16.1.9 Documentation of Statistical Methods

The following documents are provided in this section:

Statistical Analysis Plan:	
Version 1 Final 1	20 Aug 2018

ZEALAND PHARMA

CHILTERN

Sponsor:	Zealand Pharma A/S	Protocol Number:	ZP4207-16137

Zealand Pharma A/S

STATISTICAL ANALYSIS PLAN

Protocol No.: ZP4207-16137

EudraCT No.: 2017-002449-31

Treatment: Dasiglucagon injection

A phase 3, randomized, double-blind, parallel trial to confirm the clinical efficacy and safety of dasiglucagon in the rescue treatment of hypoglycemia in subjects with type 1 diabetes mellitus (T1DM) compared to placebo and with reference to GlucaGen®

Author: [redacted], MS, MBA

Document Status: Version 1, Final 1

Version Dates: Version 1, Final 1: 20AUG2018

Pages: 36

STATEMENT OF CONFIDENTIALITY

[redacted]

STATISTICAL ANALYSIS PLAN SIGNATURE FORM

Sponsor:	Zealand Pharma	Protocol Number:	ZP4207-16137
CIL Project Number:	40337	Project Manager:	[redacted]

Statistical Analysis Plan Version / Date:	SAP, Version 1, Final 1, 20AUG2018

The **Project Manager** is signing below to confirm they have reviewed and approved the Statistical Analysis Plan in accordance with the study protocol and CRF.

Approval Signature Print Name Date (dd mmm yyyy)	[redacted] cosign

☐ **Not applicable – No Chiltern PM assigned**

The **Lead Statistician** is signing below to confirm they have authored/reviewed and approved the Statistical Analysis Plan in accordance with the study protocol and CRF.

Approval Signature Print Name Date (dd mmm yyyy)	[redacted]

The **Support Statistician** is signing below to confirm they have reviewed and approved the Statistical Analysis Plan in accordance with the study protocol and CRF.

Approval Signature Print Name Date (dd mmm yyyy)	[redacted]

The **Sponsor Representative** is signing below to confirm they have reviewed and approved the Statistical Analysis Plan in accordance with the study protocol, CRF, and any other study requirements.

Approval Signature Print Name Job Title Date (dd mmm yyyy)	[redacted]

Contents

Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	AUC from time zero to infinity
AUE	Area under the effect curve
CI	Confidence interval
C_{max}	Maximum plasma concentration
CPH	Cox proportional hazards
CRO	Contract research organization
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
EudraCT	European Medicines Agency's Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA_{1c}	Glycated hemoglobin
ICH	International Conference on Harmonization
ID card	Identification card
IEC	Independent Ethics Committee
IM	Intramuscular(ly)
IMP	Investigational medicinal product
IRB	Institutional Review Board
IV	Intravenous(ly)
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities

NPH	Neutral protamine Hagedorn
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SUSAR	Serious unexpected suspected adverse reaction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
tmax	Time to the maximum plasma concentration
ULN	Upper limit of the normal range
US	United States of America

1 Introduction

This document presents the statistical analysis plan (SAP) for Zealand Pharma A/S, Protocol No. ZP4207-16137: A phase 3, randomized, double-blind, parallel trial to confirm the clinical efficacy and safety of dasiglucagon in the rescue treatment of hypoglycemia in subjects with type 1 diabetes mellitus (T1DM) compared to placebo and with reference to GlucaGen®.

This analysis plan is based on the final clinical trial protocol (Final, v3.0) dated 06OCT2017 and global protocol amendment 2 (Final, v1.0) dated 04APR2018. The SAP will be finalized and approved prior to the unblinding of the database.

The SAP provides the description of the statistical analysis for the final analyses.

2 Study Objectives

The objectives of this study are:

- Primary: To demonstrate superiority of dasiglucagon compared to placebo following a single subcutaneous 0.6 mg dose administered to subjects with type 1 diabetes mellitus with insulin-induced hypoglycemia.
- Secondary: To compare the glycemic response observed after dasiglucagon with that of GlucaGen.

2.1 Primary endpoints

The primary endpoint of this study is:

- Time to plasma glucose recovery. Plasma glucose recovery is defined as first increase in plasma glucose of ≥20 mg/dL (1.1 mmol/L) from baseline during the hypoglycemic clamp procedure without administration of rescue IV glucose.

2.2 Secondary endpoints

The secondary endpoints of this study are:

Key secondary endpoints

- Plasma glucose recovery within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection without administration of rescue IV glucose.

- Plasma glucose changes from baseline within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection or at the time of rescue.

Other secondary endpoints

- Clinical efficacy (PD) endpoints:
  - Time to first plasma glucose concentration ≥70 mg/dL (3.9 mmol/L) without administration of rescue IV glucose.
  - Plasma glucose response as area under the curve (AUC) above baseline from time zero to 30 minutes, $AUC_{0\text{-}30min}$.
- Exposure (PK) endpoints:
  - Area under the drug concentration curve from time zero to 90 minutes, $AUC_{0\text{-}90min}$.
  - Maximum plasma drug concentration (C_{max}).
  - Time to maximum plasma drug concentration (t_{max}).
- Immunogenicity endpoint:
  - Occurrence of anti-drug antibodies

Exploratory endpoints

- Plasma glucose concentration ≥70 mg/dL (3.9 mmol/L) or increase of ≥20 mg/dL (1.1 mmol/L) within 30 minutes after study drug injection without administration of rescue IV glucose.
- Plasma insulin response as area under the curve above baseline from time zero to 60 minutes, $AUC_{0\text{-}60\ min}$.

2.3 Safety endpoints

The safety endpoints of this study are summaries of the following:

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

3 Study Design

3.1 Discussion of Study Design

This trial is a global, multicenter, randomized, parallel, double-blind, clinical trial confirming the efficacy and safety of dasiglucagon for insulin-induced hypoglycemia in subjects with T1DM. The subjects will be randomized 2:1:1 to receive a single fixed SC 0.6 mg dose of dasiglucagon, placebo, or a 1 mg dose of GlucaGen and followed for at least 28 days after receiving treatment. A total of 156 subjects with T1DM are expected to complete the treatment visit. This trial is planned to be conducted at 4 to 6 trial sites in the United States of America [US], Canada, and Europe.

3.2 Study Treatment

Subjects successfully completing screening and who fulfill entry eligibility and randomization criteria will be randomized to one of three treatment groups in a 2:1:1 ratio:

- Test treatment: Dasiglucagon, liquid formulation, 1 mg/mL, 0.6 mL delivered in a prefilled syringe.
- Placebo treatment: Placebo, liquid formulation, 0.6 mL delivered in a prefilled syringe.
- Recombinant glucagon hydrochloride, 1 mg for reconstitution (GlucaGen®, Novo Nordisk) in 1 mL sterile water.

