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

PROTOCOL DATE: Original Protocol Version 1.0, 14-Dec-2017

NCT Number: NCT03941236

Document Version	Date	Comments
Version 21.0 – UK only	15-Jan-2025	
Version 20.0 – UK only	08-Nov-2024	• Protocol Version 20.0 was not implemented
Version 19.0 – all countries except Germany and UK	08-Nov-2024	
Version 18.0 – UK only	02-Sep-2024	• Defined Trial Period, Trial Completion, and Trial Finalization to add ADA follow-up period only for those ADA-positive patients for up to 2 years after End of Trial, unless they continue to receive dasiglucagon commercially or via an EAP
Version 17.0 – DE only	09-Apr-2024	• Defined Trial Period, Trial Completion, and Trial Finalization to add ADA follow-up period only for those ADA-positive patients for up to 2 years
Version 16.0 – global except DE	09-Apr-2024	• Defined Trial Period, Trial Completion, and Trial Finalization to add ADA follow-up period only for those ADA-positive patients for up to 2 years • Removed statement that no safety concerns related to ADA levels were identified in CHI
Version 15.0 – DE only	22-May-2023	FDA requested amendment: • Trial duration extended to approximately Q3 2024 (treatment period) (Section 7.1) • Endpoints added (Other Efficacy Endpoints): SMPG detected hypoglycemia episodes (Section 6.2.4) • Benefit/risk assessment further clarified (Section 7.2) • Patient participation stopping criteria introduced (Section 8.3) • Trial stopping criteria introduced (Section 8.7) • Trial duration extended to approximately Q3 2024 (treatment period) (Section 10.1)

Document Version	Date	Comments
		• SoE table updated with new footnote (g) • Footnote (j) revised to original phrasing • Footnote (n) further clarified (Section 17.1) • Appendix D Seizure Checklist added
Version 14.0 – global except DE	22-May-2023	FDA requested amendment: • Trial duration extended to approximately Q3 2024 (treatment period) (Section 7.1) • Endpoints added (Other Efficacy Endpoints): SMPG detected hypoglycemia episodes (Section 6.2.4) • Benefit/risk assessment further clarified (Section 7.2) • Patient participation stopping criteria introduced (Section 8.3) • Trial stopping criteria introduced (Section 8.7) • Trial duration extended to approximately Q3 2024 (treatment period) (Section 10.1) • SoE table updated with new footnote (g) • Footnote (j) revised to original phrasing • Footnote (n) further clarified (Section 17.1) • Appendix D Seizure Checklist added
Version 13.0 – DE only	28-Sep-2022	• Trial duration extended to Q1 2024 • Underlined text in Sections 10.2.3.1 and 11.1.3 changed to longer be underlined • Section 12.3.3 aligned with SAP with regards to censoring efficacy after any pancreatectomy (not only subtotal and total) • SoE table footnote (i) updated to reflect body text in Section 10.2.3.1
Version 12.0 – global except DE	28-Sep-2022	• Trial duration extended to Q1 2024 • Underlined text in Sections 10.2.3.1 and 11.1.3 changed to longer be underlined • Section 12.3.3. aligned with SAP with regards to censoring efficacy after any pancreatectomy (not only subtotal and total) • SoE table footnote (i) updated to reflect body text in Section 10.2.3.1.

Document Version	Date	Comments
Version 11.0 – DE only	11-Oct-2021	• Trial extended to end of 2022 • Key secondary endpoint describing rate of hypoglycemia episodes as detected by SMPG has been replaced by rate of CGM detected hypoglycemia episodes • Additional secondary efficacy endpoints added • Minor adjustments to the safety section • Clarification of reporting of vital signs • Immunogenicity section updated
Version 10.0 – global except DE	01-Oct-2021	• Trial extended to end of 2022 • Key secondary endpoint describing rate of hypoglycemia episodes as detected by SMPG has been replaced by rate of CGM detected hypoglycemia episodes • Additional secondary efficacy endpoints added • Minor adjustments to the safety section • Clarification of reporting of vital signs • Immunogenicity section updated
Version 9.0 – DE only	29-Jan-2020	• Updated to include the Dexcom CGM G6 • Section 10.2.3.2 Clinical Examinations updated
Version 8.0 – global except DE	11-Oct-2019	• Updated to include the Dexcom CGM G6
Version 7.0 – DE only	11-Jul-2019	• Device-adapted protocol to fulfill the requirements from BfArM MPG • New Section 19 added and additional device-related safety reporting added in Section 11.
Version 6.0 – global	03-Jun-2019	• Adverse events of special interest on hemodynamic changes added (FDA request) • Exclusion criterion for drugs with potential effect on QT interval (FDA request) • Timeline extended from potential End of Trial in Q4 2020 to Q4 2021
Version 5.0 – DE only	03-Jun-2019	• Minor update based on BfArM comment (blood volume)

Document Version	Date	Comments
Version 4.0 – FR, DE, IL only	25-Jul-2018	• First version submitted in DE, FR, and IL, approved in IL • Minor update to incorporate the BfArM comments provided to the 17109 Version 2.0 protocol.
Version 3.0 – UK only	24-Jul-2018	• Minor update based on MHRA comments
Version 2.0 – global	31-May-2018	• Submitted in the UK and US, approved in the US • Updated based on FDA feedback. First version submitted outside the US
Version 1.0 – global	14-Dec-2017	• Submitted in the US only

Abbreviations: ADA = antidrug antibody; BfArM = Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte); CGM = continuous glucose monitoring; CHI = congenital hyperinsulinism; DE = Germany; FDA = Food and Drug Administration; FR = France; IL = Israel; MHRA = Medicines and Healthcare products Regulatory Agency; Q = quarter; SAP = statistical analysis plan; SMPG = self-monitored plasma glucose; SoE = schedule of events; UK = United Kingdom; US = United States

PROTOCOL

PRODUCT NAME/NUMBER:	Dasiglucagon
PROTOCOL NUMBER:	ZP4207-17106
IND NUMBER:	135869
EUDRACT NUMBER:	2017-004546-15
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
PROTOCOL DATE:	Original Protocol Version 1.0, 14-Dec-2017 Amended local UK protocol final version 21.0, 15-Jan-2025
SPONSORED BY:	Zealand Pharma A/S Sydmarken 11 2860 Soeborg (Copenhagen) Denmark Telephone: +45 88 77 36 00
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REVISION HISTORY

PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
PROTOCOL DATE:	Original Protocol Version 1.0, 14-Dec-2017
	This updated global protocol version 21.0 includes:
AMENDMENT No. 1	Final Version 2.0, 31-May-2018 (All countries)
AMENDMENT No. 2	Final Version 3.0, 24-Jul-2018 (United Kingdom)
AMENDMENT No. 3	Final Version 4.0, 25-Jul-2019 (France, Germany, Israel)
AMENDMENT No. 4	Final Version 5.0, 03-Jun-2019 (Germany)
AMENDMENT No. 5	Final Version 6.0, 03-Jun-2019 (All countries)
AMENDMENT No. 7	Final Version 8.0, 11-Oct-2019 (All countries except Germany)
AMENDMENT No. 8	Final Version 9.0, 29-Jan-2020 (Germany)
AMENDMENT No. 9	Final Version 10.0, 01-Oct-2021 (All countries except Germany)
AMENDMENT No. 10	Final Version 11.0, 11-Oct-2021 (Germany)
AMENDMENT No. 11	Final Version 12.0, 28-Sep-2022 (All countries except Germany)
AMENDMENT No. 12	Final Version 13.0, 28-Sep-2022 (Germany)
AMENDMENT No. 13	Final Version 14.0, 22-May-2023 (All countries except Germany)
AMENDMENT No. 14	Final Version 15.0, 22-May-2023 (Germany)
AMENDMENT No. 15	Final Version 16.0, 09-Apr-2024 (All countries except Germany and the UK)
AMENDMENT No. 16	Final Version 17.0, 09-Apr-2024 (Germany)
AMENDMENT No. 17	Final Version 18.0, 02-Sep-2024 (UK)
AMENDMENT No. 18	Final Version 19.0, 08-Nov-2024 (All countries except Germany and UK)
AMENDMENT No. 19	Final Version 20.0, 08-Nov-2024 (UK)

1. APPROVAL SIGNATURES

PROTOCOL NUMBER:	ZP4207-17106
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the trial.

[redacted]

Zealand Pharma A/S

[redacted]

Zealand Pharma A/S

[redacted]

Premier Research

2. SYNOPSIS

PRODUCT NAME/NUMBER	Dasiglucagon
PROTOCOL NUMBER	ZP4207-17106
EUDRACT NUMBER	2017-004546-15
DEVELOPMENT PHASE	Phase 3
PROTOCOL TITLE	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
INDICATION	Congenital hyperinsulinism (CHI)
OBJECTIVES	Primary: To evaluate the long-term safety of dasiglucagon administered as subcutaneous (SC) infusion in children with CHI Secondary: • To evaluate the long-term efficacy of dasiglucagon in reducing hypoglycemia • To evaluate the long-term efficacy of dasiglucagon in reducing glucose requirements • To evaluate the long-term tolerability of dasiglucagon administered as SC infusion in children with CHI • To investigate quality of life and resource utilization
TRIAL DESIGN	This is an open-label, multinational, multicenter, long-term safety and efficacy extension trial in patients with CHI who completed either ZP4207-17103 or ZP4207-17109 (defined as a lead-in trial). The investigator is allowed to change the standard of care (SOC) medication for CHI at his or her discretion in order to optimize the treatment of each patient. To use a minimally invasive yet objective method of assessing the frequency of hypoglycemia, patients will be required to wear a continuous glucose monitoring (CGM) device throughout the entire trial period. Pauses are allowed; however, CGM should be used for the 30 days leading up to each visit, and families will also be asked to perform self-monitored plasma glucose (SMPG). Parent(s)/guardian will be trained on the use of the meters. The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial. Any post-treatment follow-up scheduled for patients in the lead-in trial will be redundant if they are enrolled in the present trial by the time of the scheduled Follow-up Visit. Patients will be seen at Months 1, 3, and 6 and every 3 months thereafter and contacted by the investigator monthly by telephone in between site visits. At site visits, patients and their parent(s)/guardian will receive a paper diary to record potential adverse events (AEs) and concomitant medication, among other information, which will be reviewed regularly by site staff at each visit. Patients will be allowed to remain in the trial until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP) or until approximately Q3 2024 (treatment period), whichever occurs first. An interim analysis may be performed as appropriate to support a marketing application/ new drug application.
PLANNED NUMBER OF PATIENTS	A maximum of 44 patients are expected to be enrolled in the lead-in trials, and approximately 30-44 of those patients are expected to be enrolled in this trial.

