16.1.9 DOCUMENTATION OF STATISTICAL METHODS

This appendix includes

Document	**Date, Version**
Statistical Analysis Plan	19 March 2018, Version Final 1.0
Data Review Meeting Protocol	25 March 2018, Version V2.0

Statistical Analysis Plan

Sponsor: Zealand Pharma A/S

Protocol number ZP4207-16136 (ZEA-DNK-01711)

Study Title:
A phase 3, randomized, double-blind, parallel group safety trial to evaluate the immunogenicity of Dasiglucagon and GlucaGen® administered subcutaneously in patients with type 1 diabetes mellitus (T1DM)

Protocol Version: 21 August 2017

EudraCT number: 2017-000062-30

IND Number: 127866

Dasiglucagon SUB code: SUB181296

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Version	Date
Draft 0.1	08 December 2017
Draft 0.2	06 February 2018
Draft 0.3	13 March 2018
Final 1.0	19 March 2018

Approval

Upon review of this document, including table, listing, and figure shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
ATC	Anatomical therapeutic chemical
$AUC_{0\text{-}30min}$	Area under the plasma concentration curve from administration to observed concentration 30 min
$AUC_{0\text{-}90\ min}$	Area under the plasma concentration curve from administration to observed concentration at 90 min
$AUE_{0\text{-}30min}$	Area under the effect curve from administration to 30 min
$AUE_{0\text{-}90\ min}$	Area under the effect curve from administration to 90 min
CE_{max}	Change from baseline plasma glucose to maximum plasma glucose measured post dose
CFB	Change from baseline
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
e.g.	For example
ECG	Electrocardiogram
EoT	End of Trial
FAS	Full Analysis Set
ICH	International conference on harmonization
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for regulatory activities
NAb	Neutralizing Antibody
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PPS	Per protocol set
PT	Preferred term
SA (set)	Safety analysis (set)
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SHCR	Contract research organization: SynteractHCR Deutschland GmbH, Albrechtstr.14, 80636 Munich, Germany
SOC	System organ class

T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings, figures
t_{max}	Time until C_{max} is reached, time to maximum effect
ULN	Upper Limit of Normal
V	Visit
WHO	World Health Organization
WHO-DDE	WHO drug dictionary enhanced
ZP4207	dasiglucagon

DEFINITIONS

Treatment-emergent AE	AEs with an onset time at or after the initial dose of study drug.
End of trial	The trial ends with the last visit of the last patient participating in the trial.
Clinical (adverse) event of interest	A clinical event of interest is an event which, in the evaluation of safety, has a special focus (e.g. required by health authorities). They will be recorded under the eCRF section adverse events. In this trial hemodynamic changes, as defined below, are considered clinical events of interest: • Post-dose clinical signs or measured vital signs indicating a clinical 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.
ADA titer	A sample is defined as ADA-positive if results of the screening and confirmatory assays are positive. If positive, a titer (the reciprocal of the highest dilution factor that still yields a positive reading, e.g. dilution 1/10 = titer 10) will be reported. Any titer above zero defines positivity.
ADA-positive/ negative-subject (after baseline)	ADA-positive after baseline is a subject with at least one treatment-induced or treatment-boosted ADA positive sample at any time during the treatment or follow-up observation period. In contrast a ADA-negative subject after baseline is a subject without any treatment-induced or treatment-boosted ADA-positive sample at any time during treatment or follow-up.
Evaluable patients	A subject with at least one sample taken after drug

	administration during the treatment or follow-up that is appropriate for ADA testing (with reportable result). This is the same definition as for the FAS population.Only evaluable subjects are considered for computing treatment-induced ADA incidence
Pre-existing/ baseline ADA	Refers to antibodies reactive with the biologic drug that are present in subjects before treatment or before the initiation of the study.
Treatment-induced ADA	ADA developed de novo (sero-conversion) following biologic drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA).
Treatment-boosted ADA	Pre-existing ADA that were boosted to a higher level following biologic drug administratio (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a scientifically reasonable margin - in this study the fifth fold increase.
Overall ADA incidence	Overall ADA incidence is defined as the percentage of the combined results of treatment-induced ADA-positive patients and treatment-boosted ADA-positive patients and the total number of evaluable patients, excluding baseline-positive patients without any samples available after drug administration.
Onset of ADA	Refers to the time period between the initial administration of the biologic drug (in a study) and the first instance of treatment-induced ADA via blood sampling date. Elapsed days between the two dates will be used for calculation and not nominal study time points. Actual documentation of blood sampling date will be taken as reference.

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analysis of data collected within the scope of Zealand Pharma A/S ZP4207-16136 (ZEA-DNK-01711) observational trial. The purpose of this plan is to provide analysis strategies for all trial data which were collected, as well as to provide specific guidance how to analyze data for the statistical analysis.

Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY DOCUMENTS

The following study documents are used for the preparation of the SAP:

- Protocol version 1, 18 JAN 2017
- Amendment 1, 08 May 2017
- Amendment 2, 21 AUG 2017
- Protocol version 3, 21 AUG 2017
- eCRF version 4.0, 05 DEC 2017
- Data Management Plan version 1.1, 18 Sep 2017

3. STUDY OBJECTIVES

The present trial aims to evaluate that immunogenicity risk with an assessment of the occurrence of ADAs and neutralizing ADAs, and of cross-reactivity with native glucagon, following repeated single doses of dasiglucagon by s.c. administration in T1DM patients. The trial further aims to evaluate the pharmacodynamics and pharmacokinetic responses and to correlate the consequence of an antibody response, if any, to pharmacodynamic and pharmacokinetic endpoints. The reference product in this trial is GlucaGen®, a recombinant human glucagon approved for the treatment of the severe hypoglycemic reactions that may occur in the management of insulin-treated children and adults with diabetes mellitus.

Primary objective

The primary objective is to describe the immunogenicity of repeated single doses of dasiglucagon and GlucaGen® following s.c. administration in T1DM patients.

Secondary objectives

The secondary objective consists of analyzing the safety, tolerability and pharmacodynamic response of repeated single doses of dasiglucagon following s.c. administration compared with s.c. GlucaGen® in T1DM patients.

4. STUDY DESIGN AND PLAN

This is a randomized, double-blind, parallel group, multicenter (EU, US, Canada) trial evaluating the immunogenicity of **3 fixed doses** of either **dasiglucagon or GlucaGen®** administered to **euglycemic T1DM patients**.

Blinding: Handling, preparation and administration of trial medication is done by unblinded trial personnel. All trial assessments on the trial site are done by blinded trial personnel. However, exposure assessments and ADA assessments are performed by unblinded personnel at the specialty laboratories, to make sure that dasiglucagon or GlucaGen® administration is matched with the applicable bioanalytical assay.

Patients with T1DM are randomized 1:1 to receive 3 s.c. injections of either dasiglucagon (0.6 mg) or GlucaGen® (1 mg), with 1 week between each dose. Patients are followed for at least 3 months from the day of the first dose to assess any immune response. Patients with previous exogenic glucagon exposure are not excluded from the trial, but the information on previous glucagon administration is recorded to enable subgroup analyses. A total of 90 patients should participate in and complete the trial (45 in each treatment arm). To qualify as completed, the patient must have been be dosed according to protocol and have blood drawn for the ADA analyses. Prematurely discontinued patients are not replaced in order to reach 90 completed patients (see Amendment 2). 112 patients in total are to be randomized and treated.

For the safety and well-being of the patients, they are not brought into hypoglycemia prior to dosing. Prior to administration of trial product patients must reach a target plasma glucose level of 70-150 mg/dL.

The trial includes the following periods (as illustrated in figure below).

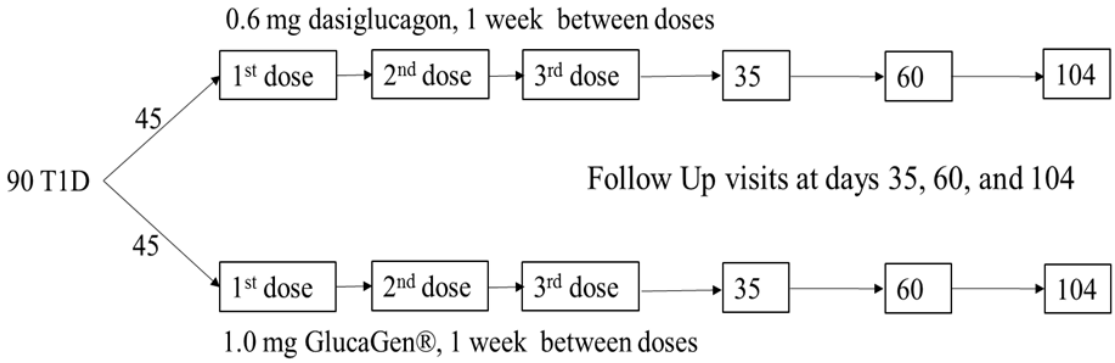


Figure 1: Overview of the trial design

The study includes the following periods:

- A screening period from day -30 to day -3 (V1)
- A treatment period, from day 0 (day of randomization), day 7 to day 14 (day of third and final dosing with trial medication), with s.c. trial medication administered on day 0, day 7, and day 14.
- A follow-up period, from the end of the treatment period, with follow-up visits at day 35, day 60, and day 104 (the EoT visit).

The overall duration of the study is about half a year from study initiation (i.e., first subject enrolled, March 2017) to study completion (i.e., last subject last visit, February 2018). The subject participation period is 3 months from enrollment to subject completion (i.e., last study visit), unless prematurely discontinued.

Key inclusion criteria at screening:

(for a complete listing of inclusion criteria please refer to the study protocol)

Subjects of any age who meet ALL of the following criteria are eligible for this study and who are willing and able to comply with the requirements of the protocol:

To be included in the trial, patients have to fulfill all of the following criteria:

- Age between 18 and 70 years, both inclusive
- Male or female patients with T1DM for at least 1 year. Diagnostic criteria as defined by the American Diabetes Association
- Hemoglobin A_{1c} (HbA_{1c}) <10%
- Stable antidiabetic treatment for at least 1 month (e.g. within 10% insulin dose adjustment)

Key exclusion criteria at screening

(for a complete listing of exclusion criteria please refer to the study protocol)

Subjects who meet **ANY** of the following criteria are not eligible for this study:

- Previous administration of dasiglucagon (previously referred to as ZP4207).
- Known or suspected allergy to trial medication(s) or related products
- History of anaphylaxis or symptoms of severe systemic allergy (such as angioedema)
- Patients on a closed loop artificial pancreas
- Receipt of any investigational drug within 3 months prior to screening
- Active malignancy within the last 5 years
- Congestive heart failure, New York Heart Association class II-IV
- Inadequately treated blood pressure as defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥90 mmHg at screening.
- Current bleeding disorder, including use of anticoagulant treatment
- Known presence or history of pheochromocytoma (i.e. adrenal gland tumor) or insulinoma (i.e. insulin-secreting pancreas tumor)
- Known or suspected HIV infection
- Use of a systemic beta-blocker drug, indomethacin, warfarin or anticholinergic drugs in the previous 28 days before Day 1 of this trial)
- Use of systemic corticosteroids, anti-inflammatory biological agents, kinase inhibitors or other immune modulating agents within the last 3 months prior to screening
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 X the upper limit of normal (ULN), bilirubin >1.5 X ULN, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) Study definition. Altered electrolytes values of clinical relevance for cardiac conduction, as judged by the investigator.
- Clinically significant abnormal ECG at screening, as evaluated by Investigator
- Donation of blood or plasma in the past month, or in excess of 500 mL within 12 weeks prior to screening
- A positive result in the alcohol and/or urine drug screen at the screening visit. Significant history of alcoholism or drug abuse as judged by the investigator or consuming more than 24 g alcohol per day for men, or more than 12 g alcohol per day for women.
- Patients with mental incapacity or language barriers that preclude adequate understanding or cooperation, who are unwilling to participate in the trial, or who in the opinion of the Investigator should not participate in the trial
- Surgery or trauma with significant blood loss within the last 2 months prior to screening
- Use of prescription or non-prescription medications known to cause QT prolongation

The following flow chart shows the investigations undertaken in this trial:

Trial period	Screening	Treatment			Follow-up		
Visit number	V1	V2	V3	V4	V5	V6	V7 (EoT)
Trial day	-3	0	7	14	35	60	104
Visit window (days)	-30 to - -3		±1	±1	±2	±5	±10
Patient related info/assessments							
Informed consent	X[1]						
Inclusion/exclusion criteria	X	X[2,3]					
Demography	X						
Body measurements	X						
Medical history	X						
Concomitant illness	X						
Prior medications	X						
Concomitant medication	X	X	X	X	X	X	X
History of alcohol/drug abuse	X						
Randomization		X					
Withdrawal criteria		X	X	X	X	X	
Dosing day exclusion criteria		X	X	X			
Safety assessments							
Physical examination	X						X
Vital signs	X	X[12]	X[12]	X[12]	X		X
ECG	X	X[10]	X[10]	X[10]	X		X
Local tolerability		X[5]	X[5]	X[5]			
Adverse events	X	X	X	X	X	X	X
Laboratory							
Hematology, biochemistry, coagulation	X[4]	X[4]		X[4]	X		X
Pregnancy test	X[11]	X[11]	X[11]	X[11]			
Urinalysis	X	X[2]		X[2]			X
Urine drug screen	X[6]	X[2,6]	X[2,6]	X[2,6]			
Alcohol breath test	X	X[2]	X[2]	X[2]			
Exposure and pharmacodynamics (PD)							
Dasiglucagon /glucagon		X[7]		X[7]			
Plasma glucose		X[8]		X[8]			
Other assessments							
Antibodies against dasiglucagon /glucagon		X[2]	X[2]	X[2]	X	X	X
Trial material							
Administration of trial medication		X[9]	X[9]	X[9]			

ECG = electrocardiogram; EoT = End of Trial; ; PD = pharmacodynamics; V = visit
[1] Informed consent can be obtained on the same day as screening, but prior to any trial-related procedures [2] Pre-dose
[3] Only check of changes between the screening visit and V2.
[4] Coagulation parameters are measured at screening visit only. On dosing days Visit 2 and 4, blood samples are collected pre-dose, and at 30 and 90 min post-dosing. The actual time for sampling should not deviate from the nominal time by more than ±5 min. Pre-dose is defined as within 5 min prior to dosing.
[5] Local tolerability assessed at 0.5 and 2 h post-dose. The actual time for assessment should not deviate from the nominal time by more than ±10 min.
[6] Urine drug screen will be performed at trial site for visits 1-4
[7] Pre-dose, 5, 10, 30, 60, and 90 min post-dosing. The actual time of blood sampling for exposure should not deviate from the nominal time by more than ±1 min. Pre-dose is defined as within 5 min prior to dosing.
[8] Pre-dose, 5, 10, 30, 60, and 90 min post-dosing. The actual time for blood sampling for plasma glucose should not deviate from the nominal time by more than ±1 min. Pre-dose is defined as within 5 min prior to dosing.
[9] Prior to administration of trial medication patients must reach a target plasma glucose level of 70-150 mg/dL. Plasma glucose levels may be adjusted by administration of a fast-acting insulin analog or by glucose ingestion at the discretion of the investigator. At visit 2 and 4 patients must be fasting for 90 min after administration of trial medication. At all dosing visits, patients will be treated individually to alleviate any potential side effects and will be observed for at least 5 h post-dose.
[10] On dosing days Visit 2, 3 and 4 ECG's are assessed pre-dose, and at 20, 35, 45 and 60 min post-dosing. The actual time of assessment should not deviate from the nominal time by more than ±5 min. Pre-dose is defined as within 5 min prior to dosing.
[11] Pregnancy test is only applicable for women of childbearing potential. At Visit 1 a serum pregnancy test should be performed. At Visit 2, 3 and 4 a pre-dose urine pregnancy test should be performed.
[12] On dosing days Visit 2, 3, and 4 vitals signs are collected pre-dose and at 30, 90 and 120 min post-dosing. The actual time of assessment should not deviate from the nominal time by more than ±5 min. Pre-dose is defined as within 5 min prior to dosing.

Table 1: Flow chart

5. DETERMINATION OF SAMPLE SIZE

The purpose of the present trial is to generate data describing the immunogenic potential of dasiglucagon and GlucaGen®. The ADA assays to be used in this trial are both validated, but specific for GlucaGen® and dasiglucagon, and the performance of the assays are thus not directly comparable. As a consequence, a formal comparison or non-inferiority analysis will not be performed.

Currently, no ADA incidences have been detected in the completed clinical trials, where up to 5 repeated doses of dasiglucagon have been administered to the same patients within a week. Across the two phase I clinical trials and a completed phase II PK/PD trial, a total of 141 subjects have been exposed to dasiglucagon and no incidences of ADA development have been observed. The obtained data indicate that dasiglucagon has a low risk for induction of ADAs in the investigated settings and as a consequence a meaningful sample size to compare both treatments cannot be estimated.

The sample size is therefore based on a certain precision of the confidence interval for the overall ADA incidence if no events are observed, respectively to ensure a certain probability for observing one event.

When no events are observed, to obtain an upper bound of 0.050 on the 90.0% confidence interval for the probability of such a rare event, would require a sample size of 45. Respectively, accepting a chance of observing at least one event of 90% and an actual probability of the event of 5%, leads to a sample size of 45 patients completing the trial. In order to account for drop-outs, it is expected that 112 patients in total will be randomized and treated.

6. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Conference on Harmonization (ICH) numbering convention will be used for all TLFs.

Continuous variables will be analyzed using standard descriptive measures as number of non-missing observations, mean, standard deviation, median, minimum and maximum. Other summaries (e.g. quartiles, 95% confidence intervals, SEM) may be used as appropriate and will be indicated in the respective sections. Categorical variables will be summarized by counts and by percentage of patients in corresponding categories. Percentages for missing values are not displayed as they do not account for the percent calculation of other non-missing categories. Percentages are therefore routinely based on the total category count excluding the missing category. Percentages showing a rate relative to the total number of patients in this group are given in special tables (e.g. adverse event tables). Footnotes will specify the percent basis in those cases.

Individual patient data obtained from the case report forms (CRFs), central clinical laboratory, ECG, pharmacokinetic/ pharmacodynamic and immunogenicity data, and any derived data will be presented by patient in data listings.

Tabulations will include in general a total summary column, if more than one column is presented in the table.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock. Any analyses performed subsequent to database lock will be considered post-hoc and exploratory. Post-hoc analyses will be labeled as such on the output and identified in the CSR.

All analyses and tabulations will be performed using SAS® Version 9.4 or higher. Determination of Pharmacokinetic (PK) and Pharmacodynamic (PD) metrics will be performed using WinNonLin® Version 5.4 or using SAS® Version 9.4 or higher. Tables, listings, and figures will be presented in ASCII format. Upon completion, all SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

7. NOTATION OF TREATMENT GROUPS, TYPES, HAEMOPHILIA SEVERITY GRADING AND VISITS

7.1 Notation of treatment groups

The following notations of dasiglucagon and GlucaGen® treatment and other important stratification criteria are mentioned below and will be used throughout the statistical analysis.

Full notation (as used in the study protocol)	***Notation as used throughout all tables, listings and figures***
Dasiglucagon (ZP4207): Liquid formulation, 0.6 mL in a strength of 1 mg/mL, Single use pre-filled syringe (Zealand Pharma A/S, Glostrup (Copenhagen), Denmark)	dasiglucagon
GlucaGen®: Recombinant glucagon hydrochloride, Powder and solvent for reconstitution as 1 mL solution for injection in a strength of 1 mg, powder and solvent for reconstitution packed together in a plastic box. A "hypo-kit" (Novo Nordisk A/S, Bagsværd, Denmark)	GlucaGen

7.2 Visit terminology

Visit	*Notation as used throughout all tables, listings and figures*	*Study part*
Visit V1: Screening visit*, trial day -3, visit window (-30 to -3)	Screening	Screening
Visit V2: Trial day 0**	Day 0	Treatment period
Rescheduled day 0	R1-Day 0, R2-Day 0, etc.	
Visit V3: Trial day 7 ± 1**	Day 7	
Rescheduled day 7	R1-Day 7, R2-Day 7, etc.	
Visit V4: Trial day 14 ± 1**	Day 14	
Rescheduled day 14	R1-Day 14, R2-Day 14, etc.	
Visit V5: Trial day 35 ± 2	Day 35	Follow-up
Visit V6: Trial day 60 ± 5	Day 60	
Visit V7: End of trial, trial day 104 ± 10	Day 104	
Unscheduled visits: A patient with a treatment induced or treatment boosted ADA response at visits 3-7 must be called in for an unscheduled visit	ADA-V1, ADA-V2, etc.	Unscheduled ADA visits

Time points will be abbreviated following the eCRF (e.g. pre-dose, 30min, 90min etc.).

* There could possibly be re-screening visits. In such a case only the latest screening visit will be tabulated. However data from each screening and re-screening – if available - will be listed.

** Note that there can possibly be a re-scheduling of the dosing days in case of meeting any dosing day exclusion criteria. The dosing day with the most recent date will be used for analyses as the 'trial day' (e.g. for display of results in tables or in case of baseline value determinations) unless not otherwise specified. In some cases results from all re-scheduled visits have to be considered. This will be indicated in the respective sections of the SAP. All data from dosing day visits will be listed.

7.3 Subgroup/ Stratification terminology

The following subgroups will be used for analyses:

Subgroup/ Stratification	***Notation as used throughout all tables, listings and figures***
Patients with previous exogenic glucagon exposure will not be excluded from the trial, but the information on previous glucagon administration will be recorded in the eCRF section 'Concomitant medication' at screening. (PT= Glucagon, ATC= H04AA)	Previous exogenic glucagon exposure
Age class: Patients are included in the trial having an age at giving at informed consent between 18 and 70. Age at informed consent will be categorized into classes: 18–40, 41–64, 65-70. Reasonable patient distribution in age classes will be discussed with the sponsor and a decision upon the final cut-offs will be made using blinded data.	Age class
Gender: Subgroup analyses will be performed for males and females	Gender
Race: Race classification can be done using categories 1= american indian or alaska native, 2= asian, 3= black or african american, 4= native hawaiian or other pacific islander, 5= white, 99= other. In case multiple answers are given, the categories will be combined.	Race
ADA positive at baseline: Patients having a positive ADA at baseline.	Baseline ADA positive
ADA negative at baseline: An ADA-negative subject is a subject not being ADA-positive at baseline.	Baseline ADA negative

8. ANALYSIS POPULATIONS/ ANALYSIS SETS

The following patient populations will be used for the analyses as specified afterwards:

1. **All patients analysis set (ALL)**: The ALL patient set includes all patients having been enrolled.
2. **Safety set (SAS):** The safety analysis set consists of data for all patients who were randomized and received at least one dose of trial medication.

3. **Full analysis set (FAS):** The full analysis set is defined as all patients of the SAS population with at least one measurement of the ADA titer at baseline (screening).
4. **Per Protocol set (PPS):** The PPS consists of all patients of the FAS for whom no relevant protocol deviations were documented.
5. **PK/PD set (PKS):** All patients in the SAS having at least one pre- and post-dose PK value at one visit.

The decision whether a protocol deviation is relevant or not for the exclusion of patients from the PPS set will be made case-by-case in a data review meeting before unblinding.

Assignment of analysis populations to analyses:

1. **ALL:** Presentation of information under sections study population (e.g. patient disposition, except termination/ withdrawal information).
2. **FAS:** Analysis of the primary endpoint, the key secondary endpoints and secondary endpoints referring to ADA response characterizations.
3. **SAS:** Safety parameters and analysis of study drug administration/ extent of exposure and termination/ withdrawal information.
4. **PKS:** Pharmacokinetic and pharmacodynamics endpoints

Main conclusions of the primary endpoint will be drawn from analyses based on the FAS. A secondary analysis of the primary endpoint will be based on the PPS.

9. HANDLING OF DROP-OUTS OR MISSING DATA

In general no imputations will be made for missing values. Summaries will be based on observed data/ valid cases only.

There are some exceptions:

1. Any AE with missing relationship will be considered as possibly related to the study drug.
2. For flagging adverse events into pre-treatment/ treatment-emergent and medication into previous and concomitant, the following rules will be applied (the calculation of durations if foreseen won't use imputed data):

Date	***Imputation rule***
Partial/ Missing Start Date	• Missing day - Impute the 1st of the month unless year and month is same as year and month of first dose of study drug or date of screening in case study drug started earlier then impute first dose date • Missing day and month – impute 1stJanuary unless year is the same as first dose date then impute first dose date • Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date
Partial/ Missing End Date	• Missing day - Impute the last day of the month unless year and month is same as year and month of last dose of study drug then impute last dose date • Missing day and month – impute 31st December unless year is the same as last dose date then impute last dose date • Completely missing – impute date of last dose • If imputed end date < imputed start date, take the imputed start date to impute the end date

10. STUDY POPULATION

Tables in this section will be provided for the SAS/ALL populations.