Subjects will attend the study site at Trial Day -3 (Screening Visit 1, Day -30 to Day -1) for informed consent, Trial Day -1 to Day 1 for dosing (Dosing Visit 2, Day 1), and followed for at least 28 days after dosing in order to perform an adequate immunogenicity evaluation of treatment (Safety Follow-up Visit, Day 28 + 5).

3.3 Study Schedule

The schedule of procedures is provided in Protocol Table 3.

3.3.1 Visit 1 (screening, Day -30 to Day -3)

Visit 1 will take place between 3 and 30 days before Visit 2, Day -1 to Day 1 (dosing day).

Informed consent can be obtained prior to or at Visit 1, however it must in any case be obtained prior to any trial related procedures. During the screening visit, the following assessments will take place:

- Informed consent (obtain or check)
- Check of subject eligibility (inclusion/exclusion criteria)
- Demography

- Body measurements
- Medical history, diabetes diagnosis, current diabetes treatment
- Concomitant illnesses
- Concomitant medications
- History of alcohol/drug abuse
- Physical examination
- Vital signs
- 12-lead ECG
- Adverse Events
- Biochemistry, hematology, coagulation, HbA_{1c}, C-peptide
- Serum pregnancy test (women of childbearing potential only)
- Urinalysis
- Urine drug screen
- Alcohol breath test

3.3.2 Visit 2 (dosing visit)

The subjects will attend the clinical center the day prior to dosing (Day -1) and should stay onsite overnight. Dosing will take place the following morning (Day 1).

On Day 1 and prior to the start of the insulin-induced hypoglycemic procedure, subject eligibility is rechecked (check of changes between the screening visit and Visit 2) and those subjects eligible to participate will be randomized to treatment with dasiglucagon, placebo, or GlucaGen.

The following assessments will also take place:

- Document all changes in concomitant medication (prior to the start of the insulin-induced hypoglycemic procedure)
- Check of withdrawal criteria (prior to the start of the insulin-induced hypoglycemic procedure)
- Check of dosing day exclusion criteria (prior to the start of the insulin-induced hypoglycemic procedure)
- Vital signs (prior to the start [within 30 minutes] of the insulin-induced hypoglycemic procedure, and at 30, 90 and 300 minutes after dosing). Blood pressure should be measured first in sitting and then in standing.
- 12-lead ECG (prior to the start [within 30 minutes] of the insulin-induced hypoglycemic procedure, and at 20, 35, 45, 60, and 300 minutes after dosing)
- Local tolerability (at 30, 120, and 300 minutes after dosing)
- AEs
- Biochemistry and hematology (prior to the start of the insulin-induced hypoglycemic procedure [within 30 minutes], and at 30 and 300 minutes after dosing)

- Urine stick pregnancy test (women of childbearing potential only; prior to the start of the insulin-induced hypoglycemic procedure)
- Urinalysis (prior to the start of the insulin-induced hypoglycemic procedure [within 120 minutes])
- Urine drug screen (prior to the start of the insulin-induced hypoglycemic procedure)
- Alcohol breath test (prior to the start of the insulin-induced hypoglycemic procedure)
- Dasiglucagon/GlucaGen plasma concentrations:
  - Pre-dose, 15, 30, 35, 40, 50, 60, 90, and 120 minutes after dosing. The actual time of blood sampling for exposure should not deviate from the nominal time by more than ±1 minute. Pre-dose is defined as within 2 minutes prior to dosing.
- Plasma glucose concentrations:
  - Pre-dose, 4, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 50, 60, 75, and 90 minutes after dosing. The actual time for blood sampling for plasma glucose should not deviate from the nominal time by more than ±30 seconds until the 20 minute collection time point and by more than ±1 minute for the subsequent collection time points. Pre-dose is defined as within 2 minutes prior to dosing.
- Antibodies against dasiglucagon/GlucaGen (prior to the start of the insulin-induced hypoglycemic procedure).
- Plasma insulin concentrations:
  - Pre-dose, 30 and 60 minutes after dosing. The actual time of blood sampling for plasma insulin should not deviate from the nominal time by more than ±1 minute. Pre-dose is defined as within 2 minutes prior to dosing.

3.3.3 Visit 3 (follow-up visit)

Visit 3 will take place on Day 28 + 5 days. The subject does not need to be fasting.

At Visit 3, the following assessments will take place:

- Document all changes in concomitant medication
- Physical examination
- Vital signs
- 12-lead ECG
- Local tolerability
- AEs
- Biochemistry, hematology
- Urine stick pregnancy test (women of childbearing potential only)
- Urinalysis
- Antibodies against dasiglucagon/GlucaGen.

3.4 Concomitant Medication

A concomitant medication is any medication, other than the trial products and current diabetes treatment (including insulin glulisine [Apidra®] for diabetes therapy wash-out), which is taken during the trial, including screening and follow-up periods.

Details of any concomitant medication must be recorded at trial entry (i.e., at screening). Any changes in concomitant medication must be recorded at each visit as they occur. The information collected for each concomitant medication includes (at a minimum) trade name or generic name, indication, start date and stop date or continuation. A change in medication due to an AE must be recorded and reported according to Protocol Section 7.2.1 "Adverse Events". If the change in medication influences the subject's eligibility to continue in the trial, the sponsor and trial monitor must be informed.

3.5 Study Analysis Samples

For presentation of data and reporting of the statistical analyses, the following analysis samples will be used, depending on the context:

- Safety analysis set: All randomized subjects who received at least one dose of trial medication.
- Full analysis set: All randomized subjects who received at least one dose of trial medication.
- Per protocol (PP) set: All subjects of the Full analysis set for whom no relevant protocol deviations were documented. This sample will primarily be used for sensitivity analysis.

The analysis of the primary endpoint and secondary endpoints will be based on the Full analysis set. A secondary analysis of the primary endpoint will be based on the PP set. All safety analyses will be based upon the Safety analysis set, which is identical to the Full analysis set, but will be labelled as Safety analysis set.

The decision regarding whether a protocol deviation is relevant or not for the exclusion of subjects from the PP set will be made case-by-case in a blinded data review meeting prior to treatment unmasking and database lock (see Protocol Section 9.2.3 "Protocol Deviations").

3.6 Withdrawn Subjects

Subjects withdrawn from the trial will be listed including the primary reason for withdrawal.

Any subject who withdraws after randomization will not be replaced. Withdrawn subjects will not be re-entered into the study.

3.7 Randomization

Subjects who have given written informed consent and meet all inclusion and none of the exclusion criteria will be randomized to one of three treatment groups in a 2:1:1 ratio:

- Test treatment: Dasiglucagon, liquid formulation, 1 mg/mL, 0.6 mL delivered in a prefilled syringe.
- Placebo treatment: Placebo, liquid formulation, 0.6 mL delivered in a prefilled syringe.
- Reference treatment: Recombinant glucagon hydrochloride, 1 mg for reconstitution.

Randomization will be performed using a fixed-block randomization scheme. The randomization scheme will be generated prior to the initiation of the study by an independent statistician/programmer who will not be a member of the study team; all investigators will not be aware of the block size of the randomization scheme. Randomization will be stratified by treatment group and by injection site (abdomen, buttocks, or thigh) and controlled via the IWRS.