TRIAL ENTRY CRITERIA	Eligible patients are those who have completed treatment in either trial ZP4207-17103 or ZP4207-17109 and are expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon, with an investigator statement documenting the positive benefit-risk assessment (based on considerations of glycemic effect, tolerability, and nature and frequency of AEs experienced in the lead-in trial).
INVESTIGATIONAL PRODUCT	Dasiglucagon injection 4 mg/mL in a 3 mL vial containing 1 mL
REFERENCE PRODUCT	None
TREATMENT REGIMENS	Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with an option to further titrate the dose to meet the needs of each patient. During the trial, SMPG assessments will be performed as instructed by the investigator. For patients using the Dexcom G5 CGM, SMPG assessments will at least be performed 2 times per day for CGM calibration. Patients will continue their SOC treatment for CHI. The combined treatment of SOC and dasiglucagon should aim to reduce gastric dextrose infusions and glucose fortified meals as much as possible, maintaining the patient's plasma glucose within 70 and 120 mg/dL at all times on normal feedings.
PLANNED TRIAL SITES	Up to 14 sites in the United States, Europe, and Israel with all sites having been involved in the lead-in trials.
CRITERIA FOR EVALUATION	Primary endpoint: • AEs Key secondary efficacy endpoints: • Total amount of gastric carbohydrates administered (nasogastric [NG] tube or gastrostomy) to treat hypoglycemia • Time to removal of NG tube or gastrostomy • Time to pancreatic surgery (sub-total or total pancreatectomy) • CGM percent time <70 mg/dL (3.9 mmol/L) • Rate of CGM-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more • Rate of clinically significant CGM-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more The primary endpoint will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and then in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis. All efficacy endpoints will be analyzed using average weekly results over Month 1, Month 1 to Month 3 and then each 3-month period between visits.
STATISTICAL METHODS	Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively; the exception to this is the time of plasma glucose (PG) within pre-specified ranges, which will not have a baseline value. For categorical endpoints, descriptive summaries will include counts and percentages. All data will be presented in the data listings.

	Analysis Populations Three analysis populations have been defined for this trial: The Safety Set: defined as all patients administered any trial drug. This population will be used to provide descriptive summaries of safety data. The Full Analysis Set (FAS): defined as all patients in the Safety Set who complete at least 1 day of trial drug. This population will be used to analyze efficacy data. The Pharmacokinetic Analysis Set (PK): defined as all patients in the Safety Set who have at least one measurement with quantifiable plasma concentration of dasiglucagon. This population will be used to provide descriptive summaries of PK data. Primary Analysis For the primary endpoint, the number of AEs will be summarized by time period (up to Month 1, Month 1 to Month 3, Month 3 to Month 6, Month 6 to Month 9, Month 9 to Month 12, etc.). Efficacy Analyses For the first and fourth key secondary endpoints, total amount of carbohydrates administered to treat hypoglycemia and CGM percent time <70 mg/dL, respectively, will be analyzed using a mixed-model for repeated measures using restricted maximum likelihood (REML). Time to event data will be analyzed using Kaplan-Meier methods. For the two last key secondary endpoints, the rate of CGM-detected hypoglycemic episodes, will be analyzed using a generalized linear mixed-model (GLMM) regression approach assuming a negative binomial distribution. For all other efficacy endpoints, continuous and categorical endpoints will be presented using summary statistics or frequencies, respectively. If warranted, continuous measures will be analyzed using a paired t-test or mixed model with region as a fixed effect and baseline value as a covariate; categorical measures will be analyzed using a Chi-square goodness-of-fit test or binomial test for proportions, as data permit, to determine whether there is a difference from the previous time point. An interim analysis will be performed as appropriate to support the application for approval of dasiglucagon. Safety Analyses Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with an onset at the time of or following the start of treatment with the trial drug through the Follow-up Visit or Early Termination Visit, whichever occurs first, and no longer than 12 weeks after treatment discontinuation will be defined as treatment emergent. The overall incidence of AEs will be displayed by system organ class, preferred term, and treatment. The incidence of AEs will also be presented by severity and by relationship to the trial drug. Vital signs, clinical laboratory measures (including hematology, biochemistry, and incidence of anti-drug antibodies [ADAs]), ECGs, physical examinations, and local tolerability data will be summarized by treatment, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. A formal statistical analysis plan (SAP) will be prepared to provide further details on the methods for statistical analysis.
SAMPLE SIZE DETERMINATION	The sample size is based upon patients rolling over from the lead-in trials; no sample size calculation was performed.

TRIAL AND TREATMENT DURATION	The sequence and maximum duration of the trial periods will be as follows:
	Trial Period (from last visit in lead-in trial until Trial Completion, as defined below):
	• Baseline: defined as the End of Treatment (EoT) Visit from lead-in trials ZP4207-17103 or ZP4207-17109.
	• Treatment Period: treatment will continue until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP), or until approximately Q3 2024, whichever occurs first, at which time an EoT Visit will be scheduled.
	• EoT Visit: see above.
	• Follow-up Visits: will occur at 4 weeks and 12 weeks after the EoT Visit.
	• Trial Completion:
	  ◦ completion of the final Follow-up Visit for the individual patient or
	  ◦ the EoT Visit if the patient continues treatment with dasiglucagon commercially or through an EAP.
	• Trial period: from baseline of the first patient to the time all patients have reached Trial Completion
	ADA Follow-up Period (from Trial Completion until Trial Finalization):
	• Monitoring of treatment-induced or treatment-boosted ADA-positive patients: monitoring of ADA-positive patients will continue until the ADA levels return to baseline (defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial) or until 2 years after the end of the trial period, whichever occurs first. Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.
	LPLV: Last visit of the last patient
	Trial Finalization: The time of finalization of all trial activities (LPLV) and submission of the End of Trial Declaration, as required according to national laws and regulation.

3. TABLE OF CONTENTS

3.1. LIST OF TABLES

3.2. LIST OF FIGURES

4. LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
$AOC_{glucose}$	area over the glucose curve
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time zero to infinity
CE	Conformité Européene
CGM	continuous glucose monitoring
CHI	congenital hyperinsulinism
C_{max}	maximum concentration
CRA	clinical research associate
CRO	contract research organization
CTR	clinical trial report
DMC	data monitoring committee
EAP	early access program
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ER/A&E	emergency room/accident & emergency department
EoT	end of Treatment
FAS	full analysis set
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GI	gastrointestinal
GLMM	generalized linear mixed-model
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
IB	investigator's brochure
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IM	intramuscular(ly)
IRB	institutional review board
ISF	Investigator Site File
IV	intravenous(ly)
LAR	legally authorized representative
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	necrolytic migratory erythema
NG	nasogastric
NME	necrolytic migratory erythema
PD	pharmacodynamics(s)
PedsQL	Pediatric Quality of Life Inventory
PG	plasma glucose
PK	pharmacokinetic(s)
PT	preferred term
QoL	quality of life
RBC	red blood cell
REML	restricted maximum likelihood
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SMPG	self-monitored plasma glucose
SOC	standard of care
SpO_2	blood oxygen saturation level
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
TMM	trial materials manual
ULN	upper limit of normal

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5. INTRODUCTION

5.1. Background and Rationale

Congenital hyperinsulinism (CHI) is a rare and challenging disorder in which β-cells in the pancreas secrete insulin irrespective of plasma glucose (PG) concentration, resulting in persistent and often severe hypoglycemia.[1] Congenital hyperinsulinism affects up to 1 in 50,000 newborns. It is typically diagnosed on the basis of signs and symptoms of hypoglycemia during the neonatal period or in infancy; however, the diagnosis may be made later in childhood. Several different genetic mutations have been described to cause CHI, which can be either focal (only a small area of the pancreas is affected) or diffuse (most of the pancreas is affected). The condition can persist into adulthood; however, the severity generally decreases with age due to the increased insulin requirements and/or reduced insulin resistance, and CHI is thus primarily a pediatric disease with regard to medical treatment needs. Hypoglycemia that results from CHI is of particular concern because it is an important cause of brain injury in neonates, infants, and children with this disease, which leads to long-term neurological impairments.[1,2] Up to approximately 50% of children with CHI experience neurodevelopmental abnormalities caused by severe hypoglycemia that results from inadequate treatment and/or delays in diagnosis.[1,3] Severe brain damage is the consequence of severe hypoglycemia, which presents as coma and/or long-lasting epileptic seizures in neonates. Major intellectual disability is, therefore, most frequent in neonatal patients with initial onset, whereas hypoglycemia is usually less severe and brain damage less frequent in children with CHI diagnosed later in childhood.[1] Since symptoms and severity of hypoglycemia can vary and pose a diagnostic challenge in neonates, infants, and children with CHI, prompt recognition and treatment of hypoglycemia is critical to reduce the risk of long-term neurological consequences.

5.2. Current Treatment and Unmet Medical Need

Medical treatment for CHI is focused on chronic therapies to avoid hypoglycemia, as well as on rescue therapy during acute episodes of severe hypoglycemia. Available medical therapies (mainly diazoxide/octreotide/glucagon for reconstitution alone or in combination with glucose infusion) are inadequate and accompanied by inability to control plasma glucose, as reflected in a large proportion of patients requiring sub-total pancreatectomy.[4,5,6] With the exception of surgery for focal CHI, which is curative in the vast majority of patients, sub-total pancreatectomy for diffuse CHI has substantial inadequacies. A recent trial[7] showed that 60% of patients who underwent near-total pancreatectomy had persistent hypoglycemia after surgery. Moreover, 96% had developed insulin-dependent diabetes within 11 years after surgery, indicating the serious and long-term consequences of the procedure.