10.1 Patient numbers in each country and investigational site

Patient numbers/ percentages in each country and patient numbers/percentages in each country and site will be presented by treatment group.

10.2 Patient disposition

Patient disposition information will be summarized for all patients by treatment group. The patient disposition summary will include:

- the number of enrolled (=signed informed consent) patients,
- the number of re-screened patients,
- the number of screening failures (as determined by the screening failure question at screening or in case of not fulfilling eligibility criteria at visit 2/ day 0),
- the number of randomized patients,
- the number of patients in the analysis set SAS
- the number of patients in the analysis set FAS
- the number of patients in the analysis set PPS
- the number of patients in the pharmacokinetic/ pharmacodynamic analysis set
- the number of patients with previous exogenic glucagon exposure
- number of patients having a regular follow-up (yes/no)
- the number of patients, who completed the study (V7)

Patient numbers/ percentages in each of the sets mentioned above will be displayed by treatment group.

10.3 In- and exclusion criteria, eligibility criteria

Details on in- and exclusion criteria not met at screening, and on re-check of in- and exclusion criteria (re-screening) and visit 2/ day 0 questions on eligibility, will be listed and not tabulated.

Check questions at dosing day referring to possible exclusion criteria (filled in at screening, visit 2/ day 0 and possible re-scheduled visits as well as unscheduled dosing visits (for ADA positive patients)) will be listed.

10.4 Trial termination form and withdrawal criteria information

Trial termination form
The number of patients who completed/ or discontinued the study will be tabulated by treatment regimen with counts and percentages for all patients. In addition, for patients who discontinued, the primary reason will be tabulated by treatment group. Number/ percentage of patients, whose treatment were unblinded or not, will be displayed as well.

Withdrawal criteria information
Patient withdrawal criteria at all regular visits and further unscheduled visits (e.g. including ADA unscheduled visits) are not mapped into SDTM domains. Therefore no data will be displayed.

10.5 Demographic and baseline characteristics

10.5.1 Demographics

A table for the demographic data will be prepared with summary statistics for age at signing the IC (years) (both as continuous and as categorized age class variable), gender, race and ethnicity. The demographics table will be generated for all patients by treatment group.

10.5.2 Informed consent

Information concerning informed consent will be listed.

10.5.3 Medical history

Medical history will be displayed for the ALL and the SAS population.

Indication specific medical history (diabetes history)
Time since detection of diabetes 1 (based on date of informed consent and start date of diabetes 1) (years) will be tabulated with descriptive statistics by treatment group. If the day is not available, the calculation of duration will be based on month and year only, setting the start day to 1. In case only the year is available, the start day will be 1 and the start month will be January.

General medical history/ surgical history including concomitant diseases
All entries in this section will be coded using MedDRA, current version 20.0 or higher. Frequency tables will be prepared by treatment group stratified by MedDRA terms (SOC,

PT) showing the number of entries in each SOC and PT and numbers/ percentages of patients being affected.

10.5.4 History of alcohol or drug abuse

Number/ percentage of patients having a history of alcohol or drug abuse will be displayed by treatment group. Results of alcohol breath test at screening and urine drug screen test will be included in the same tabulation. Results of further alcohol breath tests and urine drug screen tests can be found in the patient withdrawal criteria (see sec. 10.4) and the dosing day exclusion criteria (see sec. 10.3).

10.5.5 Other information documented at screening

Analyses of other screening or baseline variables, which are documented at screening/ baseline and/ or have further evaluations after the screening/ baseline visit will be described in the following sections:

- Physical examination: see sec. 14.3.2
- Vital signs, see sec. 14.3.1
- 12-lead electrocardiogram (12-lead ECG), see sec. 14.4
- Central safety laboratory (hematology, biochemistry, coagulation, urinalysis, urine drug screening, urine pregnancy test), see sec. 14.2
- Previous medication, see sec. 14.5
- Adverse events, see sec. 14.1

11. PRIMARY IMMUNOGENICITY AND SECONDARY IMMUNOGENICITY ENDPOINT ANALYSES

11.1 Primary immunogenicity endpoint

The primary endpoint is the evaluation of immunogenicity of repeated single doses of dasiglucagon and GlucaGen® and comprises:

Overall ADA incidence
Overall ADA incidence is defined as the percentage of the combined results of treatment-induced ADA-positive patients and treatment-boosted ADA-positive patients (as defined in the secondary endpoints section) and the total number of evaluable patients, excluding baseline-positive patients without any samples available after drug administration.

11.2 Secondary endpoints

Secondary endpoints consider key secondary endpoints and secondary endpoints as listed below:

A) Key secondary endpoints

- **Treatment-induced ADA incidence**
  Treatment-induced ADA incidence is calculated as the percentage of the total number of evaluable patients that were ADA negative at baseline and ADA positive after drug administration relative to the total number of evaluable patients, excluding baseline positive patients without any samples available after drug administration.
- **Treatment-boosted ADA incidence**
  Treatment-boosted ADA incidence is calculated as the percentage of baseline ADA-positive patients with significant increases (≥5-fold) in ADA titer after drug administration relative to the total number of evaluable patients, excluding baseline-positive patients without any samples available after drug administration.

B) Secondary endpoints

- Incidence and titer of neutralizing activity of ADA positive patients
- Incidence of cross-reactivity of ADA positive patients towards endogenous glucagon
- Kinetics of ADA: The timing and duration of detected ADA response

11.3 Baseline treatment values

ADA status measured in serum and ADA antibody serum sample results for immunogenicity measurements at day 0 pre-dose will serve as baseline.

11.4 Adjustment for covariates

N/A.

11.5 Handling of dropouts or missing data

see sec. 9 - Handling of drop-outs or missing data.

11.6 Interim analysis and data monitoring

There are no planned interim analyses for this study.

11.7 Examination of subgroups

Special attention in analyses is laid on ADA-positive and ADA-negative patients at baseline. Incidence of treatment-induced ADA patients and treatment-boosted ADA patients is determined by baseline ADA result.
Stratification by age class, gender and race will be done for the primary and secondary immunogenicity endpoints.

11.8 Multiple comparison/multiplicity

No adjustment for multiplicity is made in this study.

11.9 Multicenter studies

No subgroup analyses by center will be done for evaluating the primary or secondary endpoints.

12. METHODS OF PRIMARY IMMUNOGENICITY, KEY SECONDARY AND SECONDARY ENDPOINT ANALYSES

Tabulations will show results for FAS and PPS population.

12.1 Analyses of the primary immunogenicity endpoint overall ADA incidence

The overall ADA incidence will be derived from the number of patients having an ADA-positive sample during the course of the trial. Determination of the number of patients will include counting:

1. Patients, who were ADA-negative at baseline and ADA-positive after drug administration (=**treatment-induced ADA patients)**
2. Baseline ADA-positive patients with significant increases (≥5-fold) in ADA titer after drug administration (= **treatment-boosted ADA patients)**

Both patient numbers will be summed up for the overall ADA incidence nominator. The nominator will be derived by dividing by the number of evaluable patients (see sec. Definitions: Evaluable patients = *A subject with at least one sample taken after drug administration during the treatment or follow-up that is appropriate for ADA testing (with reportable result).*). Patients, who were baseline positive patients without any samples available after drug administration, will be excluded from the number of evaluable patients. Note that for ADA-positive patients unscheduled dosing visits are performed and results from those visits have to be respected as well.

Numbers and percentages (defined as above) of incidences in each treatment group, incidence difference between dasiglucagon and GlucaGen® with its 95% exact confidence limits will be provided. The tabulation will be replicated using stratification factors sex, age class and race.

12.2 Analyses of the key secondary immunogenicity endpoints

12.2.1 Treatment-induced ADA incidence

For presenting the treatment–induced incidence only **treatment-induced ADA patients** will be used. Incidence is based on subjects that were ADA-negative at baseline. Tabulations will follow the same strategies/ models as for the key primary endpoint.

12.2.2 Treatment-boosted ADA incidence

For presenting the treatment–boosted incidence only patients falling under the second point in the section of the key primary immunogenicity endpoint will be used. Incidence is based on patients being ADA-positive at baseline. Tabulation will present the same statistics as for the key primary endpoint.

12.3 Analyses of further secondary immunogenicity endpoints

12.3.1 Incidence and titer of neutralizing activity of ADA-positive patients

Confirmed positive antibody samples will be further evaluated for in vitro dasiglucagon and/or glucagon neutralizing potential. The in vitro neutralizing effect will be evaluated in validated cell-based assays. In case of a positive result in the neutralizing antibody assays, a titer will be estimated.

Based on all samples taken, number of ADA-negative and number of ADA-positive samples will be displayed with counts/ percentages by treatment group. The calculation will differentiate between Day 0 (pre-dose/ baseline) and the other visits (post-dose/treatment, follow-up and unscheduled ADA positive visits). In addition the number and percentage of patients with positive/ negative ADA samples will be calculated and displayed by treatment group and the timely distinction as mentioned above. Patients included in the tabulation are the ones, who have a reportable pre-dose/ baseline ADA sample.

<u>Pre-existing ADA-positive patients: Titer and boosting</u>
Descriptive statistics will be presented for the neutralizing antibody titers Nab (reciprocal of the highest dilution factor, without unit) at Day 0 and the other visits (post-dose/ treatment and follow-up) by treatment group based on all measurements for patients being baseline ADA-positive. Descriptive statistics for tabulations will include additionally the interquartile range. Tabulation will include only patients being baseline ADA-positive.

<u>Treatment-induced ADA-positive patients: ADA titer</u>
Tabulations will be the same as for the pre-existing ADA, however only patients being ADA-negative at baseline will be respected.

Display of descriptive statistics will be done in case sufficient data are available. In any case data are displayed in listings.

12.3.2 Incidence of cross-reactivity of ADA positive patients towards endogenous glucagon

Cross-reactivity of ADA positive patients towards endogenous glucagon will be measured by a special laboratory. The following parameters will be available to evaluate cross-reactivity:
Samples from confirmed positive anti-dasiglucagon antibody patients (treatment-induced or treatment-boosted) will be further evaluated for potential cross-reactivity towards endogenous glucagon. The samples will be tested in the screening and confirmatory assays, in case of a confirmed positive result, a titer will be estimated. The number of anti-dasiglucagon positive patients that have antibodies that cross react with endogenous glucagon will be determined over the entire study.

Counts and percentages for this cross-reactivity parameter for all ADA-positive patients will be presented by treatment group.

12.3.3 Kinetics of ADA: The timing and duration of detected ADA response

1) Kinetics of patients being baseline ADA-negative
For analyses of kinetics of patients being baseline ADA-negative, patients being baseline ADA-positive will be excluded.

The following parameters will be derived:

- **Onset of ADA and number of drug applications:** Time until onset of ADA will be determined using the date of initial administration of the drug and the date of first date of detection (=date of blood sampling) of treatment-induced ADA in days (after Day 0/ baseline). Number of drug applications until first onset of ADA will be determined as well. A drug application is seen as being successfully applied in case the question on trial administration has been answered with 'yes'. All dosing visits as well as the unscheduled visits for ADA-positive patients have to be taken into account.
- **Duration of ADA:** Time between first onset of an ADA-positive result until its return to negativity/ no detectability. For calculation only antibody samples after the day 0 pre-dose sampling will be used. In case of having more than one ADA positive result, time point after the last ADA-positive result will be taken to evaluate return to negativity.

Listings
All parameters mentioned above under onset of ADA and duration of ADA will be provided in a listing for each patient. A footnote will indicate that only ADA-negative patients at baseline have been respected in this display.

Figures
Individual display of patients: For each of the ADA post-dose positive patients a line plot will be generated plotting time (date of ADA sample) versus titer. If possible the referring nominal visit will be included in the time axis as well. A reference line indicating the cut-off for positivity of the titer will be included in the figure (cut-off is 10 (minimum required dilution in the assay)). Patient ID and treatment group will be displayed. Line plots will display titers on original scale and on log scale. If possible for each patient original and log scale display will be shown in a panel display.

2) Kinetics of patients being baseline ADA-positive
For analyses of these kinetics, only patients being baseline ADA-positive will be included.