3.8 Blinding and Breaking the Blind

This is a double-blind trial. As the trial products are not identical in appearance, dasiglucagon and placebo being available as a liquid formulation and GlucaGen as a powder for reconstitution, unblinded trial personnel will be responsible for handling, preparing (according to the prescription from the IWRS), and administering the trial medication, as well as for keeping the records strictly confidential and accessible only to unblinded staff until after the database has been locked. To maintain double-blind conditions, all trial assessments at the trial center will be done by blinded trial personnel not involved in the administration of trial medications. However, exposure assessments and anti-drug antibody (ADA) assessments will be performed by unblinded personnel at the special laboratories, to ensure that dasiglucagon, placebo, or GlucaGen administration is matched with the applicable bioanalytical assay.

Treatment assignment will be kept strictly confidential and accessible only to authorized persons until after the time of unblinding. Codes with treatment assignment will, however, be readily available in the IWRS to the blinded personnel in case of an emergency.

The code for a particular subject may be broken in a medical emergency if knowing the identity of the treatment allocation would influence the treatment of the subject. The emergency code break can be performed using the IWRS. Whenever a code is broken, the person breaking the code must record the time, date and reason as well as his/her initials in the source documents. The breaking of blinded codes in case of medical emergency for one subject should not unblind the trial personnel to the treatment information of other subjects. The person performing the unblinding should inform as few people as possible about the result of the unblinding. All persons unblinded for a specific subject should be documented.

If the trial center needs to break the code, the medical monitor should, if at all possible, be contacted prior to breaking the code and the monitor must be notified within 24 hours after the code has been broken.

The pharmacovigilance unit (safety contract research organization [CRO]; see Protocol Section 12.1 "List of Trial Personnel") will be able to break the code in case of a serious unexpected suspected adverse reaction (SUSAR).

The central and specialty laboratories will be provided with a copy of the randomization list.

3.9 Sample Size

Due to requirements in the size of the safety database, the sample size is set to 78 subjects treated with dasiglucagon 0.6 mg. From phase 2, the median time to an increase of 20 mg/dL of the 0.6 mg dose was approximately 10 minutes. With a 2:1:1 randomization ratio for the three treatments, dasiglucagon 0.6 mg, placebo, and GlucaGen 1 mg, and assuming an exponential time-to-recovery distributions with median times of 10 and at least 20 minutes for dasiglucagon and placebo, respectively, a two-sided log-rank test will be able to detect a difference between dasiglucagon and placebo with 90% power with a follow-up time of 45 minutes at a 5% significance level with 78 subjects treated with dasiglucagon and 39 subjects with placebo. The median time-to-recovery for placebo is expected to be longer than 20 minutes, which means that the power will be greater than 90%.

4 Statistical Methodology

4.1 Planned Analyses

Before database lock and treatment unmasking, the statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below. Further analysis details may be added or refined in the SAP.

The analysis of the primary endpoint and secondary endpoints will be based on the Full analysis set. A secondary analysis of the primary endpoint will be based on the PP set. All safety analyses will be based upon the Safety analysis set.

The decision regarding whether a protocol deviation is relevant or not for the exclusion of subjects from the PP set will be made case-by-case in a blinded data review meeting prior to treatment unmasking and database lock (see Protocol Section 9.2.3 "Protocol Deviations").

All data obtained in this trial and documented in the eCRFs will be listed and summarized with statistics or frequency tables as appropriate. In case of termination of the trial, all data collected up to that timepoint will be included in the analysis.

Raw data listings and summary tables will be generated using the software SAS© version 9.4 or higher.

Continuous variables will be summarized using means, standard deviations, medians, coefficients of variation, and minimum and maximum values. Other summaries (e.g. quartiles, 95% confidence intervals [CIs]) may be used as appropriate.

Categorical efficacy and safety variables will be summarized by counts and by percentage of subjects in corresponding categories.

4.2 Interim Analysis

No interim analysis is planned for this study.

4.3 Disposition of Subjects

Subject disposition will be tabulated including the number of screened subjects, screening failures, subjects exposed to trial product, subjects completing the trial and subjects in each analysis set. A CONSORT diagram will be included to display the disposition of subjects.

Subjects withdrawn from the trial will be listed including the primary reason for withdrawal.

4.4 Baseline and Demographic Characteristics

Baseline assessments are defined as the last non-missing result prior to administration of the first dose of study medication. In cases where there are multiple such values, the non-missing value closest to the start of study treatment will be selected. If time is available for an assessment, it will be compared with dosing time of the first dose of study medication to define the baseline value.

Baseline and demographic data will be summarized using descriptive statistics. Baseline ADA-positive subjects will be calculated as a percentage of the total number of subjects whose baseline samples were tested for ADA.

Notes:

- Age will be calculated as (screening date – date of birth + 1)/365.25 and presented to 1 decimal place. Age will be rounded down to the nearest integer before analysis.
- BMI will be calculated as weight(kg)/height(m^2)
- Medical history will be coded according to MedDRA, version 19.1.
- Active medical history is defined as histories marked as active at time of screening.
- Relevant medical histories are all medical histories recorded in the eCRF.
- Any duration [days] = end date – onset date + 1

4.5 Exposure

The exposure to trial medication (dasiglucagon or GlucaGen) for evaluation of pharmacokinetics will be assessed based on plasma concentration data from samples collected at the dosing visit (Visit 2):

- Area under the drug concentration curve from time zero to 90 minutes, $AUC_{0\text{-}90\ min}$.
- Maximum plasma drug concentration (C_{max}).
- Time to maximum plasma drug concentration (t_{max}).

Samples (including back-up samples) will be collected pre-dose, and at 15, 30, 35, 40, 50, 60, 90, and 120 minutes after dosing. The actual time of blood sampling for exposure to trial medication should not deviate from the nominal time by more than ±1 minute. Pre-dose is defined as within 2 minutes prior to dosing.

All data collected related to study drug administration will be provided in the data listings.

4.6 Prior and Concomitant Medication

Prior glucagon exposure will be recorded in the eCRF at screening. All concomitant medications will be recorded and/or updated in the eCRF at each visit, i.e., at screening (Visit 1), the dosing visit (Visit 2, prior to the start of the insulin-induced hypoglycemic procedure) and at the follow-up visit (Visit 3).

Subjects using any new concomitant medication resulting in fulfillment of a dosing day exclusion criterion (see Protocol Section 5.5 "Dosing Day Exclusion Criteria") will be excluded from the dosing visit, but can be rescheduled to one of the following days (1–7 days later). The dosing visit can only be rescheduled once.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, version 2017Dec.

Incidence of prior and concomitant medication will be presented by treatment, drug class, and preferred drug name using patients in the Safety analysis set.