First-line medical treatment is diazoxide, which is the only EU- and US-approved drug for treatment of hyperinsulinemic hypoglycemia. Diazoxide acts to open K_{ATP} channels of the pancreatic β-cells, thereby inhibiting insulin secretion. Unfortunately, many patients with CHI are resistant to diazoxide because of mutations in the genes encoding the K_{ATP} channel of the pancreatic β-cells.[6] For those who respond to diazoxide treatment, the more common side effects comprise hypertrichosis, fluid retention, and gastrointestinal (GI) symptoms; however, side effects are usually not severe. In diazoxide non-responders, second-line (and off-label) treatment is a somatostatin analog (octreotide or lanreotide [long acting]), which (among other effects) inhibits secretion of insulin and glucagon from the pancreas and suppresses glucagon-like

peptide-1 (GLP-1) secretion. Factors that limit their use comprise tachyphylaxis, as well as possible side effects, including necrotizing enterocolitis, gallstones, and hepatitis.[6]

Glucagon has been shown to be effective in the treatment of CHI. The glycogenolytic effect of glucagon and its ability to increase plasma glucose levels has been confirmed in children with CHI or neonatal hypoglycemia,[8,9] and administration of reconstituted glucagon (via intravenous [IV] infusion or as repeated subcutaneous [SC] injection) is often used in the initial phase during the establishment of CHI diagnosis and to stabilize patients with CHI before surgery or initiation of other medical treatments.[10] Furthermore, glucagon is administered as single SC doses to treat severe hypoglycemic episodes. While IV administration of glucagon to patients with CHI is used short-term in the hospital setting, e.g., before pancreatectomy,[2,10,11] long-term glucagon treatment is complicated by the fact that currently available glucagon products are unstable in nature and form fibrils within hours after reconstitution.[12] This fibril formation may lead to infusion set clotting, catheter obstruction, and dosing errors that may cause acute severe hypoglycemia. Catheter obstruction and occlusion because of glucagon fibril formation and aggregation were observed daily to 2 to 3 times weekly in a retrospective review of 9 patients with CHI receiving continuous SC infusion of glucagon for weeks or months.[11] In another series of patients, 60% of the patients treated with SC glucagon experienced catheter occlusion.[6] In a home-care setting, this fibril formation and associated risk of dosing errors carry the risk of hypoglycemic events, which is a major barrier for using currently marketed glucagon products for long-term treatment of patients with CHI.

With respect to long-term glucagon treatment in CHI, there are a few reports on home treatment with subcutaneously infused glucagon in children with CHI over extended periods (years) that suggest benefit in patient care with a potentially good safety profile as compared to diazoxide and octreotide.[6,11,13] While this attests to the potential clinical relevance of long-term glucagon treatment in CHI, the use of SC infusion of currently marketed glucagon is severely limited by the issues with fibril formation and solution instability of recombinant glucagon as described previously.

5.3. Dasiglucagon for the Treatment of Congenital Hyperinsulinism

5.3.1. Dasiglucagon

Dasiglucagon is a peptide analog of human glucagon that has been developed for the treatment and prevention of hypoglycemia in patients with diabetes mellitus via SC or IV administration. Dasiglucagon is under development for prevention and treatment of hypoglycemia in children with CHI and for the following other indications: Improving glycemic control in insulin-treated patients with type 1 diabetes mellitus, as part of a bihormonal artificial pancreas system, treatment of post-bariatric hypoglycemia and glycemic control during exercise and physical activity in patients with diabetes.

Dasiglucagon is a stable analog of glucagon that has been specifically designed to overcome the issues with fibril formation and instability in solution observed with marketed glucagon products. Compared to glucagon, dasiglucagon also comprises 29 amino acids. As a result of chemical modifications (7 amino acid substitutions compared to human glucagon), the pronounced tendency of glucagon to form fibrils and aggregate has been effectively prevented in dasiglucagon. In addition, the chemical stability in aqueous media at physiological pH has been improved.

To support the use of dasiglucagon in the pump, compatibility/in-use studies have been performed with dasiglucagon 4 mg/mL in the Hoffman-La Roche Accu-Chek Combo infusion pump using the Accu-Chek Spirit 3.15 mL cartridge system and the Accu-Chek Flexlink infusion set. The studies support an in-use time for up to 6 days at 37ºC.

Dasiglucagon was granted orphan drug designation by the European Commission on 20 June 2017 for the '*treatment of congenital hyperinsulinism.*' Furthermore, the Food and Drug Administration (FDA) granted an orphan drug designation for the '*treatment of hypoglycemia in patients with congenital hyperinsulinism (CHI)*' on 10 August 2017.

5.3.2. Nonclinical Experience

The completed nonclinical pharmacology program has determined that dasiglucagon is a specific glucagon receptor agonist with comparable in vitro potency to glucagon, promoting a rapid onset of PG increase in both normal and insulin-induced hypoglycemic animals, similar to that of glucagon. The effects of dasiglucagon and glucagon were investigated in an insulin-induced hypoglycemic rat model, which is considered particularly relevant to characterize the use of dasiglucagon for the treatment of CHI because it mimics the inappropriate insulin to PG levels in CHI and resultant hypoglycemia. The onset of PG increase with dasiglucagon was rapid and similar to that observed for glucagon, confirming comparable pharmacodynamics.

Results of the toxicity studies with dasiglucagon are comparable to what has been reported for glucagon. Those from chronic toxicity studies with dasiglucagon in rats and dogs are in line with the results of short-term toxicity studies, indicating that long-term treatment with dasiglucagon is safe and that the pharmacodynamic (PD) effects noted do not adversely affect organ function following chronic use.

5.3.3. Clinical Experience

Dasiglucagon is being developed to manage patients with CHI 1) as an initial short-term therapy to stabilize PG levels and reduce glucose infusion needs, and 2) as a long-term treatment to help maintain euglycemia.

Within the indication of prevention and treatment of hypoglycemia in children with CHI, efficacy and safety results are available from two completed trials.

Efficacy

Phase 2/3, two-period efficacy and safety trial ZP4207-17103

In this trial, 12 CHI patients (aged 7 days to 12 months) who needed continuous IV glucose administration to manage hypoglycemia completed a randomized clinical trial that consisted of a double-blind placebo-controlled crossover Part 1 followed by an open-label Part 2. Dosing of dasiglucagon approximated continuous SC infusion by delivering small doses at frequent intervals via an infusion pump according to a predefined algorithm. The focus in this trial was on the clinically relevant reduction and eventually elimination of the need for continuous IV glucose infusion, while avoiding hypoglycemia.

Compared to placebo, a statistically significant reduction in mean IV glucose infusion rate was obtained during the last 12 hours after dasiglucagon treatment (treatment difference

[95% CI]: -5.21 mg/kg/min [-8.29 to -2.13], p = 0.0037). This corresponded to a 55% reduction of weighted mean IV glucose infusion rate compared to placebo.

The total amount (g) of carbohydrates administered (regardless of the route) per day during Part 1 of the trial was statistically significantly lower after dasiglucagon treatment compared with placebo (treatment difference [95% CI]: -30.93 g/day [-56.80 to -5.05], p = 0.0238).

Phase 3, two-period efficacy and safety trial ZP4207-17109

In this phase 3 trial in 32 CHI patients aged 3 months to 12 years, dasiglucagon treatment added to standard of care (SOC) did not significantly reduce the number of intermittent SMPG-measured hypoglycemia events per week when compared to SOC alone (primary endpoint).

CGM metrics are not validated for use in patients with CHI. However, a post hoc analysis showed that dasiglucagon treatment resulted in clinically meaningful reductions in all measures of hypoglycemia assessed by blinded CGM (including number of events and time in hypoglycemia) compared to SOC treatment alone.

Safety

Phase 2/3, two-period efficacy and safety trial ZP4207-17103

A total of 12 patients aged from ≥7 days to <12 months were exposed to dasiglucagon in trial ZP4207-17103. The total duration of dasiglucagon exposure was 0.67 patient-years. Two SAEs (respiratory distress and acute respiratory failure) in the same patient were reported; both events were reported in the open-label period (where patients received dasiglucagon), and none were considered related to treatment with dasiglucagon.

Adverse events, other safety parameters, and immunogenicity

The most frequently reported AEs with dasiglucagon during Part 1 + Part 2 of the trial were anemia, vomiting, and rash papular (each reported by 3 patients). None of these AEs were reported more frequently with dasiglucagon as compared to placebo during the cross-over period (Part 1).

No confirmed cases of necrolytic migratory erythema (NME) were reported. Two hemodynamic events were reported: 2 AEs of tachycardia (1 during placebo and 1 during dasiglucagon treatment), which were both mild, intermittent, and not related to trial treatment.

No remarkable abnormalities were found in the biochemistry, hematology, vital signs, electrocardiogram (ECG), echocardiography, and physical and neurological exams. A few cases of clinically significant changes in hemoglobin, electrolytes, ALT, and AST were noted. None indicated any trends in aggregated change from baseline.

Local tolerability reactions, assessed only for patients in dasiglucagon + standard of care group, were mostly mild and attributed to the adhesive dressing. None of the local reactions were severe, and none were attributed to the trial intervention.

None of the children were tested positive for treatment-boosted or treatment-induced ADA (10 out of 12 children were tested for ADA at baseline and 8 were tested during trial).

Phase 3, two-period efficacy and safety trial ZP4207-17109

A total of 32 patients ages ≥3 months to ≤12 years were randomized and exposed to dasiglucagon in the completed ZP4207-17109 trial; total duration of dasiglucagon exposure was 3.8 patient-years. Overall, dasiglucagon treatment appeared well-tolerated in the trial. A total of 5 SAEs in 3 patients were reported in the dasiglucagon plus SOC group (central line infection, localized infection, folliculitis, influenza H1N1, and hyperglycemia); none of these were considered related to dasiglucagon treatment.