The following parameters will be derived:

- **Onset of ADA and number of drug applications:** Time until onset of ADA will be determined using the date of initial administration of the drug and the date of first onset (date of blood sampling) of treatment-boosted ADA in days (= significant increases (≥5-fold) in ADA titer after Day 0/ baseline). Number of drug applications until first onset of ADA will be determined as well. A drug application is seen as being successfully applied in case the question on trial administration has been answered with 'yes'. All dosing visits as well as the unscheduled visits for ADA-positive patients have to be taken into account.
- **Duration of ADA:** Time between first onset of an ADA-positive boost result (= significant increases (≥5-fold) in ADA titer after Day 0/ baseline) until its return to baseline titer <5-fold. . For calculation only antibody samples after the day 0 pre-dose sampling will be used. In case of having more than one ADA positive result, the time point after the last ADA-positive (boost) result will be taken to evaluate return to negativity.

Listings
All parameters mentioned above under onset of ADA and duration of ADA will be provided in a listing for each patient. A footnote will indicate that only ADA-positive patients at baseline have been respected in this display.

Figures

Individual display of patients: For each of the ADA baseline positive patients a line plot will be generated plotting time (date of ADA sample) versus titer. If possible the referring nominal visit will be included in the time axis as well. A reference line indicating the cut-off for positivity of the titer will be included in the figure (cut-off is 10 (minimum required dilution in the assay)). Patient ID and treatment group will be displayed. Line plots will display titers on original scale and on log scale using e.g. a panel display.

13. SAFETY AND TOLERABILITY ANALYSIS

Safety analyses will use the SAS population.

13.1 Safety and tolerability endpoints

Safety and tolerability will be assessed by using the following endpoints:

1. The incidence, type and severity of AEs
2. Changes from baseline in clinical laboratory parameters
3. Changes from baseline in vital signs
4. Clinically meaningful changes from baseline in physical examination
5. Clinically meaningful changes from baseline in electrocardiogram (ECG)
6. Tolerability: Local tolerability in terms of skin reaction at 0.5h and 2h after post-dosing (note that local tolerability events are reported as adverse events as well)

13.2 Baseline values

For assessments with post-dose measurements (e.g. ECG, vital signs, safety laboratory) the pre-dose value at the respective dosing visit will be taken as baseline value.

14. METHODS OF SAFETY ENDPOINT ANALYSIS

Tabulations will show results for the SAS population.

14.1 Adverse events

14.1.1 Definitions

For specific regulations of documentation of adverse events (AEs), please refer to the study protocol.

Documentation: Adverse events are recorded under the eCRF section adverse events. Clinical events of interest (hemodynamic changes) are recorded in this section as well. For a definition of clinical events of interest refer to sec. Definitions. AEs being an clinical event of interest can be depicted by using eCRF field ‘Is this a clinical event of interest?’. Furtheron signs and symptoms associated with the clinical event of interest are documented and coded. Blood pressure and pulse rate belonging to the sign is recorded.
AEs referring to local tolerability can be depicted using the eCRF field ‘Injection site reaction?’.

Coding: All AEs reported in this study will be coded using MedDRA, current version 20.0 or higher.

Causal relationship: Causal relationship between the occurrence of an AE and the administration of the study drug is assessed by the investigator according to classification scheme 0=not related, 1=unlikely related, 2=possibly related and 3=probably related. Probable and possible relationship are subsumed under the category related. All AEs must have a causal relationship assigned. In case of a missing relationship, a query will be raised in order to obtain causality assessment. In case no clarification of relationship via query is possible the missing relationship will be set to related for the analysis.

Severity/ Intensity: Severity/ intensity grading will differ between 1=mild, 2=moderate and 3=severe. For AEs having a missing severity, the severity will not be imputed and kept as missing.

Tabulation: All AE tabulations will be presented by treatment group.

Listings: An additional flagging will show adverse events accounted to the screening and to the interventional study phase. Duration of adverse events: the duration of the adverse events will be presented using start and end date of the adverse event.

Adverse events accounted to screening and to the interventional phase: For the assignment of AEs to the screening or the interventional phase, the following algorithm will be applied:

- If the onset date of the AE is at the same day or after the start of the IMP drug administration date, then the AE is classified to the treatment period and is therefore treatment-emergent. For the adverse events accounting to the screening phase the start date of the adverse event may not be later than the start date of the interventional phase (= date of first administration of the IMP).
- If any date part is missing, the procedures for imputing missing date parts should be applied first.

14.1.2 Summary of adverse events

An overview AE summary table will be prepared showing the number and percentage of subjects with at least one event and the total number of events for the following selections:

1. Adverse events during screening
2. treatment-emergent AEs (TEAEs)
3. TEAEs, which are clinical events of interest

4. TEAEs, which are injection site reactions
5. study drug-related TEAEs (Adverse Drug Reactions (ADRs))
6. serious TEAEs (SAEs)
7. study drug-related serious TEAEs (serious ADRs)
8. Deaths

The summary table is based on the number of AE verbatims.

14.1.3 Adverse event tables

In addition, frequency tables will be prepared stratified by MedDRA terms (SOC, PT) showing the following:

1. All TEAEs
2. All clinical events of interest
3. All injection site reactions
4. Study-drug related TEAEs (ADRs)
5. TEAEs by causal relationship to study drug
6. TEAEs by intensity grading
7. Serious TEAEs (SAEs)

The analysis of AEs will include summary tables displaying counts and percentages of subjects experiencing adverse events by system organ class and preferred term. If a subject has more than one AE which codes to the same preferred term, the subject will be counted only once for that preferred term. The total number of events documented per system order class (SOC) and preferred team (PT) will also be displayed.

14.1.4 Vital signs related to clinical events of interest

A descriptive statistics tabulation by treatment group will show systolic and diastolic pressure (mmHg) and pulse rate (bpm) of MedDRA coded clinical events of interest for each SOC and PT. A footnote will indicate that results are based on MedDRA coded number of clinical events and not on number of patients.

14.1.5 Local tolerability

Number/ percentage of patients experiencing any injection site reactions at 0.5 hour and 2 hours post-dose will be tabulated by treatment group for each visit.

14.2 Routine laboratory

14.2.1 General

- High (H)/ Low (L) flags will be presented in laboratory listings, where appropriate. If normal ranges are not available, the flagging cannot be performed.
- All data will be listed in the clinical study report as raw data. For the summaries the most recent value will be used in case several measurements have been performed at one visit.

Tabulations will be prepared for each laboratory parameter by treatment group:

1. Laboratory results with continuous variables will be presented with descriptive statistics for each scheduled time point. They will be marked whether they are below (L), within or above (H) the respective reference range. The numbers in each category (above/below/within reference range) will be counted and percentages presented for each laboratory test result, visit and time point.
2. If laboratory values are categorical, the results (e.g. positive/ negative) will be presented with counts and percentages for each visit and time point available.
3. Presentation of 'change from baseline' values: Change from baseline will be evaluated for all laboratory parameters. The change will be calculated by building the difference between the pre-dose value and each post-dose measurement at each visit. Change from baseline values will be presented with descriptive statistics in case of continuous parameters. In case of categorical parameters shift tables will be presented.

14.2.2 Hematology

Tabulation will follow presentation as suggested in section 14.2.1, items # 1 to #3. No figures will be prepared.

14.2.3 Clinical chemistry

Tabulation will follow presentation as suggested in section 14.2.1, items # 1 to #3. No figures will be prepared.

14.2.4 Coagulation

Coagulation parameters at screening will be tabulated with descriptive statistics by treatment group.

14.2.5 Urinalysis

Tabulation will follow presentation as suggested in section 14.2.1, items # 1 to #3. No figures will be prepared.

14.2.6 Child bearing potential and pregnancy test

Data concerning child bearing potential and results of pregnancy test will be tabulated with counts/ percentages for each visit by treatment group.

14.2.7 Drug screening (urine drug screen)

Data on drug screening will be listed.

14.2.8 Alcohol breath test

Data on alcohol breath test will be listed.

14.3 Physical examination and vital signs

14.3.1 Body measurements (weight, height, BMI) and vital signs (blood pressure, pulse rate, body temperature)

Details of vital signs (systolic and diastolic pressure (mmHg), pulse rate (bps), body temperature (C° Celsius)) will be tabulated by treatment group, visit and time point. Change from baseline for vital sign parameters will be calculated as the difference between the pre-dose value and each post-dose measurement per visit.

Body measurements, which are evaluated at screening only, i.e. weight (kg), height (cm) and BMI (kg/ m²), will be tabulated by treatment group.

Temperature, height and weight will be presented in C° Celsius, cm and kg using the following formulas:

Parameter	Re-calculation formula
Temperature	Temperature [Celsius °C] = (Temperature [Fahrenheit °F] – 32) * $^5/_9$
Height	Height (cm) = Height (inches) * 2.54
Weight	Weight (kg) = Weight (lbs.) * 0.4534

14.3.2 Physical examination

Details of physical examination results at screening will be tabulated per body system with counts/ percentages by treatment group at screening.

Changes compared to previous physical examination will be tabulated by treatment group for each visit.

14.4 12-lead ECG

Number of patients with normal/abnormal clinically significant/abnormal not clinically significant investigator assessments of 12-lead ECG will be tabulated with counts/ percentages by treatment group, visit and time point.

Descriptive measures by visit for PR interval time (msec), QRS interval time (msec) and QT interval time (msec) will be presented by treatment group for each visit and time point.

For visits having pre-dose and post-dose measurements the change from baseline will be derived using the pre-dose value as baseline value for calculation of the difference to each post-dose measurement. For visits having no post-dose measurements the pre-dose value at visit V2 will be used as baseline. Tabulation will present descriptive statistics for change from baseline parameters by treatment group for each visit.

14.5 Previous and concomitant medication

Previous and concomitant medication (ticked as type=concomitant medication in the eCRF) will be coded according to WHO-Drug Dictionary DDE 2017-01 or higher.

All prior and concomitant medications will be listed as documented in the CRF. In this listing the WHO-Drug coding including the drug name as documented in the CRF, the drug name used for the coding, the Preferred Term, the ATC-Code and the ATC-Term will be included as well. Coding will be done using ATC level 4, which will be presented in listings. Summary tables of the WHO-Drug coding will be prepared by ATC Class (ATC Level 2 shown) and Preferred Term presenting number/ percentages of medication applied. All other details concerning medication will be listed and not tabulated.

The distinction between previous and concomitant medication will be done as follows (in case of missing date parts use sec. 9).

- Prior medication is all medication which stopped before first IMP administration within the trial context independent from start date.
- Concomitant medication is all medication that started prior first IMP administration and are still ongoing/ stopped at date of first study drug intake, or medication that started at/ after date of first drug intake.

15. PHARMACOKINETIC (PK) AND PHARAMCODYNAMIC (PD) PROPERTIES

Pharmacokinetic and pharmacodynamic endpoints

Pharmacokinetic and pharmacodynamic characteristics are assessed by using the following endpoints:

1. Pharmacokinetics: Plasma dasiglucagon and GlucaGen® (glucagon) concentrations from 0-90 min after dosing will be evaluated based on the following endpoints: $AUC_{0\text{-}30min}$, $AUC_{0\text{-}90\ min}$, C_{max}, $t_{max.}$ Samples will be taken at visit 2 and visit 4 after first and third administration of trial medication. Samples will be collected pre-dose, and at 5, 10, 30, 60, and 90 min post-dosing.
2. Pharmacodynamics on plasma glucose concentrations after administration of first and third doses of trial medication. Samples will be collected pre-dose, and at 5, 10, 30, 60, and 90 min post-dosing:
   - Plasma glucose profiles over the period from 0-90 min after dosing will be evaluated based on the following endpoints: $AUE_{0\text{-}30min}$, $AUE_{0\text{-}90\ min}$, CE_{max}, t_{max}
   - Achieving a plasma glucose increase of ≥20 mg/dL within 30 minutes after treatment

16. METHODS OF PHARMACOKINETIC (PK) AND PHARAMCODYNAMIC (PD) ENDPOINT ANALYSIS

Pharmacokinetic and pharmacodynamic analyses will use the PKS population.

16.1 PK and PD parameters

The pharmacokinetic metrics as listed below will be obtained from individual plasma concentration-time data by non-compartmental analysis using the computer programs WinNonLin® Version 5.4 or SAS Version 9.4.

The following PK parameters will be calculated for dasiglucagon and GlucaGen® analytes from the individual plasma concentration versus time profiles after each active treatment per visit.

Symbol	Definition	Calculation
C_{max}	Measured maximum serum concentration after administration	Taken directly from analytical data, selected from individual concentration data
t_{max}	Sampling time until reaching C_{max}	Taken directly from analytical data, selected from individual concentration data
$AUC_{0\text{-}30min}$	Area under the concentration-time curve from zero up to the concentration at 30min	Linear trapezoidal rule for the ascending part of the concentration-time curve, logarithmic trapezoidal rule for the descending part.
$AUC_{0\text{-}90min}$	Area under the concentration-time curve from zero up to the concentration at 90min	Linear trapezoidal rule for the ascending part of the concentration-time curve, logarithmic trapezoidal rule for the descending part.