Prior medications are those that started and stopped before exposure to study medication; concomitant medications are all medications taken during the study period, including those started before but ongoing at first dose of study drug.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

4.7 Efficacy / Primary and Secondary Analysis

For the confirmatory analyses, the primary and key secondary endpoints for the dasiglucagon 0.6 mg and placebo treated subjects will be compared. A hierarchical procedure will be applied for the control of multiplicity. The primary and secondary endpoints will be evaluated on the Full analysis set. In the primary analysis, recovery cannot be achieved in those subjects where IV glucose treatment is administered. Those subjects who receive IV glucose will be censored (i.e., set to 'not recovered') at 45 minutes after dosing. In sensitivity analyses, the time to plasma glucose recovery will be analyzed 1) without censoring for those subjects who require rescue IV

glucose before 45 minutes and 2) with censoring at the time of administration of rescue IV glucose before 45 minutes.

4.7.1. Hierarchical testing procedure

For the confirmatory analyses, the following a priori defined hierarchical inferential test order will be applied for the control of the type 1 error rate across the planned multiple comparisons. The primary endpoint and key secondary endpoints will be inferentially evaluated within the Full analysis set in the following order, where inference will proceed at the two sided 0.05 criterion significance level until the first failure to reject the null hypothesis for a dasiglucagon versus placebo comparison:

- Primary: Time to plasma glucose recovery
- Key secondaries 1-4: Plasma glucose recovery within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection without administration of rescue IV glucose.
- Key secondaries 5-8: Plasma glucose changes from baseline within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection or at the time of rescue.

The GlucaGen versus placebo comparisons will not be included in the inferential testing hierarchy, since the efficacy of GlucaGen is previously established, and these comparisons are intended to support the validity of the study for the dasiglucagon versus placebo comparisons.

Analogous supportive sensitivity analyses will be conducted in the PP set, but without inference intent.

4.7.2. Primary endpoint

- Time to plasma glucose recovery. Plasma glucose recovery is defined as first increase in plasma glucose of ≥20 mg/dL (1.1 mmol/L) from baseline during the hypoglycemic clamp procedure without administration of rescue IV glucose.

The planned time points at 0, 6, 8, 10, 12, 15, 17, 20, 25, 30, 40, 50 and 60 minutes will be used in the analyses.

4.7.2.1 Primary analysis

The primary endpoint will be summarized using Kaplan-Meier (KM) estimates stratified by treatment group and injection site. The treatment group difference between dasiglucagon and placebo will be evaluated inferentially using a two-sided log-rank test stratified by injection site. Time to plasma glucose recovery will also be summarized using Kaplan-Meier estimates stratified by treatment group alone.

Time to plasma glucose recovery will be summarized using Kaplan-Meier estimates stratified by treatment group and investigational site.

In the primary analysis, recovery cannot be achieved in those subjects where IV glucose treatment is administered. Those subjects who receive IV glucose will be censored (and set to 'not recovered') at 45 minutes after dosing.

In sensitivity analyses, the time to plasma glucose recovery will be analyzed 1) without censoring for those subjects who require rescue IV glucose before 45 minutes and 2) with censoring at the time of administration of rescue IV glucose before 45 minutes.

As a supportive analysis to the stratified log-rank test for the time to plasma glucose recovery described above, dasiglucagon will be compared to placebo using a Wilcoxon test stratified by injection site.

To graphically describe recovery in time, a histogram showing the proportion of patients that recovered within each time interval will be created, one for each treatment group.

If the site of injection does not appear to have an effect on time to recovery, the factor can be disregarded and further presentations will not be stratified by injection site.

The primary endpoint will additionally be analyzed using a Cox proportional hazards (CPH) time to event statistical model, if the hazards by treatment group can be assumed proportional using a graphical comparison of log-minus-log survival curves and no more than two-thirds of the recovery times are censored in each treatment group. The CPH model will be used for descriptive purposes, with treatment group and injection site modeled as categorical effects, and baseline plasma glucose modelled as a continuous covariate. The treatment group rate ratios, active versus placebo, will be estimated together with the 95% confidence intervals, and pairwise treatment group inferences (dasiglucagon vs placebo, GlucaGen vs placebo) will be evaluated using two-sided likelihood ratio tests.

Due to the discrete nature of blood sampling in time, and the fact that there must be a true, but unmeasured, ordering of the recovery times, the method using the "exact discrete" partial likelihood for tied failure times will be applied. In SAS, this is implemented in the `phreg` procedure with the option `ties=discrete`. The influence of injection site on time to recovery will also be evaluated in the proportional hazards model by a 'type 3' test in the `phreg` procedure.

To obtain an estimate of these true, but unassessed, patient recovery times, a linear interpolation (between the two time points before and after recovery is observed) will be carried out to estimate the patients' actual time of recovery. These derived recovery times will be described and analysed in the same manner as for the discrete times above.

Table 4-1: Definition of Events, Censoring, and Populations for Time to Event Analyses

Time to Event Endpoint	Initiating Event	Terminating Event(s)	Censoring Event(s) /Competing Risk(s)	Analysis Sample	Study Endpoint /Statistical Analyses
Time to plasma glucose recovery	Administration of IMP	First increase in plasma glucose of ≥20 mg/dL (1.1 mmol/L) from baseline w/out rescue IV glucose admin.	Rescue IV glucose administration will be censored at 45 minutes after IMP dosing	Full analysis set, PP	Primary/ Pairwise two-sided log rank test

4.7.2.2 Primary analysis: Missing Baseline Glucose Value

In a blind review of anonymised plasma glucose values, it was observed that the baseline glucose value, which is used for evaluation of the primary endpoint, is missing for one subject. Since plasma glucose levels were monitored at site by using an US FDA-approved glucose analyzer (Yellow Springs Instrument, YSI), a substitute baseline value can be obtained for this subject.

Even though some differences in the plasma glucose level are expected between local YSI measures obtained at site and clinical laboratory measures, it has been decided to use the baseline plasma glucose value from the YSI in the analysis for this subject. The actual pre-dose YSI value used for this subject will be reported in the Clinical Trial Report.

In a sensitivity analysis, the time to plasma glucose recovery will be analyzed without the subject missing the baseline clinical laboratory plasma value.

4.7.3 Secondary endpoints

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

4.7.3.1 Confirmatory analysis

The key secondary incidence variables (plasma glucose recovery within 30 minutes, within 20 minutes, within 15 minutes, within 10 minutes, in hierarchical order for inference) will be analyzed using descriptive statistics (frequency and percentage) by treatment group. Inferential treatment group comparisons will be assessed via pairwise tests of independent binomial proportions (dasiglucagon versus placebo, GlucaGen versus placebo) using Fisher's exact test for each pairwise comparison.

The key secondary endpoints of plasma glucose changes from baseline within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection or at the time of rescue, will be analyzed with the plasma glucose changes from baseline at rescue carried forward in those subjects who require rescue IV glucose before plasma glucose ≥20 mg/dL recovery. Each of these changes from baseline variables will be analyzed using an Analysis of Covariance model, with treatment group modelled as a fixed effect and with the baseline plasma glucose modelled as a covariate. The dasiglucagon versus placebo treatment group difference will be evaluated inferentially as a least squares means contrast, using a two sided t-test at the 0.05 significance level, first for the 30 minute changes from baseline, and then sequentially for the 20 minute, 15 minute, and 10 minute variables, until the first failure to reject.