Adverse events, other safety parameters, and immunogenicity

In trial ZP4207-17109, vomiting was reported more frequently in the dasiglucagon treatment group as compared with those receiving SOC treatment, consistent with these gastrointestinal events being well-known side effects of glucagon treatment. More cases of skin and subcutaneous tissue disorders (including two confirmed events of necrolytic migratory erythema NME) were reported for dasiglucagon relative to SOC treatment, but no skin-related events led to discontinuation of dosing. Also, a minor imbalance of events was noted within the system organ class of infections and infestations during the initial 4-week trial period (12 with dasiglucagon versus 4 with SOC only).

No remarkable abnormalities were found in the biochemistry, hematology, vital signs, ECG, echocardiography, or physical and neurological examinations. A few cases of transient increases in ALT and AST were noted for dasiglucagon; of those reported as AEs, all were assessed as not/unlikely related to the trial product. No hemodynamic events were reported.

With respect to dasiglucagon antibody development, 7 out of 30 children (23.3%) with ADA assessments were ADA-positive during the trial (1 with treatment-boosted and 6 with treatment-induced ADA). Of these 7 children, 1 (14.3%) had cross-reactivity to glucagon and another (14.3%) had dasiglucagon in vitro neutralizing antibodies at the follow-up visit. In vitro neutralizing antibodies were not detected for the remaining 5 children with treatment-induced ADA.

QT prolongation

A comprehensive evaluation of the effect of dasiglucagon on cardiac repolarization and its proarrhythmic potential has been made based on 1) nonclinical data, 2) data from trial ZP4207-17144 in healthy subjects, in which potential ECG effects were evaluated through serial ECG monitoring and concentration-QTc analysis, and 3) data from phase 2/3 clinical trials to support the indication of treatment of severe hypoglycemia. It is concluded that there is no indication of dasiglucagon exerting a clinically relevant effect on QTcF interval or having a proarrhythmic potential.

The above conclusion is supported by the data from the completed CHI trials.

5.3.4. Literature Data

In a retrospective review of 223 cases of diffuse or focal CHI, glucagon was reported to be used in 55% of patients with diffuse CHI and in 31% of patients with focal CHI.[10] In an observational trial of 55 newborns who received glucagon because of hypoglycemia after birth, applied doses were mainly in the range of 0.5 to 1.0 mg/day, and results indicated an increase in PG from a

mean of 36.3 md/dL to a mean of 93.0 mg/dL, observed within 4 hours after the start of glucagon infusion.[9] The frequency of hypoglycemic episodes was significantly reduced, and no further episodes of severe hypoglycemia were observed.

The long-term use of glucagon in patients with CHI is limited by the instability of marketed glucagon after reconstitution. A literature review on the long-term medical treatment of CHI revealed that only 1% of 619 patients identified received glucagon as part of their medical management.[6] A retrospective review of 9 children with CHI who received continuous SC infusion of glucagon for weeks or months showed that introduction of glucagon allowed the reduction or discontinuation of central glucose infusion in all patients.[11] Six of 9 patients were discharged with continued glucagon therapy that their parents were able to continue without further symptomatic hypoglycemia, convulsions, or unconsciousness. In 3 children, glucagon therapy was continued for 1 to 4 years, which led to stable euglycemia.

The data reported on marketed glucagon use in patients with CHI indicate that continuous SC infusion of a glucagon agonist could provide therapeutic benefit to patients by stabilizing PG levels and reducing the frequency of hypoglycemic episodes.[5,6,9,10,11]

5.3.5. Anticipated Medical Benefit of Dasiglucagon in the Treatment of Congenital Hyperinsulinism

With its physio-chemical stability in liquid formulation, dasiglucagon could provide significant added benefit in the treatment of CHI relative to currently marketed glucagon by enabling long-term reliable IV infusion to control blood glucose. Long-term subcutaneous infusion of dasiglucagon through a pump may be an attractive alternative or addition to diazoxide and octreotide, as it may reduce the dependency on intensive nutritional support whilst maintaining euglycemia by harnessing physiological mechanisms for combating hypoglycemia. It is anticipated that reduced need for frequent tube feedings or continuous gastric infusion of nutrients, and increased fasting tolerance will be demonstrated, together with improvements in the quality of life of the patients and their families/guardians. If long-term euglycemia is achieved with medical therapy, pancreatectomy for the treatment of diffuse CHI could eventually be avoided, or at least postponed beyond the neonatal or very young infant period. In 1 cohort of non-surgically treated children, the mean clinical remission rate was 5 (1.5-12) years for diffuse CHI.[5] This suggests that a significant proportion of infants with CHI could avoid surgery if medical treatment allowed for the effective long-term control of hyperinsulinism.

5.3.6. Anticipated Risks of Dasiglucagon in the Treatment of CHI

Overall, in the two completed trials, the most commonly reported types of AEs in patients with CHI were skin disorders (various rashes and eczema), gastrointestinal disorders (including vomiting), and infections.

Glucagon exerts positive inotropic and chronotropic effects and may, therefore, cause tachycardia and hypertension. Across completed trials supporting the CHI indication, one event of tachycardia was reported with dasiglucagon, and one with placebo. Both events were mild and transient and considered not related to trial treatment.

Accidental overdose may occur due to inappropriate handling of the infusion pump or due to pump malfunction. Overdose may result in nausea, vomiting, inhibition of GI tract motility, short-term increase in heart rate or blood pressure, and/or hypokalemia. Symptomatic care for

nausea and vomiting, as well as monitoring of heart rate, blood pressure, and hypokalemia, is advised.

Administration site reactions are seen with many injectable peptides. Administration site reactions occurred sporadically in completed trials supporting pump use, as well as in a previously published trial with marketed glucagon delivered by pump. For the CHI indication, local tolerability reactions were mostly mild and attributed to the adhesive dressing. None of the local reactions were severe.

As with all therapeutic peptides and proteins, there is an inherent risk for the induction of an ADA response against dasiglucagon. In the completed CHI trials, no ADA formation was observed in trial ZP4207-17103; in ZP4207-17109 23.3% of the patients developed ADA. The impact of ADA on safety or efficacy of dasiglucagon treatment in children with CHI remains to be established.

Administration of glucagon or dasiglucagon may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins.

From sporadic reports of extended SC/IV infusion of marketed glucagon and in glucagonoma patients,[14] sustained exposure to high levels of glucagon may lead to development of skin condition necrolytic migratory erythema (NME), a highly specific migrating, erythematous rash with predilection for perioral, perianal, and lower leg distribution.[11] In the ZP4207-17109 trial, two confirmed events of NME were reported for dasiglucagon relative to SOC treatment, but no skin-related events led to discontinuation of dosing. No confirmed cases of NME were reported in the ZP4207-17103 trial.

For further information on risks, please refer to the current version of the investigator's brochure (IB).

5.3.7. Summary of Potential Benefits and Risks

As with all treatment interventions, the anticipated benefits to trial patients should be balanced against the potential risks. The accumulated experience from nonclinical studies and clinical trials with dasiglucagon supports that dasiglucagon is a specific glucagon receptor agonist and is well tolerated. Glucagon and its analogs belong to a well-known drug class with known mode of action. The clinical investigators involved in the trial will all have had experience with use of glucagon in patients with CHI.

The investigator will inform the patients/parent(s)/guardian of the potential risks of dasiglucagon treatment and other trial-related procedures before they enter the trial. The investigator must become familiar with all sections of the dasiglucagon IB before the start of the trial.

In summary, with its marked improvements in stability in solution and solubility in aqueous media compared to currently marketed glucagon products, dasiglucagon is expected to have significant clinical benefits in the treatment of CHI and to substantially reduce the disease burden in these patients. This includes enabling convenient and reliable long-term treatment via a pump device in a home setting, which holds the potential to delay and ultimately avoid pancreatectomy and its related exo/endocrine complications, particularly the development of insulin-dependent diabetes.

Dasiglucagon may overall provide significant added benefit in the treatment of CHI relative to currently marketed glucagon products by enabling long-term reliable SC infusion to control PG.

The proposed trial population is still experiencing hypoglycemia despite medical treatments being escalated to the highest therapeutically permissible or tolerated doses, or despite having undergone subtotal pancreatectomy. Therefore, these patients are dependent on continuous or very frequent delivery of carbohydrates, often through invasive routes (NG tube or gastrostomy). This limits their ability to lead normal lives, including participating in everyday activities, and therefore, impacts their development. For this trial population, the major and clinically relevant benefit is the expected reduction in number and volume of nutritional interventions while avoiding hypoglycemia. The reduced volume of nutritional interventions should limit the risk of volume overload, especially in patients treated with significant doses of diazoxide. Achievement of euglycemia could lead to reduction of other CHI medication, further limiting the potential for adverse events associated with those treatments. In addition, the need for pancreatectomy, or re-surgery in those who already underwent pancreatic surgery is reduced and potentially eliminated.

Overall, the benefit to risk ratio for patients entering the ZP4207-17106 trial is considered acceptable.

6. OBJECTIVES

6.1. Objectives

6.1.1. Primary Objective

To evaluate the long-term safety of dasiglucagon administered as SC infusion in children with CHI.

6.1.2. Secondary Objectives

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

6.2. Endpoints

The primary endpoint will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and then in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis. All efficacy endpoints will be analyzed using average weekly results over Month 1, Month1 to Month 3 and then the 3-month period between visits.

