
FA	full analysis
ICH	international council for harmonization
LOCF	last observations carried forward
MedDRA	medical dictionary for regulatory activities
N	Number
NA	not applicable
PG	plasma glucose
PK	pharmacokinetic
PP	per-protocol

Abbreviation	Definition
QOL	quality of life
SADE	serious adverse event associated with device
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SD	standard deviation
SMPG	self-monitored plasma glucose
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	world health organization
WHO-DD	world health organization drug dictionary