4.7.4 Secondary clinical efficacy (PD) endpoints

- Time to first plasma glucose concentration of ≥70 mg/dL (3.9 mmol/L) without administration of rescue IV glucose.
- Plasma glucose response as area under the curve above baseline from time zero to 30 minutes, $AUC_{0\text{-}30min}$.

Secondary clinical efficacy endpoints will be assessed based on plasma concentration data from samples collected at the dosing visit (Visit 2).

Unless otherwise stated, the population base of analysis will be the Full analysis set.

4.7.4.1 Analysis of secondary clinical efficacy (PD) endpoints

1. Time to first plasma glucose concentration ≥70 mg/dL from baseline. This time to-event endpoint will be evaluated using a Kaplan-Meier approach, with treatment group as a stratification factor, analogous to that used for the primary endpoint analysis. Differences between the KM curves (dasiglucagon versus placebo, GlucaGen versus placebo) will be evaluated inferentially using pairwise two-sided log rank tests. If the ≥70 mg/dL endpoint is not met within 45 minutes post-dosing, the time of the last valid plasma glucose measurement up to 45 minutes will be the censoring time.
2. The AUC will be calculated as the baseline-adjusted area under the plasma glucose profile over time:
    a. $AUC_{0\text{-}30min}$: restricting the time window to the 0 to 30 minutes interval.

    The log-transformed AUC endpoint will be analyzed using an analysis of covariance (ANCOVA) model with treatment as fixed effect and baseline plasma glucose modelled as a covariate. The least squares means treatment group differences will be back transformed (anti logged) for presentation as a ratio of the treatment group geometric means, with their corresponding 95% CI.

4.7.5 Exposure (PK) endpoints

- Plasma dasiglucagon and GlucaGen concentrations from time zero to 90 minutes:

  $AUC_{0\text{-}90min}$, Cmax, and tmax.

4.7.5.1 Analysis of exposure (PK) endpoints

AUC will be derived as the area under the individual plasma dasiglucagon/GlucaGen concentration profile for PK from 0 to 90 minutes or last valid measurement if this measurement is assessed sufficiently close to 90 minutes (decision to be taken at the blinded data review meeting). The standard trapezoidal method will be used, based on actual rather than nominal timepoints.

Cmax will be determined as the maximum of all valid plasma dasiglucagon/GlucaGen concentrations.

Tmax will be determined as the timepoint where the maximum of all valid plasma dasiglucagon/GlucaGen concentration measurements for each measurement series is observed.

The log-transformed PK endpoints AUC and Cmax will be analyzed in the same way as the AUC endpoints.

As tmax is a highly discrete endpoint, Wilcoxon's rank sum test for unpaired observations will be used to assess differences between the two treatment groups.

Exposure endpoints will be summarised for the Full analysis set, which is identical to the Safety analysis set.

Table 4-2: Overview of Efficacy Analyses

Efficacy Endpoint	Statistical Analyses	SAS Procedure
Endpoints with binary response outcomes: • Plasma glucose recovery within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection without administration of rescue IV glucose.	• Fisher's exact test for each pairwise comparison	• FREQ • LOGISTIC
Endpoints with continuous outcomes: • Plasma glucose changes from baseline changes from baseline within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection or at the time of rescue.	• Changes from baseline: Analysis of Covariance model, with treatment group modeled as a fixed effect and with the baseline plasma glucose modeled as a covariate • Changes from baseline: Two sided t-test at the 0.05 significance level	• GLM
Endpoints with time-to-event outcomes: • Time to plasma glucose recovery • Time to plasma glucose recovery without censoring at the time of recovery for those subjects who require rescue IV glucose before 45 minutes • Time to plasma glucose recovery with censoring at the time of administration of rescue IV glucose before 45 minutes	• Kaplan-Meier (KM) estimates stratified by treatment group and injection site • Pairwise two-sided log rank test • Cox proportional hazards (CPH) time to event statistical model with treatment group and injection site modeled as categorical effects, and baseline plasma glucose modeled as a continuous covariate • Kaplan-Meier plots, both stratified by injection site and without stratifying by injection site	• LIFETEST • PHREG or TPHREG

4.8 Exploratory Analysis

Exploratory analyses will include descriptive statistics and modeling analogous to that done for key secondary endpoints. However, treatment group comparisons will be summarized without inference intent.

- Plasma glucose concentration ≥70 mg/dL (3.9 mmol/L) or increase of ≥20 mg/dL (1.1 mmol/L) within 30 minutes after study drug injection without administration of rescue IV glucose.
- Plasma insulin response as area under the curve above baseline from time zero to 60 minutes, $AUC_{0\text{-}60\ min}$.

Plasma insulin concentrations measured pre-dose and at 30 and 60 minutes after dosing (see Protocol Table 3 "Schedule of Procedures") will be presented individually. A summary table per timepoint will be provided. The $AUC_{0\text{-}60min}$ will be determined and a summary presented.

4.9 Safety Analysis

4.9.1 Adverse events

Adverse events and serious adverse events will be summarised separately by treatment by presenting the number and percentage of subjects having any event, having a related event, having an event leading to withdrawal, having an event in each MedDRA system organ class and preferred term, having each individual event and the severity, relationship and outcome of each event. Number of events is also presented. Missing severity, relationship or outcome will be classed as unknown.

A subject with more than one occurrence of the same adverse event in a particular system organ class will be counted only once in the total of those experiencing adverse event in that particular system organ class. If a subject experiences the same adverse event at more than one severity, or with more than one relationship to investigational product, the most severe rating or the stronger causal relationship to investigational product will be given precedence. Any missing severity, causality, or outcome will not be imputed and classed as unknown.

Summaries classifying both events according to severity and relationship will be presented.

AEs will be coded according to MedDRA, version 19.1. AE summary tables will include the number and percentage of subjects who experienced AEs summarized by system organ class and preferred term.

Only treatment-emergent adverse events (TEAEs) will be reported. TEAEs are undesirable events not present prior to medical treatment, or an already present event that worsens in intensity following the treatment.

Related events are defined as events that are probably or possibly related to study medication or with an unknown relationship.

Adverse event of special interest (AESI) is an event which, in the evaluation of safety, has a special focus (e.g. required by health authorities). In this trial hemodynamic changes, as defined below, are considered AESIs:

- Post-dose clinical signs, or measured vital signs, indicating a clinically significant drop in blood pressure including signs of orthostatic hypotension, vasovagal responses or bradycardia.

- Post-dose change in pulse or blood pressure considered an event of hypo- or hypertension as judged by the investigator.