6.2.1. Primary Endpoint

- Adverse events

6.2.2. Key Secondary Efficacy Endpoints

- Total amount of gastric carbohydrates administered (nasogastric [NG] tube or gastrostomy) to treat hypoglycemia
- Time to removal of NG tube or gastrostomy

- Time to pancreatic surgery (sub-total or total pancreatectomy)
- Continuous glucose monitoring (CGM) percent time <70 mg/dL (3.9 mmol/L)
- Rate of CGM-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more
- Rate of clinically significant CGM-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more

6.2.3. Secondary Efficacy Endpoints

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

6.2.4. Other Efficacy Endpoints

- CGM percent time in range 70-180 mg/dL (3.9-10.0 mmol/L)
- CGM percent time >180 mg/dL (10 mmol/L)
- CGM percent time <54 mg/dL (3.0 mmol/L)
- Number of parent reported hypoglycemic events pr. week that required an intervention AND with PG <70 mg/dL (3.9 mmol/L) as detected by self-monitored plasma glucose (SMPG) or CGM
- Number of SMPG-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) per week based on SMPG measurements as captured in patient device
- Number of clinically significant SMPG-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) per week based on SMPG measurements as captured in patient device
- Number of emergency department visits for hypoglycemia
- Number and length of hospitalizations caused by CHI or CHI-related events
- Number of outpatient visits to health care providers (family doctors, specialist, etc.) caused by CHI or CHI-related events
- Number of home visits by paramedics due to hypoglycemia

- Quality-of-life (Pediatric Quality of Life Inventory [PedsQL™][Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score] and CHI-specific questionnaire)

6.2.5. Other Safety Endpoints

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

7. TRIAL DESIGN

7.1. Overall Trial Design and Plan

This is a phase 3, open-label, multinational, multicenter, long-term safety and efficacy extension trial in patients with CHI who completed either ZP4207-17103 or ZP4207-17109 (defined as a lead-in trial). To qualify for participation, patients are expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon due to CHI, with an investigator statement documenting the positive benefit-risk assessment.

The primary objective of this trial is to assess the long-term safety of dasiglucagon administered as SC infusion.

Informed consent (and assent as applicable) for participation in this trial will be obtained from eligible patients. Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with possible further dose adjustments to optimize treatment to each patient's needs.

The investigator is allowed to change the standard of care (SOC) medication for CHI at his or her discretion in order to optimize the treatment of each patient. To use a minimally invasive yet objective method of assessing the frequency of hypoglycemia, patients will be required to wear a CGM device throughout the entire trial period. Pauses are allowed; however, CGM must be used for the 30 days leading up to each visit, and families will also be asked to perform SMPG.

The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial. Any post-treatment follow-up scheduled for patients in the lead-in trial will be redundant if they are enrolled in the present trial by the time of the scheduled Follow-up Visit.

Patients will be seen at the trial site at Months 1, 3, and 6, and every 3 months thereafter, and contacted by the investigator monthly by telephone in between site visits. At site visits, patients and their parent(s)/guardian will receive a paper diary to record potential AEs and concomitant medication, among other information, which will be reviewed regularly by site staff at each visit. Patients will be allowed to remain in the trial until approval and commercial availability of

dasiglucagon in the country of participation or through an early access program (EAP), or until approximately Q3 2024 (Treatment Period), whichever occurs first. Any post-treatment Follow-up Visits will be redundant for the patients who are continuing treatment with dasiglucagon commercially or through an EAP, and they will end trial participation at their End of Treatment (EoT) Visit. Figure 1 depicts the trial design.

Patients who are treatment-induced or treatment-boosted ADA-positive at Trial Completion will be offered continued ADA monitoring until the ADA levels return to baseline or until 2 years after the end of the trial period, whichever occurs first. Baseline is defined as the ADA level prior to dasiglucagon dosing in the lead-in trial.

Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.

An interim analysis may be performed as appropriate to support a possible marketing authorization application/new drug application (NDA).

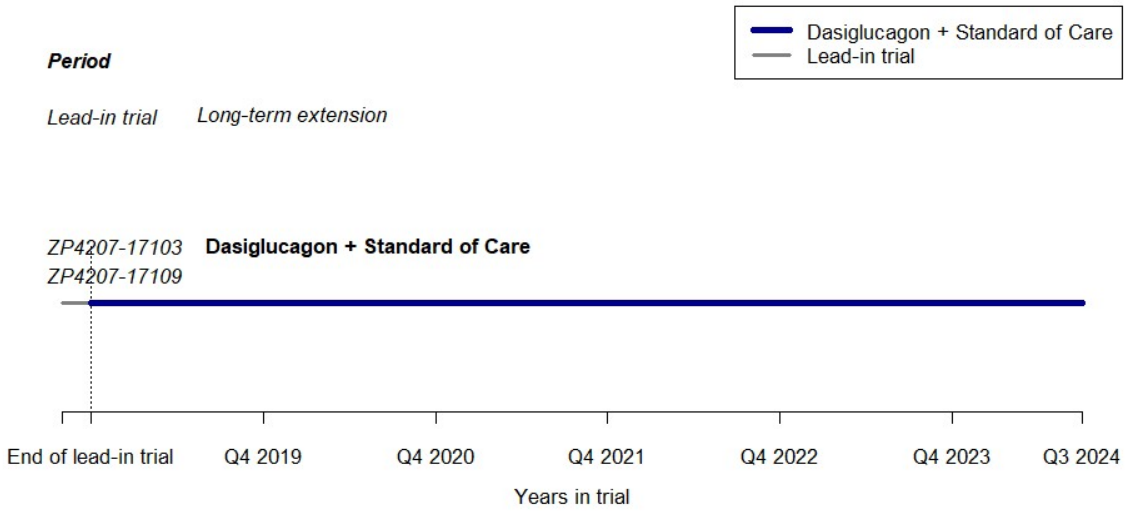


Figure 1 Trial Design

7.2. Trial Duration and Milestones

The sequence and maximum duration of the trial periods will be as follows:

Trial Period (from last visit in lead-in trial until Trial Completion, as defined below):

1. Baseline: defined as the EoT Visit from lead-in trials ZP4207-17103 or ZP4207-17109.
2. Treatment Period: treatment will continue until approval and commercial availability of dasiglucagon in the country of participation or through an EAP, or until approximately Q3 2024, whichever occurs first, at which time an EoT Visit will be scheduled.

3. EoT Visit: see above.

4. Follow-up Visits: will occur at 4 weeks and 12 weeks after the EoT Visit.

5. Trial Completion:

    a. completion of the final Follow-up Visit or

    b. the EoT Visit if the patient continues treatment with dasiglucagon commercially or through an EAP

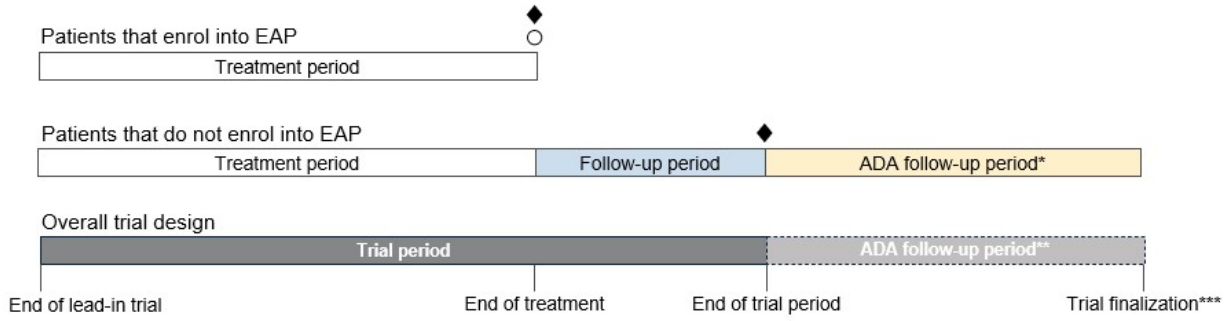
6. Trial period: from baseline of the first patient to the time all patients have reached Trial Completion

ADA Follow-up Period (from Trial Completion until Trial Finalization):

7. Monitoring of treatment-induced or treatment-boosted ADA-positive patients: monitoring of ADA-positive patients will continue until the ADA levels return to baseline (as defined in Section 10.1.3.1) or until 2 years after the end of the trial period, whichever occurs first. Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.

LPLV: last visit of the last patient

Trial Finalization: The time of finalization of all trial activities (LPLV) and submission of the End of Trial Declaration, as required according to national laws and regulation.



♦ Trial Completion
○ EAP enrolment
* ADA positive patients at FU2
** Until the ADA levels return to baseline or until 2 years after end of the trial period, whichever occurs first
*** Submission of End of trial declaration as required according to national laws and regulation

Figure 2 Trial Duration and Milestones

7.3. Discussion of Trial Design

This trial pools patients with CHI from 2 lead-in trials, one in children ≥7 days and <12 months of age (Trial ZP4207-17103) and the other in children between 3 months and 12 years of age

(Trial ZP4207-17109) and investigates safety and efficacy of dasiglucagon during extended exposure. Patients completing Trial ZP4207-17103 will generally have attained an age that is within the age span for Trial ZP4207-17109, and the pooling of the two trial populations for this extension trial is considered justified.

The open-label treatment from the last treatment period of lead-in trials ZP4207-17103 and ZP4207-17109 was chosen because the added treatment burden of a blinded trial design was not considered ethically justified.

Investigators will be required to reaffirm and document a positive benefit/risk assessment of continued treatment with dasiglucagon at each site visit, in close collaboration with the parent(s)/legally authorized representative (LAR) to ensure that patients are not unnecessarily exposed to the trial product. Treatment should be stopped if continued benefit is not evident or if safety issues overweigh the benefit of treatment.

A hypoglycemia threshold of PG <70 mg/dL (3.9 mmol/L) was chosen as an alert value for the key secondary hypoglycemia endpoints in alignment with the metabolic disease field experts, although clinicians might use lower thresholds for guiding treatment decisions for treatment of hypoglycemia in patients with CHI.

7.4. Trial Sites

The trial will take place at up to 14 sites experienced in the treatment of CHI in the United States and Europe, all of which will have been involved in the lead-in trials. A maximum of 44 patients are expected to be enrolled in the lead-in trials, and approximately 30-44 of those patients are expected to be enrolled in this trial.