Table 2: Pharmacokinetic metrics

The following PD measures for glucose will be calculated from the plasma results for each treatment group and visit:

Symbol	Definition	Calculation
CE_{max}	Change from baseline plasma glucose to maximum plasma glucose measured post-dose	Taken directly from analytical data, selected from individual concentration data
t_{max}	Time to maximum change from baseline CE_{max}	Taken directly from analytical data, selected from individual concentration data
$AUE_{0\text{-}30min}$	Area under the baseline-adjusted effect curve from zero up to the concentration measured at 30min	Linear trapezoidal rule for the ascending part of the effect-time curve, logarithmic trapezoidal rule for the descending part.
$AUE_{0\text{-}90min}$	Area under the baseline-adjusted effect curve from zero up to the concentration measured at 90min	Linear trapezoidal rule for the ascending part of the effect-time curve, logarithmic trapezoidal rule for the descending part.

Symbol	Definition	Calculation
$Inc20_{0\text{-}30min}$	Increase of ≥ 20 mg/dL within 30 minutes after treatment	Binary variable derived from raw glucose concentration measured at 30min after dosing. In case glucose has reached at least 20 mg/dL the parameter is set to 'yes', otherwise to 'no'

Table 3: Pharmacodynamic metrics

16.2 Data handling

Serial blood samples for pharmacokinetic and pharmacodynamic assessments will be drawn at the following intervals: pre-dose and 5min±1min, 10min±1min, 30min±1min, 60min±1min and 90min±1min after start of dosing.

Summary tables for raw plasma concentrations, evaluation of concentration versus time data:

i.) For all pre-dose samples, the sampling time will be set to zero.
ii.) For post-dose samples, the planned sampling time will be used in summary tables and the actual sampling times will be used for all figures of individual concentrations
iii.) All pre-dose concentration values < LLOQ[1] will be set to zero.
iv.) Post-dose concentration values < LLOQ after tmax will be set to zero if there are no further concentrations > LLOQ at later time points.
v.) Post-dose concentration values < LLOQ after tmax will be set to the lower limit of quantitation if there are further concentrations > LLOQ at later time points.
vi.) Missing post-dose values will not be replaced.

Determination of PK/PD metrics:

i.) For all pre-dose samples, the sampling time will be set to zero.
ii.) For post-dose samples, the actual sampling time will be used.
iii.) All pre-dose concentration values will be set to zero.
iv.) Post-dose concentration values < LLOQ before tmax will be set to zero if there are no further concentrations > LLOQ at later time points.

[1] LLOQ: Lower Limit of Quantification

v.) *Post-dose concentration values < LLOQ before tmax will be set to the lower limit of quantitation if there are further concentrations > LLOQ at later time points.*
vi.) *Post-dose concentration values < LLOQ after tmax will be ignored if there are no further concentrations > LLOQ at later time points.*
vii.) *Post-dose concentration values < LLOQ after tmax will be set to the lower limit of quantitation if there are further concentrations > LLOQ at later time points.*
viii.) *Missing post-dose values will not be replaced.*

PK and PD metrics will be determined by SynteractHCR. Plasma concentration data will be transferred from external laboratory (York Bioanalytical Solutions (YBS), MLM laboratories) to SynteractHCR as detailed in separate data transfer specifications.

16.3 Analysis of PK parameters

Summary statistics of plasma concentration table: For each time point summary statistics (N, arithmetic mean, standard deviation (SD), minimum, median, maximum) of the analyte concentration by treatment group, visit and time point will be presented.

PK metrics: For each patient PK metrics will be tabulated (see cf. table 2). In the same tabulation for each treatment group PK metrics will be summarized using n, arithmetic mean, standard deviation (SD), minimum, median, maximum. Presentation of results will be by visit, treatment group and total.

Figures:

1. Mean concentrations versus nominal time by treatment group using the original (untransformed) scale of concentrations. The curves of each visit and each treatment group will be put into one graph, having an overlay plot in the end with two curves for each treatment group.
2. Individual analyte concentrations versus nominal time curves using the original concentration scale.

16.4 Analysis of PD parameters

The same tabulations and figures will be prepared for the glucagon plasma concentrations and PD metrics.

17. STUDY DRUG ADMINISTRATION – EXTENT OF EXPOSURE

Analyses will be performed for the SAS population.

17.1 Extent of exposure

An overview table (not visit specific) will show information of derived summary parameters concerning study drug administration by treatment group:

- Total dose administered (summing up all successful dosing days including unscheduled dosing days (trial medication has been administered=’yes’)). dasiglucagon is administered in doses of 0.6mg per dosing day, GlucaGen® in doses of 1.0mg per administration.
- Number of days with IMP administration
- Total duration of exposure [weeks] (date of last exposure – date of first exposure + 1)

17.2 Time between visits and total study duration

Time between visits (unscheduled visits will not be displayed) as well as total study duration will be derived and tabulated with descriptive statistics (duration of total study (days) = date of study completion or discontinuation – date of informed consent + 1. Visit dates will be listed.

18. PROTOCOL DEVIATIONS

Protocol deviations as documented during the data review meeting will be listed.

19. COMMENTS

Comments if given will be listed.

20. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

20.1 Changes to endpoints

N/A.

20.2 Changes to analyses

N/A.

21. APPENDICES

Appendix A: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, shading, 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 are to be used in tables and data listings.
- Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., µ, a, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes should be used sparingly and must add value to the table, figure, or data listing.

Tables

- Titles will be left aligned.
- Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.
- Means and medians will be presented to one more decimal place than the raw data. Standard deviations will be presented to two more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) should be presented to one decimal place more than the raw/derived data.
- For all inferential analyses, p-values will be rounded to four decimal places (or at the highest level of precision) with a leading zero (0.0001). P-values less than 0.0001 will be presented as "<0.0001".

Figures

- Legends will be used for all figures with more than one variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Figures will be in black and white (no color) unless colors add value to the clarity and readability of a figure. Lines should be wide enough to see the line after being copied. Legends will be used for all figures with more than one variable or item displayed. Treatment group sizes (n=xx) will be included, as appropriate.
- Scatter plots will include the regression line if applicable.
- Line graphs over time of change from baseline results will include a horizontal dashed reference line at zero if requested/ specified.
- For box plots, the horizontal line will represent the median, + represents the group mean, the length of the box represents the interquartile range (25th-75th percentiles), and the whiskers will represent the minimum and maximum.

Listings

- Titles will be left aligned.
- Formal organization of the listing may be changed during programming if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints, etc.
- If not otherwise specified, all data listings will be sorted by treatment, patient number, visit, and date/time as appropriate.
- All date values will be presented in SAS date or ISO date format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.

Appendix B: SAS programming QC requirements

Programmer/ validator review

1. **Program Review**
   - **1.1. Program name** follows standard naming conventions and is consistent with other study program names.
   - **1.2. Program header** uses standard template with all relevant information completed.
   - **1.3. Program flow** is logical (i.e., header → initialization code → macro variable definitions → format definitions → main body).
   - **1.4. Programmer comments** are included throughout program to describe purpose of individual sections or macros and provide understanding of specific code, if necessary. All comments are clear and up-to-date.
   - **1.5. Hard coding,** if any, is implemented correctly and documented in program header with: date, reason, and reference to sponsor approval. A comment is also inserted at the location of the hard coding.
   - **1.6. SAP Derivation** rules, if any, are followed. Significant deviations from mock table or SAP text are documented in the SAS Program Header.
   - **1.7. Permanent intermediate datasets** utilized as source data have either been fully validated elsewhere or are fully validated within the scope of this QC .
   - **1.8. Endpoints** are generally derived in source datasets and not within the program itself.
   - **1.9. Program runs** properly and output dataset is generated as intended.

2. **SAS Log Review**
   - **2.1. Scan of entire log** confirming that each data step and procedure completed properly.
   - **2.2. Critical messages** such as: errors, warnings, merge notes, or uninitialized variables are not found in log. Unavoidable critical messages are verified to not adversely affect the output and the reasons why they are unavoidable are documented.
   - **2.3. Other messages** such as “PUT” or “INFO” messages (e.g., overwritten variables following merge) are handled appropriately, if they are found in log.

3. **Output Review**
   - **3.1. Output file name** follows standard naming conventions and is consistent with other study output file names.
   - **3.2. Titles and footnotes** are verified against mock figure (if available), corresponding table and/or SAP list of figures. Discrepancies, including

footnotes added for clarification or to match corresponding table, are noted and verified.

3.3. **Axis/legend labels** are verified against mock figure and/or corresponding table.

3.4. **Axis ranges** capture all available data and, if required, are consistent across other figures. Tick marks are spaced appropriately.

3.5. **Pages breaks** are as intended throughout the document.

3.6. **Inappropriate data**: checked for outliers, invalid numbers, missing results, etc.

4. Verification of Results

Verification of results may be performed using one of the following methods. The choice of QC method must be approved by the Biostatistics Project Lead.

4.1. Manual comparison to the corresponding table, where the table is validated and all data points on the figure are compared to the corresponding value on the table.

4.2. Independent confirmatory program is written to match output results.

4.3. Manual calculations (if feasible based on small Ns or frequency counts).

4.4. Manual comparison and program review, where the related table, if produced, is validated and a subset of data points are compared to the table. Program code and logs are reviewed to confirm the intended data is used appropriately throughout the program.

4.5. Study specific alternative method (if applicable) that is agreed upon by the sponsor and defined prospectively in a study specific document (e.g., Validation Plan, SAP or a modified QC requirement template TMP-SOP-0205-003).

5. Documentation

5.1 The Programmer and Validator must document completion of QC (e.g., date of QC and method used) in BIO-0205-TMP-002 Program Status Document.

5.2 Validator findings and/or comments may be tracked in the Program Status Document along with a description of how the finding was resolved and resolution date.

5.3 The following must be retained electronically within the study folder by the Programmer as supporting documentation for SDTM and TDM datasets:

- Figure output generated at time of QC completion.
- If comparison to corresponding validated table is performed, the corresponding table output that verifies results (Section 4.1).
- If independent confirmatory program is created, a portion of the resulting output that verifies results (Section 4.2).

5.4 If manual calculations are performed, insert a comment into the output file to indicate verification of results (Section 4.3).

Senior Level Review

1. **Output Package**
   - **1.1. All analysis tables, listings and figures**, as outlined in the SAP are contained in the package. If any are missing, the reason is documented appropriately.
   - **1.2. Dates and times of electronic output files** are consistent with each other and with the corresponding dates of the source data sets.
   - 1.3. Output files are sorted in a user-friendly format such as by table, listing, and figure number. Table of Contents document is included to decode file names, or TLF number is included in the filename itself.

2. **Database and Documentation**
   - **2.1. File dates of datasets** within the clinical database, SDTM datasets, and analysis datasets are consistent. All clinical database datasets were updated together at the appropriate time, SDTM datasets (if any) were updated following the update of the clinical database, and analysis datasets were updated following the update of the clinical source datasets and SDTM datasets (if any).
   - **2.2. QC of all programs** has been completed by both the Programmer and Validator, as confirmed by **BIO-0205-TMP-002 Program Status Document**.
   - **2.3. All datasets, SAS programs, and SAS program logs** have been saved and are ready for archival.
   - **2.4. The randomization assignments** have been verified to be accurate in all datasets at the time of the final batch run of programs**.**

3. **Output Review**
   - **3.1. Titles are appropriate** and match the corresponding mocks and Table of Contents (if available). Title format and numbering is consistent across all TLFs.
   - **3.2. Footnotes are appropriate** and match the corresponding mocks and Table of Contents (if available). Reference numbers are consistent in format and correspond to the body of the output. Version of output is represented accordingly (e.g., DRAFT designation is removed, if final).
   - **3.3. Formatting is consistent** across all analysis tables, listings, and figures (i.e., case/punctuation in column and row headers, underlining of column headers, page breaks, etc.).

3.4. **Invalid data** such as blatant data point errors, outliers, missing data are scanned for in the outputs.

3.5. **Population denominators** are consistent across summary tables and figures.

3.6. **Potential discrepancies**, if any, found during review have been corrected and/or handled appropriately.

4. Statistical Review

4.1. **The primary efficacy analysis** and any key secondary efficacy or safety analyses are carefully reviewed for consistency and plausibility. Any potential issues are investigated and discussed with the Programmer and/or Biostatistician.

Appendix C: List of Tables, Figures, and Listings

The following TLF numbering is completed according to ICH guidelines. The ICH heading number and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP. Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.