4.9.1.1 Subsets

An overall summary table will be provided showing the number and percentage of subjects with any:

- TEAE
- Severe TEAE
- Serious TEAE
- Drug-related TEAE
- Drug-related severe TEAE
- Drug-related serious TEAE
- TEAE leading to withdrawal
- TEAE with outcome death
- AESI

All other information collected (e.g., action taken) will be listed as appropriate.

Only treatment-emergent adverse events (commencing during or after exposure to study treatment) will be included in the adverse and serious adverse event summaries. Non-treatment-emergent events (starting prior to exposure to study treatment) will be included in the subject listings and flagged but not included in the above summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

4.9.2 Immunogenicity data

Immunogenicity data will be analyzed descriptively by treatment group. No statistical tests are planned. Baseline ADA-positive subjects will be calculated as a percentage of the total number of subjects whose baseline samples were tested for ADA. Titer will be reported as median and interquartile range.

4.9.3 Clinical laboratory assessments

Clinical laboratory test results will be flagged as to whether the result is below, within, or above the respective reference range. The number of values outside of the reference range will be counted.

Results from the following laboratory parameters, recorded at the Screening, Dosing, and Follow-up visits will be summarised by treatment and time point:

- **Clinical biochemistry**: sodium, potassium, calcium, glucose, urea, creatinine, total bilirubin, AST, ALT, gamma-glutamyltransferase, alkaline phosphatase, total protein, C-reactive protein. HbA1c and C-peptide at screening visit only.
- **Hematology**: hemoglobin, red blood cell count (erythrocytes), hematocrit, platelet count (thrombocytes), total white blood cell count (leukocytes).
- **Coagulation**: international normalized ratio, fibrinogen (at screening visit only).
- **Urinalysis**: pH, blood (leukocytes and erythrocytes), protein, glucose, ketones, nitrite.

Categorical and numeric variables will be presented separately.

Shift tables for the hematology and biochemistry laboratory parameters comparing values below, within, and above the normal reference range will be presented using standard reference ranges.

Abnormal laboratory findings (e.g. biochemistry, hematology, and urinalysis) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the trial or are present at baseline and significantly worsen following the start of the trial will be reported as AEs or SAEs.

4.9.4 Other safety data

Incidence of rescue infusion of IV glucose during the hypoglycemic clamp procedure will be analyzed using descriptive statistics (frequency and percentage) by treatment group. Inferential treatment group comparisons will be assessed via pairwise tests of independent binomial proportions (dasiglucagon versus placebo, GlucaGen versus placebo).

Time to first rescue infusion of IV glucose during the hypoglycemic clamp procedure will be evaluated using a KM time to event statistical model, with treatment group and injection site (abdomen, buttock, or thigh) as stratification factors. Differences between the KM curves (dasiglucagon versus placebo, GlucaGen versus placebo) will be evaluated inferentially using pairwise two-sided stratified log-rank tests. If the endpoint is never met, the time of the last plasma glucose measurement will be the censoring time.

Vital signs, physical examination, 12-lead ECG and local tolerability data will be summarized using descriptive statistics.

4.9.5 Vital signs

The following vital signs will be summarized for the Safety analysis set subjects:

- Systolic and diastolic blood pressure (mmHg)
- Pulse rate (beats/min)
- Body temperature (°C)

At the dosing visit, measurements will be taken prior to the start of the insulin-induced hypoglycemic procedure (within 30 minutes) and at 30, 90, and 300 minutes after dosing. The

actual time of the assessment should not deviate from the nominal time by more than ±10 minutes. In addition to the pre-specified assessments, blood pressure and pulse may be assessed at any time during the trial at the discretion of the investigator.

Vital signs data and changes from baseline in vital signs will be summarized by treatment group and time point where appropriate using standard descriptive statistics.

4.9.6 Physical examination

A complete physical examination will be performed at Screening and Follow-up visits; after study drug has been administered any clinically significant changes in physical examination findings will be recorded as AEs. Physical examination data will be summarized using descriptive statistics and will be provided in the listings.

4.9.7 12-Lead ECG

At the dosing visit, measurements will be taken prior to the start of the insulin-induced hypoglycemic procedure (within 30 minutes), and at 20, 35, 45, 60 and 300 minutes after dosing. The actual time of the assessment should not deviate from the nominal time by more than ±5 minutes.

The quantitative ECG assessments (heart rate, PQ, QRS, QT, QTcB) will be summarised using descriptive statistics for actual values and changes from baseline to each time point by treatment and time.

4.9.8 Local tolerability

At the dosing visit, immediately prior to treatment administration, it should be verified that the injection site is normal. To ensure all injection site assessments are performed at the injection site, the site will be marked with a pen prior to injection. Local tolerability at the injection site will be assessed at 30, 120, and 300 minutes after dosing. The actual time of the assessment should not deviate from the nominal time by more than ±10 minutes.

The local tolerability at the injection site will be evaluated by means of the following assessments: spontaneous pain, pain on palpation, itching, redness, edema, induration/infiltration, and other. Each of these assessments will be reported on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). The evaluation and the actual time of the assessment will be recorded. Local tolerability data will be summarized using descriptive statistics by injection site and overall, and will be provided in the listings.

4.10 Adjustment for Covariates

The primary endpoint will be additionally analyzed using a Cox Proportional Hazards (CPH) time to event statistical model. The CPH model will be used for inferences, with treatment group and injection site (abdomen, buttock, or thigh) modelled as categorical effects, and baseline plasma glucose modelled as a continuous covariate. The treatment group rate ratios, active versus placebo, will be estimated together with the 95% confidence intervals, and pairwise

treatment group inferences (dasiglucagon vs placebo, GlucaGen vs placebo) will be evaluated using two-sided likelihood ratio tests.

The key secondary endpoints of plasma glucose changes from baseline changes from baseline within 30 minutes, within 20 minutes, within 15 minutes, and within 10 minutes after study drug injection or at the time of rescue, will be analyzed with the plasma glucose changes from baseline at rescue carried forward in those subjects who require rescue IV glucose before plasma glucose ≥20 mg/dL recovery. Each of these changes from baseline variables will be analyzed using an Analysis of Covariance model, with treatment group modelled as a fixed effect and with the baseline plasma glucose modelled as a covariate. The dasiglucagon versus placebo treatment group difference will be evaluated inferentially as a least squares means contrast, using a two-sided t-test at the 0.05 significance level, first for the 30 minute changes from baseline, and then sequentially for the 20 minute, 15 minute, and 10 minute variables, until the first failure to reject.

4.10.1 Center/Study Site Effects

This study will be conducted in 4 countries at 5 study sites. Subjects from all study sites will be pooled. No adjustment for study site will be carried out.