7.5. Point of Contact

A point of contact will be identified to provide information to each patient's parent(s)/guardian about where to obtain information on the trial, the patient's rights, and whom to contact in case of trial-related injury. This information will be provided in the patient information and informed consent form (ICF).

8. PATIENT POPULATION

8.1. Selection of Trial Population

A screening log of potential trial candidates must be maintained at each trial site.

8.2. Trial Entry Criteria

8.2.1. Inclusion Criteria

A patient will be eligible for trial participation if he or she meets all of the following criteria:

1. Completed treatment in either Trial ZP4207-17103 or ZP4207-17109.
2. Expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon (based on considerations of glycemic effect, tolerability, and nature and frequency of AEs experienced in the lead-in trial), with signed investigator statement documenting the positive benefit-risk assessment made.
3. Has a negative serum pregnancy test at baseline (only for females of child-bearing potential).

4. Sexually active female patients and their partners must use acceptable contraception or refrain from sexual activity from baseline until 30 days after the last dose of trial drug. Females must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception. Abstinence can only be accepted if this is true abstinence in line with the preferred and usual lifestyle of the patient.

   Acceptable methods of contraception are:

   a) Hormonal contraceptives (e.g., oral contraceptive pill, depot, patch, intramuscular implant or injection, sponge, or vaginal ring), stabilized for at least 30 days if first use

   or

   b) Barrier method, e.g., (i) condom (male or female) and (ii) diaphragm with spermicide

Germany: *Only highly effective methods of birth control are accepted (i.e., one that results in less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices), or sexual abstinence.*

5. Able and willing to comply with trial procedures.
6. Following receipt of oral and written information about the trial, the patient (depending on local institutional review board [IRB]/independent ethics committee [IEC] requirements) must provide assent and one or both parents* or guardian of the patient must provide signed informed consent before any trial-related activity is carried out. ***France, Germany, Israel:*** *The consent must correspond to the patient's presumed will where such a will can be ascertained.*

* If required by local regulations, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

8.2.2. Exclusion Criteria

A patient will be excluded from the trial if he or she meets any of the following criteria:

1. The patient developed any conditions prohibited by the lead-in trial, requires medication prohibited by the lead-in trial, or has other new complications that preclude participation in the investigator's opinion.
2. Has participated in an interventional clinical trial (investigational or marketed product) within 3 months before baseline or 5 half-lives of the drug under investigation (whichever comes first) or plans to participate in another clinical trial. Excluded from this is participation in Trial ZP4207-17103, Trial ZP4207-17109, and/or 18F-Dopa positron emission tomography computed tomography/magnetic resonance imaging investigation (when performed as a part of a clinical trial) for diagnosis of focal CHI.

8.3. Patient Participation Stopping Criteria

8.3.1. Efficacy Reasons

Treatment should be discontinued if there is no longer any evidence of beneficial effect of dasiglucagon due to inadequate or complete lack of response, or in case continuation of treatment is not considered needed any longer due to natural course of the disease, i.e. improvement or full resolution.

The decision should be taken at the discretion of the investigator and involve the parents/LAR in the decision making. The decision should be based on all efficacy and safety assessments performed during participation in the trial. A temporary treatment interruption can be applied in order to inform the decision. If deemed needed, the patient can be admitted to the hospital during the treatment interruption.

8.3.2. Safety Reasons

Treatment should be permanently discontinued in case risk outweighs the benefit, i.e. unacceptable safety issues related to the treatment that are life-threatening, or associated with significant comorbidity.

8.4. Premature Patient Withdrawal

Patients' parent(s)/guardian will be advised that they are free to withdraw their children from participation in this trial at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep patients in the trial. However, patients must be withdrawn from the trial if their parent(s)/guardian withdraw consent to participate.

Investigators must attempt to contact patients' parent(s)/guardian who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Attempts to contact the patient must be documented. At least 3 phone calls and 3 written attempts to contact the patient will be made prior to considering them lost to follow-up. Should an AE be the cause of withdrawal, it must be documented, reported, and followed as described in Section 11.2.

If a patient/parent(s)/guardian withdraws consent, the reason for withdrawal and the date of withdrawal will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the trial should be performed at the time of premature withdrawal.

8.5. Treatment Discontinuation

To prevent missing data, patients should to the extent possible be kept in the trial. Therefore, treatment discontinuation is often the preferred option in case of, e.g., substantial non-compliance with trial procedures or initiation of prohibited treatment that interferes with the efficacy and safety evaluation. If it is an investigator decision to discontinue the patient's treatment, the investigator should, whenever possible, discuss the potential discontinuation of the treatment with the medical monitor. If the patient is discontinued from trial treatment by the investigator or by parent(s)/guardian's decision, the reason and date of treatment discontinuation will be recorded on the appropriate page of the eCRF. The patient should be asked to continue in the trial by following the planned visit schedule. At a minimum, the patient will be asked to attend the Follow-up Visits at 4 weeks and 12 weeks (± 7 days) after discontinuation of trial treatment. If the patient is treatment-induced or treatment-boosted ADA-positive at Trial Completion the patient will be offered continued ADA monitoring until their ADA levels return to baseline (defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial) or until 2 years after the end of the trial period, whichever occurs first. See Section 10.1.3.1 and Section 17.1.

8.6. Patient Replacement Criteria

Patients who withdraw from the trial prematurely will not be replaced.

Enrolled patients who are subsequently withdrawn from the trial may not reenter. The patient number for a withdrawn patient will not be reassigned to another patient.

8.7. Trial Stopping Criteria

In case of 2 or more serious safety concerns of similar nature potentially related to treatment, that are either life-threatening or associated with significant comorbidity and/or permanent disability, the trial will be temporarily paused. If relationship between the concerns and IMP is confirmed or there is reasonable evidence that the concerns are probably or possibly related to the IMP and overall benefit of dasiglucagon is outweighed, the trial will be permanently stopped.

9. TREATMENTS

9.1. Identification of Investigational Product

Dasiglucagon injection 4 mg/mL will be supplied by the sponsor in a 3 mL vial containing 1 mL.

Dasiglucagon will be provided in the form of solution for injection for subcutaneous administration through an infusion pump.

Trial drug products, as applicable, must be transferred from the vial to an Accu-Chek® Spirit Cartridge. The amount of drug product dosed via the pump will vary between patients.

Cartridges and infusion sets should be replaced as indicated in the instructions for use.

9.1.1. Packaging and Labeling

Trial drug products will be packaged and labeled by the sponsor.

Dispensing unit configuration: 6 vials containing dasiglucagon, 4 mg/mL, packaged in an outer carton. The vial and carton will be packaged and labeled in local language indicating the content (open label).

The storage conditions for trial drug products will be described on the trial drug product label. The labels will supply no information about the patients. Each treatment unit (containing 6 vials) will have a unique Dispensing Unit Number for drug allocation, drug accountability, and traceability purposes.

Labelling will be performed according to Annex 13 of the Good Manufacturing Practice guidelines of the European Commission, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, local laws, and regulations.

9.2. Treatments Administered

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

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

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

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

The combined treatment of SOC and dasiglucagon should aim to reduce gastric dextrose infusions and glucose fortified meals as much as possible, maintaining the patient's PG within 70 and 120 mg/dL (3.9-6.7 mmol/L) at all times.

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

Plasma glucose assessments will be performed throughout the trial as instructed by the investigator.

For patients using the Dexcom G5 CGM, SMPG assessments will be performed at least 2 times per day for CGM calibration.

For PG monitoring, the same hand-held PG meter as in the lead-in trials will be used.

Details on the administration instructions and guidelines for preparation and handling of the trial drug product are in the pharmacy manual/trial materials manual (TMM).

9.3. Trial Supplies

The device and ancillaries listed in the following table will be supplied by the sponsor throughout the trial. Trained trial personnel will train parent(s)/guardian on the use of the devices.

Instructions for the use of all these supplies will be provided in a separate manual.

Item	Name	Manufacturer
Pump	Accu-Chek Spirit Combo	Hoffman-La Roche AG, Basel, Switzerland
Cartridge	Accu-Chek Spirit 3.15 mL Cartridge system	Hoffman-La Roche AG, Basel, Switzerland
Infusion sets	Accu-Chek FlexLink Infusion set (Accu-Check® UltraFlex Infusion set in US) and Accu-Chek Rapid-D Link Infusion set	Hoffman-La Roche AG, Basel, Switzerland
Infusion set inserter	Accu-Chek LinkAssist Insertion device (can be used with FlexLink & UltraFlex)	Hoffman-La Roche AG, Basel, Switzerland
PG monitoring	StatStrip Xpress2	Nova Biomedical, Waltham, MA, USA
CGM	Dexcom G5 Dexcom G6	Dexcom Inc., San Diego, CA, USA

The infusion pump system is Conformité Européene (CE)-marked for the management of diabetes mellitus in persons requiring insulin, as prescribed by a physician. In this trial, the pump system is used outside the CE-marked intended use since the pump system will be delivering dasiglucagon to patients with CHI. The PG meter is used as intended according to the CE mark, except for the use by a lay person in a home care setting. The CGM devices are used as intended according to the CE mark, except for the age group and the disease.

The pump, the SMPG, and the CGM will be packaged and labeled for use in investigational trials.

9.4. Dispensing and Storage

The trial drug product supplied by the sponsor is to be dispensed exclusively to patients in this clinical trial according to the instructions of this protocol and the pharmacy manual/TMM. The investigator is responsible for dispensing the trial drug product according to the dosage scheme.

Dasiglucagon for injection 4 mg/mL must be stored at 2–8°C in a refrigerator.

The investigator must ensure the availability of proper storage conditions. All trial drug product provided for this trial will be stored in a secure area with restricted access at the trial site.

The temperature should be monitored by recording the actual, minimum, and maximum temperatures using a calibrated thermometer or thermocouple, or by continuous recording using a qualified temperature monitoring system. The temperature should be evaluated and documented at least on working days on a temperature log. This log must be included in the Investigator Site File (ISF) upon trial termination.

The investigator must contact the clinical research associate (CRA) in case of temperature deviations outside the acceptable range.