List of tables and figures for analysis

ICH Heading	Table/ Figure Number	Table Description	Analysis Set	Mock reference
14.1		**DEMOGRAPHIC DATA**		
	14.1.1	Patient number by country	ALL	#DESC
	14.1.2	Patient number by site and country	ALL	#DESC
	14.1.3	Patient disposition	ALL	#DESC
	14.1.4	Trial termination form	SAS	#DESC
	14.1.5	Demographic and baseline characteristics		
	14.1.5.1	Demographics	ALL	#DESC
	14.1.5.2	Medical history		
	14.1.5.2.1	Indication specific medical history (diabetes history)	ALL, SAS	#DESC
	14.1.5.2.2	General medical history/ surgical history including concomitant diseases	ALL, SAS	#AE
	14.1.5.3	History of alcohol or drug abuse	ALL	#DESC
14.2		**IMMUNOGENICITY ANALYSES**		
	14.2.1	Primary immunogenicity endpoint: Overall ADA incidence		

	14.2.1.1	Overall ADA incidence: Incidence and incidence difference - unstratified	FAS, PPS	#ENDPOINT
	14.2.1.2	Overall ADA incidence: Incidence and incidence difference – by sex	FAS, PPS	#ENDPOINT
	14.2.1.3	Overall ADA incidence: Incidence and incidence difference – by age class	FAS, PPS	#ENDPOINT
	14.2.1.4	Overall ADA incidence: Incidence and incidence difference – by race	FAS, PPS	#ENDPOINT
	14.2.2	Key secondary endpoint: Treatment–induced ADA incidence		
	14.2.2.1	Treatment–induced ADA incidence : Incidence and incidence difference - unstratified	FAS, PPS	#ENDPOINT
	14.2.2.2	Treatment–induced ADA incidence : Incidence and incidence difference – by sex	FAS, PPS	#ENDPOINT
	14.2.2.3	Treatment–induced ADA incidence : Incidence and incidence difference – by age class	FAS, PPS	#ENDPOINT
	14.2.2.4	Treatment–induced ADA incidence : Incidence and incidence difference – by race	FAS, PPS	#ENDPOINT
	14.2.3	Key secondary endpoint: Treatment–boosted ADA incidence		
	14.2.3.1	Treatment–boosted ADA incidence : Incidence and incidence difference - unstratified	FAS, PPS	#ENDPOINT
	14.2.3.2	Treatment–boosted ADA incidence : Incidence and incidence difference – by sex	FAS, PPS	#ENDPOINT

	14.2.3.3	Treatment–boosted ADA incidence : Incidence and incidence difference – by age class	FAS, PPS	#ENDPOINT
	14.2.3.4	Treatment–boosted ADA incidence : Incidence and incidence difference – by race	FAS, PPS	#ENDPOINT
	14.2.4	Analyses of further secondary immunogenicity endpoints		
	14.2.4.1	Incidence and titer of neutralizing activity of ADA-positive patients		
	14.2.4.1.1	Incidence of neutralizing activity of ADA-positive patients		#LONG1, #LONG2
	14.2.4.1.2	Pre-existing ADA-positive patients: Titer and boosting		#LONG1, #LONG2
	14.2.4.1.3	Treatment-induced ADA-positive patients: Titer		#LONG1, #LONG2
	14.2.4.2	Incidence of cross-reactivity of ADA positive patients towards endogenous glucagon		#LONG1, #LONG2
	14.2.4.3	Kinetics of ADA: The timing and duration of detected ADA response		
	14.2.4.3.1	Kinetics of patients being baseline ADA-negative		
	14.2.4.3.1.1	Figures: Individual display of titers		
	14.2.4.3.2	Kinetics of patients being baseline ADA-positive		
	14.2.4.3.2.1	Figures: Individual display of titers		
14.3		**SAFETY ANALYSES**		
	14.3.1	Adverse events		

	14.3.1.1	All adverse events - overview	SAS	#AESUM
	14.3.1.2	Adverse events - details		
	14.3.1.2.1	All TEAEs	SAS	#AE
	14.3.1.2.2	All clinical events of interest	SAS	#AE
	14.3.1.2.3	All injections site reactions	SAS	#AE
	14.3.1.2.4	Study-drug-related TEAEs (ADRs)	SAS	#AE
	14.3.1.2.5	TEAEs by causal relationship	SAS	#AE
	14.3.1.2.6	TEAEs by intensity grading	SAS	#AE
	14.3.1.2.7	Serious TEAEs	SAS	#AE
	14.3.1.3	Vital signs related to clinical events of interest	SAS	#DESC
	14.3.1.4	Local tolerability	SAS	#LONG1, #LONG2
	14.3.2	Routine laboratory		
	14.3.2.1	Hematology		
	14.3.2.1.1	Descriptive statistics: Hematology	SAS	#LAB
	14.3.2.1.2	Change from baseline: Hematology	SAS	#LONG3 / #SHIFT
	14.3.2.2	Clinical chemistry		
	14.3.2.2.1	Descriptive statistics: Clinical chemistry	SAS	#LAB
	14.3.2.2.2	Change from baseline: Clinical chemistry	SAS	#LONG3 / #SHIFT
	14.3.2.3	Coagulation		#LAB
	14.3.2.4	Urinalysis		
	14.3.2.4.1	Descriptive statistics: Urinalysis	SAS	#LAB
	14.3.2.4.2	Change from baseline: Urinalysis	SAS	#LONG3 / #SHIFT
	14.3.2.5	Child bearing potential and results of pregnancy test	SAS	#LONG1, #LONG2
	14.3.3	Physical examination and vital signs		
	14.3.3.1	Vital signs	SAS	#LONG3

	14.3.3.2	Body measurements	SAS	#DESC
	14.3.3.3	Physical examination		
	14.3.3.3.1	Physical examination: Body systems at screening	SAS	#DESC
	14.3.3.3.2	Physical examination: Changes to previous visits	SAS	#LONG1, #LONG2
	14.3.4	12-lead ECG		
	14.3.4.1	12-lead ECG: Abnormal findings	SAS	#LONG1, #LONG2
	14.3.4.2	12-lead ECG: Descriptive statistics for PR interval, QRS interval and QT interval time	SAS	#LONG1, #LONG2
	14.3.4.3	12-lead ECG: Change from baseline for PR interval, QRS interval and QT interval time	SAS	
	14.3.5	Previous and concomitant medication		
	14.3.5.1	Previous medication	SAS	#CONMED
	14.3.5.2	Concomitant medication	SAS	#CONMED
14.4		**PHARMACOKINETIC (PK) AND PHARAMCODYNAMIC (PD) PROPERTIES**		#LONG3
	14.4.1	Pharmacokinetics		
	14.4.1.1	Summary statistics of plasma dasiglucagon and GlucaGen concentration table	PKS	#PKCONC
	14.4.1.2	PK metrics	PKS	#PKMETRIC
	14.4.1.3	Figures: Mean analyte concentrations versus time – original scale	PKS	#PK_FDAY
	14.4.1.4	Figures: Individual analyte concentrations versus time curves- original scale	PKS	
	14.4.2	Pharmacodynamics		

	14.4.2.1	Summary statistics of plasma glucose concentration table	PKS	#PKCONC
	14.4.2.2	PD metrics	PKS	#PKMETRIC
	14.4.2.3	Figures: Mean concentrations versus time – original scale	PKS	#PK_FDAY
	14.4.2.4	Figures: Individual concentrations versus time curves- original scale	PKS	
14.5		**STUDY DRUG ADMINISTRATION**		
	14.5.1	Extent of exposure	SAS	#DESC
	14.5.2	Time between visits and total study duration	SAS	#DESC

List of data listings for analysis

ICH Heading	Listing Number	Listing Description	Comment
16.2		**PATIENT DATA LISTINGS**	
16.2.1		**Discontinued patients**	
	16.2.1.1	Trial termination form	
	16.2.1.2	Screening failures	
16.2.2		**Protocol deviations**	
	16.2.2.1	Protocol deviations	
	16.2.2.2	(Re-check of) Inclusion/ exclusion criteria	
	16.2.2.3	Check of dosing day exclusion criteria	
	16.2.2.4	Randomization	
16.2.3		**Patients excluded from the efficacy analysis**	
	16.2.3.1	Subject assignment to analysis populations	
16.2.4		**Demographic data and baseline characteristics**	
	16.2.4.1	Demographics	
	16.2.4.2	Medical history	
	16.2.4.2.1	General medical/ surgical history (incl. concomitant diseases)	
	16.2.4.2.2	Diabetes history	
16.2.5		**Compliance and/or drug concentration data**	
	16.2.5.1	Informed consent	
	16.2.5.2	Visit dates, number of visits at site, and study duration	
	16.2.5.3	Study drug administration	
	16.2.5.3.1	Assignment of trial medication	
	16.2.5.3.2	Total dose applied, number of days dosed, total duration of exposure	derived data
16.2.6		**Primary endpoint, (key) secondary endpoints**	
	16.2.6.1	Immunogenicity measurements	
	16.2.6.2	Antibody serum sample for immunogenicity measurements	
	16.2.6.3	Neutralizing antibody measurements (NAb titer)	
	16.2.6.4	Overall ADA incidence, treatment-induced ADA incidence, treatment boosted ADA-incidence	derived data

ICH Heading	Listing Number	Listing Description	Comment
	16.2.6.5	Kinetics: Timing and duration of detected ADA response	derived data
16.2.7		**Adverse events and safety endpoints**	
	16.2.7.1	Adverse events	
	16.2.7.1.1	Adverse events – CRF entries	
	16.2.7.1.2	Adverse events – MedDRA coding	
	16.2.7.1.3	Study-drug related adverse events (ADRs)	
	16.2.7.1.4	Serious adverse events	
	16.2.7.1.5	Deaths	
	16.2.7.1.6	Vital signs related to clinical events of interest	
	16.2.7.1.7	Injection site reactions	
	16.2.7.2	Local tolerability	
	16.2.7.3	Vital signs including change from baseline	incl. derived data CFB
	16.2.7.4	Body measurements	
	16.2.7.5	Physical examination and changes	
	16.2.7.6	12-lead ECG including change from baseline	
	16.2.7.7	Previous and concomitant medication	
16.2.8		**Laboratory**	
	16.2.8.1	Hematology including change from baseline	incl. derived data CFB
	16.2.8.2	Biochemistry including change from baseline	incl. derived data CFB
	16.2.8.3	Coagulation	
	16.2.8.4	Urinalysis including change from baseline	incl. derived data CFB
	16.2.8.5	Child bearing potential and pregnancy test	
	16.2.8.6	History of alcohol or drug abuse, alcohol breath test and urine drug screen	
16.2.9		**Pharmacokinetics and pharmacodynamics**	
	16.2.9.1	Plasma dasiglucagon and GlucaGen measurements	
	16.2.9.2	Individual PK metrics	derived data
	16.2.9.3	Plasma glucose measurements	
	16.2.9.4	Individual PD metrics	derived data
16.2.10		**Comments**	

Appendix D: Table Layouts

Sponsor **Page 1 of x**
Protocol Number
Table
Title
Analysis Set

Descriptive Statistics/ Counts (%)

	dasiglucagon (N=xx)	GlucaGen (N=xx)	Total (N=xx)
Categorical Parameter 1			
Category 1	x (xxx.x)	x (xxx.x)	x (xxx.x)
Category 2	x (xxx.x)	x (xxx.x)	x (xxx.x)
Categorical Parameter 2			
Category 1	x (xxx.x)	x (xxx.x)	x (xxx.x)
Category 2	x (xxx.x)	x (xxx.x)	x (xxx.x)
Category 3	x (xxx.x)	x (xxx.x)	x (xxx.x)
Category 4	x (xxx.x)	x (xxx.x)	x (xxx.x)
Metric Parameter [unit]			
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx
Max	xx	xx	xx
n	xx	xx	xx

Source: xxx
path\t_program.sas date time

Programmer notes:
Qualitative/ Quantitative variables (Type : DESC)
Rows: Categories/classes of a specific variable
Cells: Qualitative variables: Absolute and relative count within each treatment and class,
Cells: Quantitative variables: Mean, Median, SD (standard deviation), Min, Max, n (valid cases)

Descriptive Statistics

		Screening	Treatment period/ Visit	Follow-up	Unscheduled ADA visits
dasiglucagon	Mean	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
	n	xx	xx	xx	xx
GlucaGen	Mean	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
	n	xx	xx	xx	xx
Total	Mean	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx	xx	xx	xx
	Max	xx	xx	xx	xx
	n	xx	xx	xx	xx

Source: xxx
path\t_program.sas date time

Programmer notes:
Longitudinal tabulation, horizontal display (Type : LONG1)
Columns: Time/Visit
Cells: Quantitative variables: Mean, Median, SD (standard deviation), Min, Max, n (valid cases)

	Descriptive Statistics/ Counts (%)		
	dasiglucagon (N=xx)	GlucaGen (N=xx)	Total (N=xx)
Screening			
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx
Max	xx	xx	xx
N	xx	xx	xx
Treatment period/ Visit			
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx
Max	xx	xx	xx
N	xx	xx	xx
...			