Region	Country	Number of Study Sites	Total Subjects
Europe	*Austria*	1	80
N. America	*Canada*	1	40
Europe	*Germany*	2	35
N. America	*USA*	1	30

4.11 Protocol Violations or Deviations

Before data are released for statistical analysis, a treatment-masked review of all data will take place to identify protocol deviations that may potentially affect the results. This review will be performed without revealing to which trial product the subjects were assigned. The masking of the trial products will be maintained for everyone involved in allocating subjects to the analysis sets until data are released for statistical analysis. Furthermore, spurious outliers will be evaluated. In addition, protocol deviations that may potentially affect the results will be identified and it will be evaluated if subjects and/or data should be excluded from the analysis. Protocol deviations will be classified as minor or major in a consistent way. Major deviations from the protocol may lead to the exclusion of a subject from the PP set.

Major protocol deviations may include deviations related to trial inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment. Unless explicitly decided

otherwise during the masked data review, the following will be considered major protocol deviations:

- Violation of one or more major inclusion/exclusion criteria
- Interruption of administration of trial product
- Significant deviation from time windows
- Incorrect treatment allocation
- Missing primary endpoint.

The violation of several major inclusion/exclusion criteria or the complete absence of efficacy data might lead to exclusion of the subject from Full analysis set. In that case, the decision should be taken at the blinded data review meeting, and the exclusion from efficacy analysis justified in the signed notes of the meeting.

Obviously erroneous data points may be excluded from the analyses or reanalyzed (in case of e.g., serum concentrations). The decision to reanalyze or exclude data points from the statistical analysis is the joint responsibility of the sponsor and the trial statistician.

The subjects or observations to be excluded and the reason for their exclusion will be documented and signed by those responsible prior to database release. The documentation will be stored together with the remaining trial documentation. The subjects and observations excluded from analysis sets, and the corresponding reasons, will be described in the clinical trial report.

4.12 Subject Withdrawals and Missing Data

Failure is defined for the primary time-to-recovery endpoint as censored with time to recovery set to the maximum follow-up time, here 45 minutes. Individuals will be set to 'failure' in case of receiving rescue IV glucose, discontinuation due to treatment or discontinuation in connection with the induced hypoglycemia state. Only if an intermediate assessment is missing independent of rescue treatment, study treatment or an adverse event including hypoglycemia, a linear interpolation can be applied to impute a missing value.

The same construct of imputation for missing values applies for the analysis of the plasma glucose AUC0-30min.

In the case of subject withdrawal, no imputation of values for PK or PD measurements will be done. Analyses will be done on valid cases only, i.e., no imputation techniques such as last observation carried forward will be applied.

Methods for Handling Missing Dates

All analyses and descriptive summaries will be based on the observed data. For the subject data listings, no imputation of incomplete dates will be applied. The listings will present the incomplete dates without any change.

Missing or Partial Death Dates

- If the entire date is missing, the death date will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, the death date will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - If day is missing, day will be 1st of the month
  - If both day and month are missing, death month and day will be January 1st.

Missing Dates in Adverse Events/Concomitant Therapies

Dates missing the day or both the day and month of the year will adhere to the following conventions:

- The missing day of onset of an AE or start date of a therapy will be set to:
  - first day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment
  - the day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment
  - the date of informed consent, if the onset yyyy-mm is before the yyyy-mm of the first treatment
- The missing day of resolution of an AE or end date of a therapy will be set to:
  - the last day of the month of the occurrence. If the subject died in the same month, then set the imputed date as the death date
- If the onset date of an AE or start date of a therapy is missing both the day and month, the onset date will be set to:
  - January 1 of the year of onset, if the onset year is after the year of the first study treatment
  - the date of the first treatment, if the onset year is the same as the year of the first study treatment
  - the date of informed consent, if the onset year is before the year of the first treatment
- If the resolution date of an AE or end date of a therapy is missing both the day and month, the date will be set to:

- December 31 of the year of occurrence. If the subject died in the same year, then set the imputed date as the death date

- If date is completely missing, then no imputation will be done and the event will be considered as treatment emergent (for AEs) or concomitant (for medications) unless the end date rules out the possibility.

4.13 Deviations from SAP

Any deviations from the statistical analysis plan will be described and justified in the final clinical trial report.

4.14 Changes in Conduct or Planned Analyses from the Protocol

There have been no changes in planned analyses from those defined in the protocol.

If any analysis, definitions, or summaries that have been written in the protocol have been amended for the purpose of the analysis, these will be described and justified in the final clinical trial report. This may include:

- Changes to populations
- Additional analysis
- Changes to equations
- Additional data to analyze

4.15 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 ...varn;
    BY byvar; (optional)
    OUTPUT OUT=outname
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that need exact or asymptotic 95% CIs between groups for proportions:**

```
PROC FREQ DATA=dset;
```

BY byvar; (optional)
*TABLES var1 * var2 / MEASURES RISKDIFF ALPHA=0.05;*
EXACT MEASURES;
RUN;

Notes: 1 Estimates are computed for 2x2 tables only
2 This code also gives exact 95% CIs within group for binomial proportions

- **Tables that need 95% CIs within group for binomial proportions:**

PROC FREQ DATA=dset;
BY byvar; (optional)
TABLES var1;
EXACT BINOMIAL;
RUN;

- **Tables that need 95% CIs within group for continuous variables:**

DATA outdata;
SET outname;
LCL=mean-(TINV(0.975,n-1)(std/SQRT(n)));*
UCL=mean+(TINV(0.975,n-1)(std/SQRT(n)));*
RUN;

- **Tables that require generalised linear modelling, including 95% CIs:**

PROC GENMOD DATA= dset;
CLASS class variables;
MODEL 'Responses / Attempts'= <effect> < treatment> /DIST=BIN;
LSMEANS treatment / DIFF CL;
ESTIMATE Drug 1 vs. Placebo' treatment 1 0 0 –1 / EXP;
ESTIMATE Drug 2 vs. Placebo' treatment 0 1 0 -1 /EXP;
ESTIMATE 'Drug 3 vs. Placebo' treatment 0 0 1 -1 /EXP;
BY byvar; (optional)
WHERE wherever; (optional)
RUN;

Note: (Treatment order: 1=drug 1,2= drug 2,3= drug 3, etc… 5= placebo)

- **Tables that require analysis of (co)variance and 95/90% CIs between arms for continuous variables:**

PROC GLM DATA= dset OUTSTAT=outset;
CLASS class variables;
MODEL response = <effect> <treatment> / SOLUTION;
*LSMEANS treatment / STDERR PDIFF CL; *ADD: ALPHA=0.1 for 90% CIs;*
*ESTIMATE 'T1 - T2' treatment 1 -1 0; *or 'T2 – T1' treatment -1 1 0 if applic.;*
ESTIMATE 'T1 - T3' treatment 1 0 -1;
ESTIMATE 'T2 – T3' treatment 0 1 -1;
BY byvar; (optional)

WHERE wherever; (optional)
RUN;
QUIT;

Note: (Treatment order: 1=drug 1,2= drug 2,3= drug 3, etc… 5= placebo)

- **Tables that present Fisher's Exact or CMH:**
PROC FREQ DATA=dset NOPRINT;
BY byvar; (optional)
*TABLES var1*var2/CMH score=MODRIDIT EXACT;*
OUTPUT OUT=outname CMH EXACT;
RUN;