Please refer to the pharmacy manual/TMM for additional information on handling of the trial drug.

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the trial drug product, including the date, quantity, batch or code number, and identification of patients (patient number) who received the trial drug. The investigator will not supply the trial drug product to any person except subinvestigators, designated trial personnel, and patients in this trial. The trial drug product may not be relabeled or reassigned for use by other patients. If any of the trial drug product is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and the appropriate regulatory agencies as required.

9.5. Method of Assigning Patients to Treatment Groups

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

9.6. Blinding and Unblinding Treatment Assignment

This is an open-label trial.

9.7. Selection of Doses in the Trial

Both the starting dose and the maximum allowed doses are based on experience with glucagon products in this patient population.[11]

At the time of protocol development, no pediatric PK data were available for dasiglucagon. An approximate estimation of expected drug concentration in a 3 kg patient was made by extrapolation of a previously made PK model for pediatric patients with weights between 25 and 45 kg.[15]

The predicted plasma concentration is expected to give a low PD response in the lowest dose level and be above maximum effect at the highest dose level. The maximum expected plasma concentrations of dasiglucagon is in the range of what is achieved following a rescue dose to adults. The doses of dasiglucagon will be titrated to meet the needs of the individual patient. The titration will stop when no additional PD effects are observed as the infusion rate is increased. The infusion rate of dasiglucagon will be monitored and adjusted to meet the needs of the individual patient throughout the trial period. Since the dasiglucagon dose is titrated individually based on the desired PD response, it does not need to be related to any measure of the patient's size.

9.8. Selection of Timing of Dose for Each Patient

Dosing details are provided in Section 9.2.

9.9. Dose Adjustment Criteria

Dosing details are presented in Section 9.2.

9.10. Treatment Compliance

Compliance data will be collected. Infusion details will be recorded in the patient's eCRF, and drug accountability will be performed as detailed in the pharmacy manual/TMM.

9.11. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.11.1. Permitted Therapies

Concomitant CHI treatments (e.g., somatostatin analogs) that were initiated prior to trial entry are permitted throughout the trial. Somatostatin analogs may also be added throughout the trial at the investigator's discretion if the maximum dose level of dasiglucagon (70 µg/hr) has been reached or if further titration is not possible due to undesirable side effects.

Other CHI-specific treatments to be added during the trial need to be discussed with the medical monitor.

Caution is advised when beta-blockers, indomethacin, anticholinergic drugs, and warfarin are prescribed, due to reports of interaction with marketed glucagon products.

9.11.2. Prohibited Therapies

The following therapies are prohibited during the trial:

- Systemic corticosteroids, e.g., hydrocortisone >20 mg/m^2 body surface area (or equivalent)
- Anti-inflammatory biological agents, kinase inhibitors, or other immune-modulating agents
- Exogenous insulin
- Use of paracetamol/acetaminophen is strongly discouraged for the duration of trial when patients are using the Dexcom G5 CGM because it interferes with the accuracy of the device. Parent(s)/guardian should contact the trial site before dosing child with paracetamol/acetaminophen. Both the site staff and the parent(s)/guardian should explore other options of treating fever and mild pain before deciding paracetamol/acetaminophen is needed.
  When patients are using the Dexcom G6 CGM the use of paracetamol/acetaminophen is allowed.
- Other investigational agents
- Marketed glucagon products throughout the trial unless necessary for rescue therapy to treat severe hypoglycemia, as per local standard of care
- Prescription or non-prescription medications known to cause QT prolongation

Continuation in the trial after the patient received excluded therapies will be at the discretion of the investigator after consultation with the medical monitor.

10. TRIAL PROCEDURES

The patient (depending on local IRB/IEC requirements) must provide assent and one or both parent(s)/guardian (according to local law) must provide written informed consent before any trial-related procedures are initiated, including the cessation of prohibited concomitant therapy. ***France, Germany, Israel:*** *The consent must correspond to the patient's presumed will where such a will can be ascertained. Depending on local IRB/IEC requirements, the patient should also provide assent before any trial-related procedures are initiated.*

For the timing of assessments and procedures throughout the trial, refer to the Schedule of Events (Section 17.1). Throughout the trial, trial personnel should make every reasonable effort

to follow the timing of assessments and procedures in Section 17.1 for each patient. If a patient misses a trial visit for any reason, the visit should be rescheduled as soon as possible.

At enrollment and throughout the trial, the investigator will ensure:

- Appropriate re-training of patient's parent(s)/guardian in the use of dasiglucagon in the Accu-Chek Spirit Combo pump based on the training material provided
- Parent(s)/guardian are trained appropriately on the use of CGM device
- Parent(s)/guardian are trained appropriately on how to perform SMPG measurements and on how to complete the diary. They will check their child's SMPG as instructed by the investigator. When the patient is using the Dexcom G5 CGM, the SMPG should be measured at least 2 times per day for calibration of the CGM device.
- Parent(s)/guardian are instructed not to change the dose of trial drug without prior consultation with the investigator
- Parent(s)/guardian are instructed how to recognize and handle signs of hypoglycemia
- Parent(s)/guardian are instructed to call the investigator/site staff in case of questions

10.1. Assessments

Quality of life should be the first assessment performed at each visit according to the Schedule of Events (Section 17.1).

Medical history, including current illness, should be transferred from the lead-in trial (ZP4207-17109 or ZP4207-17103).

Specific for CHI diagnosis: Data on genotyping results from patients rolled over from the ZP4207-17109 lead-in trial should be captured when available. Data on genotyping results should not be captured from patients rolled over from the ZP4207-17103 lead-in trial, as it was collected as part of the trial (see Section 17.1).

10.1.1. Efficacy

10.1.1.1. Plasma Glucose Monitoring

Plasma glucose assessments will be performed regularly throughout the trial. During the trial, SMPG assessments (using StatStrip Xpress2) will be performed as instructed by the investigator. When a patient is using the Dexcom G5 CGM, SMPG assessments will be performed at least 2 times per day for CGM calibration.

At each visit the investigator will ensure that SMPG data are downloaded from the patient's device. The investigator will check for patient compliance in SMPG measurements. The procedure for download of SMPG data will be described in the pharmacy manual/TMM.

10.1.1.2. Continuous Glucose Monitoring

Both the Dexcom G5 and Dexcom G6 can be used for continuous glucose monitoring during the trial. The Dexcom G5 will be taken off the market by the supplier during 2020 and all patients should be shifted to the Dexcom G6 CGM device.

The CGMs (Dexcom G5 and Dexcom G6), supplied for use throughout the trial, will be used to guide treatment decisions, as well as to evaluate efficacy. Continuous glucose monitoring should be used for the entire trial period. Pauses are allowed, but CGM must be used for the 30 days leading up to each site visit (see Section 17.1).

At each visit, the investigator will ensure that CGM data are downloaded from the patient's device. The procedure for download of CGM data will be described in the pharmacy manual/TMM.

The CGM devices should be calibrated and used according to the manufacturer's instructions; the Dexcom G5 should be calibrated 2 times per day, the Dexcom G6 does not require calibration.

The contract research organization (CRO) or delegate will handle the device sourcing, configuration for use in the trial, procedures for data extraction, device service, and return handling.

10.1.1.3. Quality of Life

Quality of life (Appendix B) will be assessed using the PedsQL and additional CHI disease-specific QoL questions (parent-reported versions) according to the Schedule of Events (Section 17.1).

The PedsQL Measurement Model is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL Measurement Model integrates seamlessly both generic core scales and disease-specific modules into one measurement system.

The 23-item PedsQL Generic Core Scales was designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. The 4 Multidimensional Scales and 3 Summary Scores are:

Scales	Summary Scores
• Physical Functioning (8 items)	• Total Scale Score (23 items)
• Emotional Functioning (5 items)	• Physical Health Summary Score (8 items)
• Social Functioning (5 items)	• Psychosocial Health Summary Score (15 items)
• School Functioning (5 items)	

The CHI disease-specific questions were developed by the patient association Congenital Hyperinsulinism International and taken from the patient-reported registry, the HI Global Registry. The HI Global Registry questions are grouped mostly under general QoL; however, some questions relate specifically to diet and feeding, surgical management, glucose monitoring, and child development. The HI Global Registry is governed by a Global Steering Committee, including key global clinical experts.

10.1.1.4. Other Assessments

Resource Utilization:

- Emergency department visits for hypoglycemia
- Number and length of hospitalizations caused by CHI or CHI-related events
- Number of visits to health care providers (family doctors, specialist, etc.) caused by CHI or CHI-related events
- Number of home visits by paramedics due to hypoglycemia

Diary:

The patient's parent(s)/guardian will be provided with a paper diary at all visits, except at the End of Treatment and Follow-up Visits. The investigator will instruct the patient's parent(s)/guardian on how to complete the diary. The diary should be completed throughout the trial until the end of treatment. The following information should be recorded in the diary:

- Hypoglycemic events for which there was an intervention, regardless whether the event was detected via SMPG or CGM
- Concomitant medications
- AEs
- Hospitalizations, visits to health care providers or emergency room/ accident & emergency department (ER/A&E), and visits by paramedics
- Data regarding suspicion of NME and neurological findings

Diary entries should be reviewed at each visit and the review be documented in the diary. Data from the diary entries should be transcribed to the eCRF on an ongoing basis.

Prescribed continuous gastric carbohydrates:

Total amount of prescribed carbohydrates as part of continuous gastric infusion and infusion duration as listed in this section will be collected on the 7 days prior to the the following visits: Start of the lead-in trial (ZP4207-17103 or ZP4207-17109), Visit 1, Visit 4, Visit 6 and at End of Treatment.

In ZP4207-17103 start of trial is defined as the 7 days prior to the run-in period and in ZP4207-17109 start of trial is defined as the 7 days prior to the randomization visit.