Source: xxx
path\t_program.sas date time

Programmer note:
Longitudinal tabulation, vertical display (Type : LONG2)
Rows: Time/Visit: Screening, further visits, or time T1, T2, etc., Columns: Columns: Treatment group or other specification, Cells: Quantitative variables: Mean, Median, SD (standard deviation), Min, Max, n (valid cases)

Descriptive Statistics/ Counts (%)

	dasiglucagon (N=xx)	GlucaGen (N=xx)	Total (N=xx)
Screening / Pre-dose			
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx
Max	xx	xx	xx
n	xx	xx	xx
Visit x / time point X			
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx
Max	xx	xx	xx
n	xx	xx	xx
Change from screening / pre-dose			
Mean	xx.x	xx.x	xx.x
Median	xx.x	xx.x	xx.x
SD	xx.xx	xx.xx	xx.xx
Min	xx	xx	xx
Max	xx	xx	xx
n	xx	xx	xx
p-value*	x.xxxx	x.xxxx	x.xxxx

Footnote: *.... (only if requested)
Source: xxx
path\t_program.sas date time
Programmer note: Longitudinal tabulation, vertical display (Type: LONG3)

Sponsor
Protocol Number
Table
Title
Analysis Set

Laboratory panel name = xxxx
Laboratory test name = xxxx

	Screening/ Pre-dose					
	Negative		Positive		Total	
Visit X/ time point X	N	%	N	%	N	%
dasiglucagon						
Negative	xxx	x.xx	xxx	x.xx	xxx	x.xx
Positive	Xxx	x.xx	Xxx	x.xx	xxx	x.xx
GlucaGen						
Negative	Xxx	x.xx	Xxx	x.xx	xxx	x.xx
Positive	xxx	x.xx	xxx	x.xx	xxx	x.xx
Total	xxx	x.xx	xxx	x.xx	xxx	x.xx

Source: xxx
path\t_program.sas date time

Programmer notes: Laboratory shift table (Type: SHIFT)

		Count (%)		
		dasiglucagon (N=xx)	GlucaGen (N=xx)	Difference in incidences (95% CI of dasiglucagon-GlucaGen)
Overall ADA incidence	Yes	xx (xx.x)	xx (xx.x)	
	No	xx (xx.x)	xx (xx.x)	xxx.xx (xx.xx, xx.xx)
	95% CI[1]	(xx.x, xx.x)	(xx.x, xx.x)	

Footnote:
[1]: CI for proportion of responder=Yes
Source: xxx
path\t_program.sas date time

Programmer note: Display of incidences and confidence intervals, (Type: ENDPOINT)

Sponsor
Protocol Number
Table
Title
Analysis Set

Number of Subjects (%)
Event Count

	dasiglucagon (N=xx)	GlucaGen (N=xx)	Total (N=xx)
Adverse events during screening	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Treatment-emergent AEs (TEAEs)	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
Study drug-related TEAEs (Adverse Drug Reactions (ADRs)) [1]	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
...	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

[1] Treatment-related: text to be inserted as defined in AE section of the SAP
Table is based on number of verbatims.
Source: xxx
path\t_program.sas date time

Programmer notes:
Overview of Adverse Events (Type : AESUM)

SOC Preferred Term	Number of Subjects (%) Event Count dasiglucagon (N=xx)	GlucaGen (N=xx)	Total (N=xx)
Any AE	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
SOC Class 1			
Any PT	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
SOC Class 2			
Any PT	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
SOC Class xx			
Any PT	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term 3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT Term xx	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
...			

A subject with more than one event in a specific category was only counted once
Percentages based on total no. of subjects in each treatment group
Table is sorted by descending subject count on the SOC and within each SOC on PT level
Source: xxx
path\t_program.sas date time
Programmer notes: Adverse Event Summary Table (Type : AE)

Number of Subjects (%)
Event Count

ATC class **Preferred Term**	dasiglucagon (N=xx)	GlucaGen (N=xx)	Total (N=xx)
Number of patients with at least one concomitant medication	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
etc.	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
ATC2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
etc.	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
...			
ATCX	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT1	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT2	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
PT3	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx
etc.	xx (xx.x) xx	xx (xx.x) xx	xx (xx.x) xx

Source: xxx
path\t_program.sas date time
Programmer note: Concomitant medication tabulation (Type CONMED)

Laboratory panel name = xxxx
Laboratory test name = xxxx

								Below reference range		Within reference range		Above reference range		CS		NCS	
	N	Mean	Median	SD	SEM	Min	Max	N	%	N	%	N	%	N	%	N	%
dasiglucagon																	
Screening	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
GlucaGen																	
Screening	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Total																	
Screening	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx
Visit X	xx	x.xx	x.xx	x.xx	x.xx	x.xx	x.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx	xx	xx.xx

Source: xxx
path\t_program.sas date time

Programmer notes: Laboratory Summary Table (Type: LAB)

Sponsor
Protocol Number
Table
Title
Analysis Set

		Descriptive statistics Nominal time after medication administration							
Treatment		**x**	**x**	**x**	x	**x**	**x**	**x**	....
dasiglucagon	n	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx
GlucaGen	N	xx	xx	xx	xx	xx	xx	xx	xx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
	Min	xx	xx	xx	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx	xx	xx	xx

Source: xxx
path\t_program.sas date time

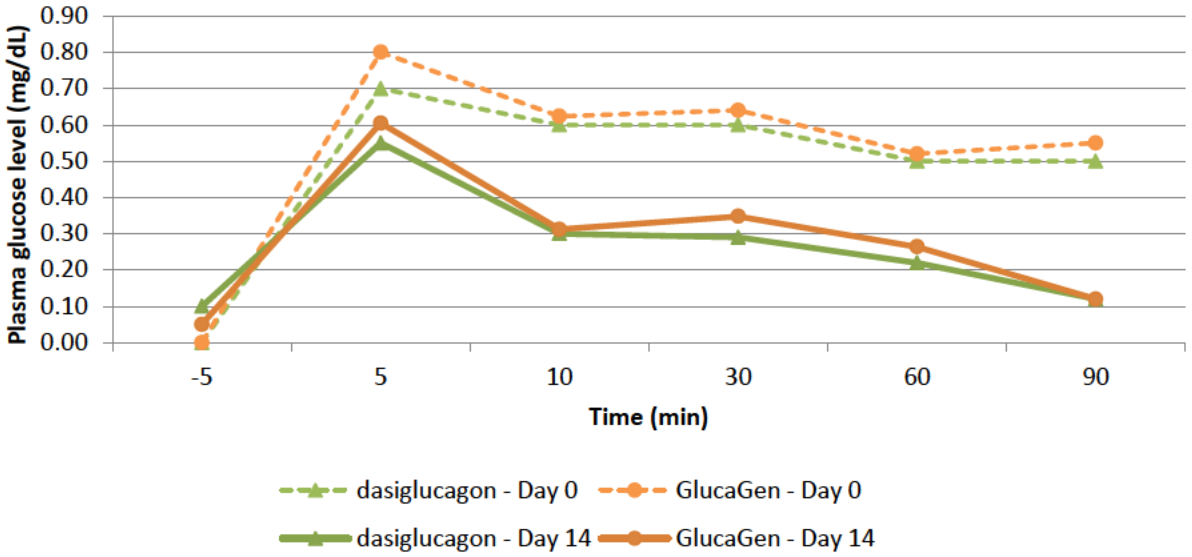
Programmer note :
PK concentration tabulation (Type PKCONC)

Treatment	Subject	C_{max} (Unit)	t_{max} (Unit)	$AUC_{0-30min}$ (Unit)	$AUC_{0-90min}$ *(Unit)*
dasiglucagon	xxx	xxx	xxx	xxx	xxx
	xxx	xxx	xxx	xxx	xxx
	…				
	n	x	x	x	x
	Mean	xxx		xxx	xxx
	SD	xxx		xxx	xxx
	Min	xxx		xxx	xxx
	Median	xxx	xxx	xxx	xxx
	Max	xxx	Xxx	xxx	xxx
GlucaGen	xxx	xxx	xxx	xxx	xxx
	xxx	xxx	xxx	xxx	xxx
	…				
	n	x	x	x	x
	Mean	xxx	xxx	xxx	xxx
	SD	xxx	xxx	xxx	xxx
	Min	xxx	xxx	xxx	xxx
	Median	xxx	xxx	xxx	xxx
	Max	xxx	xxx	xxx	xxx

Source: xxx
path\t_program.sas date time
Programmer note:
PK metrics tabulation (Type PKMETRIC)

Table will be adapted to PD metrics.

Figure
Title
Analysis Set



Source: XXX
path\t_program.sas date time
Programmer note: PK metrics figure (Type PK_FDAY)

DATA REVIEW MEETING PROTOCOL

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Version	Date	Changes
V0.1	23-Feb-2018	Initial draft
V1.0	16-Mar-2018	Updated version including PD listings (6) released on 16Mar-2018
V1.1	20-Mar-2018	Updated draft following the BDRM held on 20Mar-2018
V2.0	25-Mar-2018	Final version

1 LOCATION AND PARTICIPANTS FOR THE BLIND-REVIEW MEETING

Date/Time: [redacted]

Location: WEBEx/TC

Participants:

Sponsor
- [redacted], Clinical Project Director
- [redacted], Director, Statistics
- [redacted], Medical Project Director
- [redacted], ADA specialist, Bioanalysis
- [redacted], PK specialist, Bioanalysis

Synteract:
- [redacted], Sr. Director Biostatistics
- [redacted], Lead Data Manager
- [redacted], Medical Monitor
- [redacted], Clinical Trial Manager
- [redacted], Project Leader

2 GENERALITIES

2.1 Meeting objectives

After soft lock of the clinical database a blind review of data according to the ICH-guideline E9was conducted. The purpose of this meeting was to classify the trial population into the different analysis sets by applying the corresponding criteria and deciding whether a protocol deviation was major or minor. Subjects with major protocol deviation are excluded from the Per Protocol anaylsis set.

The SAP was finalised and signed before the data review meeting.

3 Criteria for classification of subjects to analysis subsets

3.1 Definition of analysis populations

The Study Protocol and the Statistical Analysis Plan (v0.2) detail the following analysis sets:

1. **All patients analysis set (ALL)** includes all patients that have been enrolled.
2. **Safety set (SAS) includes** all patients who were randomized and received at least one dose of trial medication.
3. **Full analysis set (FAS)** is defined as all patients included in the SAS population with at least one ADA measurement at baseline (Visit 2).
4. **Per Protocol set (PPS)** consists of all patients included in the FAS for whom no relevant protocol deviations were documented
5. **PKPD set (PKS)** is defined as all patients included in the SAS with at least one pre- and post-dose PK/PD value at one visit (Visit 2/4).

Assignment of analysis populations to analyses:

The study population including including information on subject disposition and protocol deviations will be presented based on the ALL analysis set.

Analysis of primary endpoint, key secondary endpoints and secondary endpoints referring to ADA response characterizations will be made for the FAS analysis set.

A secondary analysis of the primary endpoint will be based on the PPS.

The SAS set will be used to analysis safety parameters and study drug administration/extent of exposure.

The PKS set will be used for the analysis of pharmacokinetic and pharmacodynamics endpoints.

Adherence to the study protocol is defined based on defined protocol deviation categories. The decision whether a subject adhered to the protocol was made by classifying reported and/or derived deviations into major and minor protocol deviations.

Major protocol deviations led to exclusion from the PP set.
The decision whether a protocol deviation is major or minor was done at the Blind Data Review Meeting.

3.2 Criteria leading to an exclusion from a population independent of protocol deviations

The following criteria to include/ exclude subjects from a population independent of protocol deviations can be set up:

a) The patient was included into the trial, but did not receive any dose trial medication
→ Patient will be excluded from the Safety Set (SAS)

For this trial, a total of 132 patients were included into the trial. Out of 112 randomized patients N=111 patients received at least one dose of trial medication and will be included into the SAS.

b) The subject received at least one dose of trial medication but did not have at least one baseline ADA measurement → ***Patient will be excluded from the Full Analysis Set (FAS)***

For this trial, all dosed patients (N=111) have at least the ADA measurement at Visit 2 and will be included into the FAS.

c) The patient received at least one dose of trial medication, but did not complete the treatment period (Visit 2 – Visit 4) and/or the follow-up period (Visit 5 - Visit 7) OR at least one ADA measurements is missing (Visit 2- Visit 7) OR relevant protocol deviations were documented.