- **Tables that need to use WILCOXON:**
PROC NPAR1WAY DATA=dset WILCOXON;
CLASS class variables;
VAR variable;
RUN;

- **Tables that need a regression slope and 90 % CI:**
PROC MIXED DATA=dset NOCLPRINT NOITPRINT;
MODEL lnauc=lntrt /S CL ALPHA=.1;
MAKE 'SOLUTIONF' OUT=outstats NOPRINT;
RUN;

- **Tables that need number of events/censored and probabilities of failure/survival at cut off times:**
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM INTERVALS=12, 24,;
*TIME duration*censor (0 or 1);*
ID subject;
STRATA treatment;
RUN;

- **Tables that need life table with estimates of survival, with CIs and log rank test:**
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM;
*TIME duration*censor (0 or 1);*
ID subject;
STRATA treatment;
RUN;

- **The calculation of AUC using trapezoidal method (Area of segment (ab) = (b-a)*(f(a) + f(b))/2:**
DATA auc (KEEP = pid area);
RETAIN A FA AREA 0;
SET dset;
BY pid time;

```
    IF FIRST.pid THEN DO;
        A = TIME;
        FA = <FEV1>;
        AREA = 0;
    END;
    ELSE DO;
        AREA = AREA + (TIME -A)*((FA+<FEV1>)/2);
        A    = TIME;
        FA   = VALUE;
    END;
    IF LAST.pid THEN OUTPUT;
RUN;
```

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.4 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and 7or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. PK and PD data will be reported with 3 significant digits. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 06OCT2017. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, subject and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

The following conventions apply for calculation of PK parameters:

- Any BLQ (<LLOQ) values that occur before the first quantifiable concentration will be replaced with zero.
- If a BLQ (<LLOQ) value occurs after a quantifiable concentration in a profile and is followed by a value of LLOQ or above, then the BLQ (<LLOQ) will be replaced with LLOQ/2.
- If two BLQ (<LLOQ) values occur in succession, the profile will be deemed to have terminated at the final quantifiable concentration and subsequent LLOQ or above values will be treated as 'missing'.

5.3 Tables

5.3.1 Section 14.1: Baseline and Demographic Data

Table 14.1.1 Patient Disposition
Table 14.1.2 Discontinuation and Drop-outs
Table 14.1.3 Demographic and Baseline Characteristics
Table 14.1.4 Medical History/Concomitant Illness
Table 14.1.5 Summary of Diabetes Duration

Table 14.1.6 Concomitant Medication
Table 14.1.7 History of Alcohol/Drug Abuse

5.3.2 Section 14.2: Efficacy Analysis Data

Table 14.2.1 Summary of Plasma Glucose Concentrations
Table 14.2.2 Summary of Plasma Dasiglucagon Concentrations
Table 14.2.3 Summary of Plasma GlucaGen Concentrations

5.3.3 Section 14.2: Primary Confirmatory Endpoint

Table 14.2.4 Time to Plasma Glucose Recovery
Table 14.2.5 Time to Plasma Glucose Recovery without Censoring Rescue IV Glucose Subjects
Table 14.2.6 Time to Plasma Glucose Recovery with Censoring at the Time of Rescue IV Glucose Administration

5.3.4 Section 14.2: Secondary Endpoints

Table 14.2.7 Plasma Glucose Recovery within Defined Time Points
Table 14.2.8 Plasma Glucose Changes from Baseline within Defined Time Points
Table 14.2.9 Time to First Plasma Glucose Concentration of >/=70 mg/dL

5.3.5 Section 14.2: Exposure (PD/PK) Endpoints

Table 14.2.10 Summary Statistics of Pharmacodynamics Endpoints
Table 14.2.11 Statistical Analysis of Pharmacodynamics Parameters
Table 14.2.12 Summary Statistics of Pharmacokinetic Endpoints
Table 14.2.13 Statistical Analysis of Pharmacokinetic Parameters

5.3.6 Section 14.2: Exploratory

Table 14.2.14 Time to First Plasma Glucose Concentration of >/=70 mg/dL or Increase of >/= 20 mg/dL within 30 Minutes
Table 14.2.15 Summary Statistics of Plasma Insulin Response

5.3.7 Section 14.3: Safety Analysis Data

5.3.7.1 Adverse events

Table 14.3.1.1 Overview of Incidence of TEAEs
Table 14.3.1.2 Summary of TEAEs by MedDRA System Organ Class and Preferred Term
Table 14.3.1.3 Summary of TEAEs by Severity, Relationship, Seriousness, and Outcome
Table 14.3.1.4 Summary of TE AESIs by Severity, Relationship, Seriousness and Outcome

5.3.7.2 Laboratory results

Table 14.3.2.1 Summary of Hematology Data – Actual and Change from Pre-Dose Measurement
Table 14.3.2.2 Summary of Biochemistry Data – Actual and Change from Pre-Dose Measurement

5.4 Listings

Listing 16.2.4.2 Adverse Events of Special Interest
Listing 16.2.5.1 Abnormal Laboratory Results: Hematology
Listing 16.2.5.2 Abnormal Laboratory Results: Biochemistry
Listing 16.2.5.3 Abnormal Laboratory Results: Coagulation
Listing 16.2.5.4 Abnormal Laboratory Results: Urinalysis
Listing 16.2.6 Vital Signs
Listing 16.2.7 12-Lead ECG
Listing 16.2.8 Physical Examination
Listing 16.2.9 Local Tolerability
Listing 16.2.10 Urine Drug Screen
Listing 16.2.11 Alcohol Breath Test
Listing 16.2.12 Pregnancy Test

5.5 Figures

Figure 14.2.X.X Individual PD Plasma Glucose Profile of Each Treatment Group
Figure 14.2.X.X Individual PD Plasma Glucose Profile by Treatment Group
Figure 14.2.X.X Individual PD Plasma Glucose Profile of Each Subject
Figure 14.2.X.X Individual PK Dasiglucagon Profile of Each Treatment Group
Figure 14.2.X.X Individual PK Dasiglucagon Profile by Treatment Group
Figure 14.2.X.X Individual PK Dasiglucagon Profile of Each Subject
Figure 14.2.X.X Individual PK GlucaGen Profile of Each Treatment Group
Figure 14.2.X.X Individual PK GlucaGen Profile by Treatment Group
Figure 14.2.X.X Individual PK GlucaGen Profile of Each Subject
Figure 14.2.X.X Mean Dasiglucagon/GlucaGen Profiles
Figure 14.3.X.X Box-and-Whisker Plots of Pharmacodynamics Endpoints vs. Treatment
Figure 14.4.X.X Box-and-Whisker Plots of Pharmacokinetic Endpoints vs. Treatment

5.6 Appendices

All analyses will require raw SAS output, but may or may not be required to be collated into an appendix document.

5.7 References

1. Allison, Paul D. 2010. *Survival Analysis Using SAS®: A Practical Guide, Second Edition.* Cary, NC: SAS Institute Inc.