The following 11 patients will be excluded from PP, as they did not complete the trial and/or at least one ADA measurements is missing (Visit 2-Visit 7):

Center	Subject ID	Primary reason for premature termination	Specification of protocol violation or other reason for termination	Date of completion/ last contact/ last visit	DOSES OF TRIAL MEDICATION ADMINISTERED
02	02-017	protocol violation	POSITIVE URINE DRUG SCREEN	[redacted]	2
02	02-018	other	STUDY WAS DISCONTINUED ON [redacted]	[redacted]	0
03	03-001	protocol violation	POSITIVE [redacted] URINE DRUG SCREEN	[redacted]	1
03	03-003	adverse event		[redacted]	1
03	03-012	protocol violation	POSITIVE URINE DRUG SCREEN	[redacted]	1
04	04-004	other	PATIENT WAS UNABLE TO [redacted] COME IN FOR THE THIRD INJECTION	[redacted]	2
04	04-016	adverse event		[redacted]	2
05	05-009	other	DEVIATION FROM PROTOCOL WINDOW DURING TREATMENT VISIT. SUBJECT MISSED SCHEDULED V3 [redacted]	[redacted]	1
05	05-011	protocol violation	AS PER INVESTIGATOR AND PROTOCOL SUBJECT WAS PREMATURELY DISCONTINUED FROM TREATMENT, DUE TO POSITIVE URINE DRUG SCREEN [redacted].	[redacted]	2
05	05-027	adverse event		[redacted]	1

For details on completed trial visits per subject, please refer to the attached file Visit Dates_Discontinued patients_20180316

05	05-017	Completer, Visit 7 on [redacted]	Missed Visit 6, missing ADA sample at:	Visit 6	Doses administered: 3

d) PK/PD subset

All subjects included in the SAF had at least one pre-dose and one post dose sample taken (at V2 or V4) for PK/PD assessments. As the study conditions are blinded and no access to the actual PK/PD results is possible, we need to assume that all samples taken and processed by the laboratory actually do produce a result.

→ None of the subjects included in the SAF are excluded from the PK/PD subset.

3.3 Criteria based on protocol deviations

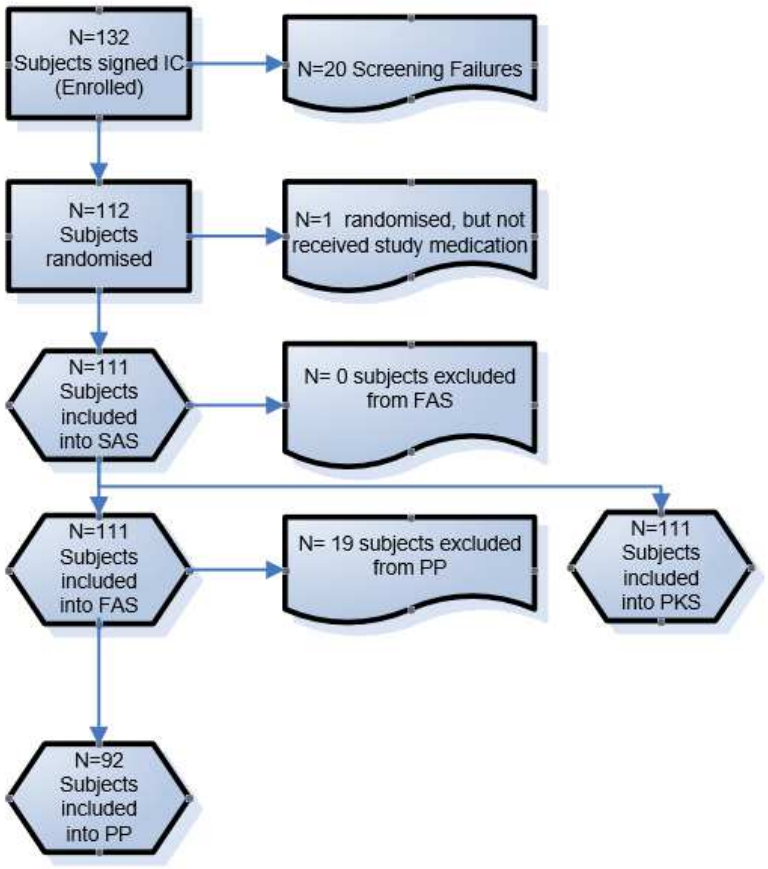
List of protocol deviations to be discussed during the Data Review Meeting:

Table 1: List of protocol deviation categories and sub-categories

ID	PD main category	PD sub category	Source of PD	Method for derivation	Rules for classification as major	Comments
1	CRA reported PDs	Deviations documented in the CRA PD tracker in Marvin	CRA PD tracker	As documented by CRA and classified by sponsor	Classification of major/minor	
2	**Inclusion / Exclusion Criteria**	**Deviations from inclusion/exclusion criteria**	**e-CRF entries, Laboratory data**	**Computerised /manual checks**		
2.1	Inclusion / Exclusion Criteria	Known deviations from Inclusion/Exclusion Criteria (documented in the e-CRF by ticking the relevant criterion).	e-CRF entries	Computerised PD check	Case-by-case	No findings
2.2	Inclusion / Exclusion Criteria	*Incl 1: Informed Consent not obtained before any trial-related assessments*	e-CRF entries	Computerised PD check		No findings
2.3	Inclusion / Exclusion Criteria	*Incl 3: Patient age <18 years or >70 years*	e-CRF entries	Computerised PD check		No findings
2.4	Inclusion / Exclusion Criteria	*Incl 4: Diagnosis of T1DM less than 1 year before date of Informed Consent*	e-CRF entries	Computerised PD check		No findings
2.5	Inclusion / Exclusion Criteria	*Incl 5: HbA1C >= 10%*	Safety Lab data	Computerised PD check		No findings
2.6	Inclusion / Exclusion Criteria	*Excl 1: Previous exposure to dasiglucagon*	e-CRF entries	Computerised PD check		No findings
2.7	Inclusion / Exclusion Criteria	*Excl 5: Positive pregnancy test*	Safety laboratory data	Computerised PD check		No findings
2.8	Inclusion / Exclusion Criteria	*Excl 10: SBP >= 160 mmHg OR DBP >=90 mmHg*	e-CRF entries	Computerised PD check		No findings
2.9	Inclusion / Exclusion Criteria	*Excl 17: Clinically significant ECG at Visit 1*	e-CRF entries	Computerised PD check	Major	
2.10	Inclusion / Exclusion Criteria	*Excl 19: Positive Alcohol and or Urine drug screen at Visit 1, or significant history of alcoholism/drug abuse answered yes.*	e-CRF entries	Computerised PD check	Minor/Major	Case-by-case review
2.11	Inclusion/ Exclusion Criteria	*Excl. 2, 3, 6, 8, 9, 11, 12, 13, 21,22: Exclusionary medical history*	e-CRF entries	Manual Review by medical monitor at Synteract	Minor/Major	Case-by-case review

3	**Concomitant Medication**	**Prohibited concomitant medication**	**e-CRF entries**	**Manual Review**		
3.1	Concomitant Medication versus Inclusion / Exclusion Criteria	*Excl 14, 15, 18, 23: Prohibited concomitant medication*	e-CRF entries	Manual Review by medical monitor at Synteract	Minor/Major	Case-by-case review
4	**Subject Visit Schedule**	**Visit Window Violations**	**e-CRF entries**	**Computerised PD check**		
4.1	Subject Visit Schedule	Screening visit within 30-3 days before Randomization (Day 0)	e-CRF entries	Computerised PD check	Minor	
4.2	Subject Visit Schedule	Visit 3 not within 6-8 days after Randomization (Day 0)	e-CRF entries	Computerised PD check	Minor/Major	Minor if within 1 week
4.3	Subject Visit Schedule	Visit 4 not within 13-15 days after Randomization (Day 0)	e-CRF entries	Computerised PD check	Minor/Major	Minor if within 1 week
4.4	Subject Visit Schedule	Visit 5 not within 33-37 days after Randomization (Day 0)	e-CRF entries	Computerised PD check	Minor/Major	Minor if within 1 week
4.5	Subject Visit Schedule	Visit 6 not within 55-65 days after Randomization (Day 0)	e-CRF entries	Computerised PD check	Minor/Major	Minor if within 2 weeks
4.6	Subject Visit Schedule	Visit 7 not within 94-114 days after Randomization (Day 0)	e-CRF entries	Computerised PD check	Minor/Major	Minor if within 4 weeks
4.7	Subject Visit Schedule	Any scheduled trial visit missed (including follow-up visits 5-7)	e-CRF entries	Computerised PD check	Major	include disposition information
4.8	Subject Visit Schedule	Visit 2-4: At least one Patient Withdrawal Criteria answered with Yes, but patient was not withdrawn from treatment	e-CRF entries	Computerised PD check	Minor/Major	Cross-check against the DS form; case-by case decision
5	**Study procedures/ assessments**	**Vital signs, Laboratory data, ECG**	**e-CRF**	**Computerised PD check**		
5.1	Study procedures/ assessments	Visit 2-4: Missed assessments/samples (safety lab/PKPD samples not taken, ECG/vital signs not taken)	e-CRF	Computerised PD check	Minor	
6.	**ADA (Immunogenicity)**	**ADA measurement**	**e-CRF**	**Computerised PD check**		
6.1	ADA (Immunogenicity)	Visit 2-7: ADA sample not taken	e-CRF	Computerised PD check	Major	
6.2	ADA (Immunogenicity)	Visit 2-4: ADA sample not taken pre-dose	e-CRF	Computerised PD check	Major	
7	**Treatment Administration**	**Visit 2-4: Less than 3 doses of trial medication administered**	**eCRF**	**Computerised PD check**	**Major**	

4 SUBJECT DISPOSITION



5 SUBJECTS EXCLUDED FROM PP ANALYSIS and/OR LIST OF SUBJECTS WITH ANY MAJOR PROTOCOL VIOLATION

Subjects randomised, but not treated:

Subject Identifier for the Study	Enrolled Population Flag	Randomized Population Flag	Safety Population Flag	Full Analysis Set Population Flag	Per-Protocol Population Flag	PK/PD Set Population Flag	Completers Population Flag
02-018	Y	Y	N	N	N	N	N
N = 1							

Subjects excluded from PP:

Subject Identifier for the Study	Enrolled Population Flag	Randomized Population Flag	Safety Population Flag	Full Analysis Set Population Flag	Per-Protocol Population Flag	PK/PD Set Population Flag	Completers Population Flag
02-017	Y	Y	Y	Y	N	Y	N
03-001	Y	Y	Y	Y	N	Y	N
03-003	Y	Y	Y	Y	N	Y	N
03-004	Y	Y	Y	Y	N	Y	Y
03-005	Y	Y	Y	Y	N	Y	Y
03-006	Y	Y	Y	Y	N	Y	Y
03-007	Y	Y	Y	Y	N	Y	Y
03-008	Y	Y	Y	Y	N	Y	Y
03-009	Y	Y	Y	Y	N	Y	Y
03-011	Y	Y	Y	Y	N	Y	Y
03-012	Y	Y	Y	Y	N	Y	N
03-013	Y	Y	Y	Y	N	Y	Y
04-004	Y	Y	Y	Y	N	Y	N
04-016	Y	Y	Y	Y	N	Y	N
05-009	Y	Y	Y	Y	N	Y	N
05-011	Y	Y	Y	Y	N	Y	N
05-017	Y	Y	Y	Y	N	Y	Y
05-027	Y	Y	Y	Y	N	Y	N
06-003	Y	Y	Y	Y	N	Y	Y
N = 19							

6 PROTOCOL DEVIATIONS FOR RANDOMIZED SUBJECTS

List of detected protocol deviations

➔ Please refer to the attached spreadsheet ZP4207-16136_Protocol Deviations by Category_20180326.xls

7 SIGNATURES

Signatures	Date
[redacted] Title: Senior Director Biostatisti[redacted]	[redacted]
[redacted] Title: Senior Clinical Data Manager SynteractHCR Deutschland GmbH	[redacted]
[redacted] Title: Clinical Project Director, Zealand Pharma A/S	[redacted]