- Total amount (g) of prescribed carbohydrates as part of continuous gastric infusion
- Total duration (h) of prescribed continuous gastric infusion
- Total duration (h) of prescribed nightly (8 pm – 8 am) continuous gastric infusion

10.1.2. Pharmacokinetics/Drug Exposure

Blood samples will be collected to measure dasiglucagon levels at steady-state (Schedule of Events; Section 17.1).

Details on sampling/collection, shipment, and analysis will be provided in the laboratory manual.

10.1.3. Safety

Safety assessments will include the evaluation of AEs, clinical laboratory assessments (hematology, biochemistry, and ADAs), vital signs, physical examination, ECGs, echocardiography, and local tolerability.

10.1.3.1. Laboratory Safety Assessments

Trial procedures require a maximum total of approximately 4 mL blood per visit. No more than 1 mL blood per kg body weight should be sampled per visit day. Where this limit is exceeded,[16,17] safety laboratory tests (2 mL per sampling) will be prioritized over immunogenicity (1 mL) and drug exposure (0.4 mL) samples.

All measurements described in this section are recognized standard methods.

Hematology and Biochemistry

Samples for hematology and biochemistry will be collected at the time points specified in the Schedule of Events (Section 17.1).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count, including differential
Biochemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine, sodium, potassium, chloride, estimated glomerular filtration rate (eGFR), urea, insulin, ketones (measured at the local laboratory or with PG meter), free fatty acids, and hemoglobin A1c (HbA1c)

Laboratory specimens will be analyzed at local laboratories.

Immunogenicity

Blood samples will be collected to test for antibodies against dasiglucagon at Visits 1, 3, 4, 6; in intervals of 6 months throughout the Treatment Period, at final drug administration, and at the Follow-up Visits (Section 17.1); and processed and shipped according to instructions provided in the laboratory manual.

Patients who are treatment-induced or treatment-boosted ADA-positive at Trial Completion will be offered continued ADA monitoring until the ADA levels return to baseline or until 2 years after the end of the trial period, whichever occurs first. The patients will be invited to come to the site for ADA blood sampling visits 1 to 3 times a year with a minimum of 4 months between the visits. Baseline is defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial.

Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.

Samples for ADA measurement will be analyzed in batches during the trial. The ADA samples will be analyzed at a special laboratory.

The clinical ADA assays have been validated in accordance with existing guidelines and recommendations.[18,19]

Samples will be measured in anti-dasiglucagon antibody screening and confirmatory assays. Due to the limited sample volume, in the CHI pediatric patients, the ADA characterization of confirmed positive samples will be conducted according to the following priority:

- Cross-reactivity against endogenous glucagon (cross-reactivity Yes/No)
- Establishment of anti-dasiglucagon binding titer
- Dasiglucagon in-vitro neutralizing potential of the antibodies
- Glucagon in-vitro neutralizing potential of the antibodies (only if positive for crossreactivity)
- Neutralizing antibody titers, in case of a positive result in the in-vitro neutralizing antibody assays

The in vitro neutralizing effects of antibodies will be measured using an assay based on glucagon receptor-transfected human embryonic kidney cells. The sensitivity in the 1st generation NAb assay initially used was approximately 51.8 ng/mL. In the recently developed 2nd generation NAb assay, the sensitivity is 89.8 ng/mL. The assays were also validated for recombinant glucagon with similar results. The cell-based neutralizing antibody analyses will be performed by a special laboratory (BioAgilytix, Durham, NC, USA). No further serum sampling will be needed since the ADA samples can be used for neutralizing antibody analysis.

The neutralizing potential in samples from ADA-positive patients will be evaluated on the basis of drug exposure/PD data (steady-state exposure and plasma glucose) if the assessment for NAb activity in confirmed ADA-positive samples is not possible due to the limited sample volume.

The ADA samples will be analyzed in batches during the trial, and patients who developed treatment induced anti-dasiglucagon antibodies (treatment induced or treatment boosted, titer increase above 4 fold) will be offered follow up until the ADA level is back to baseline or until the outcomes related to anti-drug antibodies are no longer detected.

For patients with a body weight <10 kg, it will not be possible to collect back-up ADA samples. However, any residual serum samples may be stored until approval of market authorization by the health authorities.

For patients with a body weight ≥10 kg, a back-up ADA sample and residual serum samples may be stored until approval of market authorization since further characterization of the antibody response may be requested.

Pregnancy Testing

A serum pregnancy test will be performed every 3 months in females of child-bearing potential.

Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all trial personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of patient samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the laboratory manual. The investigator is responsible for ensuring that all trial samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

Evaluation of Laboratory Values

The normal ranges of values for the laboratory assessments in this trial will be provided by the responsible laboratory and submitted to the sponsor before the beginning of the trial. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, the investigator must evaluate if the value is clinically significant and record his or her assessment in the appropriate eCRF.

All laboratory values that in the investigator's opinion are clinically relevant during or after termination of the treatment have to be reported as AEs and followed, as described in Section 11.2.

10.1.3.2. Clinical Examinations

Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and blood oxygen saturation level (SpO_2) will be measured according to the Schedule of Events (Section 17.1).

Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed while the child is in a sleeping or calm state according to the time points specified in the Schedule of Events (Section 17.1). If it is not practical or possible, then a 2-lead ECG may be used.[20] If arrhythmia is detected on a 2-lead ECG, this should be followed by 12-lead ECG. All ECG recordings will be identified with the patient number, date, and time of the recording and will be attached to his or her medical record.

The ECG parameters (heart rate, PQ, QRS, QT, and QTcF) and any abnormality will be recorded and described in the eCRF, including the investigator's assessment of clinical significance (Abnormal, Clinically Significant; or Abnormal, Not Clinically Significant). At subsequent visits, any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant findings, will be recorded as AEs.

Echocardiogram

An echocardiogram will be performed according to the time points specified in the Schedule of Events (Section 17.1).

Physical Examination and Neurological Examination

A complete physical examination of body systems (excluding breast and genitourinary, nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait, all as applicable for the patient's age) will be performed according to the Schedule of Events (Section 17.1).

Local Tolerability

Local tolerability data will be collected separately from AEs. Within the eCRF, data will be collected on the nature of any reaction (erythema, pain, swelling, etc.), the severity (mild, moderate, severe), and any action take (e.g., no action, interruption of infusion). The likely cause of the reaction will also be collected (e.g., insertion site, drug, adhesive dressing).

Other skin findings will be collected along with other AEs. If clinical suspicion of NME is made, data describing the lesion(s) will be collected as an AE of special interest (AESI, see Section 11.1.8), together with a photograph or series of photographs of the lesion(s) uploaded to a central repository.

10.1.3.3. Reporting of Hypoglycemia Events

Hypoglycemic episodes (below 70 mg/dL / 3.9 mmol/L) that require intervention are to be reported via the dedicated hypoglycemia eCRF form. Hypoglycemic episodes that fulfill the definition of an SAE should furthermore be recorded as an SAE. The following information should be collected:

- Date, start time, source (SMPG/CGM)
- Selected symptoms (e.g., unconsciousness, seizures)
- Intervention:
  - type and amount of food, route of administration (oral vs. NG tube/gastrostomy)
  - use of marketed glucagon as rescue therapy
  - contact with trial doctor or emergency services, paramedic visit, ER/A&E admission, hospitalization

10.1.3.4. Technical Complaints

Reporting of Technical Complaints

Technical complaints should be reported to the sponsor on any of the following products, if technical issues occur between their first and last use:

- Dasiglucagon 4 mg/mL-vial containing 1 mL
- Accu-Chek Spirit pump
- Accu-Chek Spirit 3.15 mL Cartridge system, Accu-Chek Flex-link Infusion set (Accu-Check UltraFlex Infusion set in the US), and Accu-Check Rapid-D Link infusion set
- Accu-Chek Link-Assist Insertion device
- SMPG meter, StatStrip Xpress2
- Dexcom G5/G6 system

The investigator must report whether the technical complaint is associated with any AEs or SAEs. Any AE/SAE associated with a technical complaint must be reported in accordance with

Section 11.2; the relationship between the technical complaint and the AE/SAE must be assessed by the investigator.

Technical complaints must be reported on a dedicated technical complaint form.

The investigator must complete the technical complaint form in the eCRF according to the following timelines, starting from the time the trial site becomes aware of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

Use the paper technical complaint form when reporting a technical complaint for an item that is not yet allocated to a patient. The form should be sent by email to the safety CRO, refer to Appendix A for contact details.

Collection, Storage, and Shipment of Technical Complaint Item(s)

The investigator must collect and store the item(s) and notify the CRA (including photo documentation) **within 5 calendar days** of obtaining the item at trial site. Upon request, the CRA must coordinate the shipment as per instruction from the sponsor.

10.1.3.5. Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 11 and in Appendix D.

11. ADVERSE EVENTS AND PREGNANCIES

Timely, accurate, and complete reporting and analysis of safety information from clinical trials are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical trial patient administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not related to the product.

AEs include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory AE: a clinical abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, e.g., change of dose or more frequent follow-up due to the abnormality

The following should **not** be considered as AEs:

- Pre-existing conditions, including those found as a result of baseline procedures (pre-existing conditions should be reported as medical history or concomitant illness)

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the patient has signed the informed consent

11.1.2. Severity

When assessing the severity of an AE, the following definitions are used:

Mild: No or transient symptoms, no interference with the patient's daily activities

Moderate: Marked symptoms, moderate interference with the patient's daily activities

Severe: Considerable interference with the patient's daily activities, which the patient find unacceptable. A severe reaction does not necessarily deem the AE as serious (SAE) and an SAE is not always severe in nature.

11.1.3. Causality

When assessing the cause of an AE, the following definitions are used:

Probable: Good reason and sufficient documentation to assume a causal relationship

Possible: A causal relationship is conceivable and cannot be dismissed

Unlikely: The event is most likely related to etiology other than the product

Not related: No relationship to product

Causality will take into consideration whether the cause of the AE was related to the trial drug. For SAEs it will additionally be reported if the event is at least possibly related to any concomitant drug/therapy, study procedure or other (including any device).

11.1.4. Outcome

When assessing the outcome of an AE, the following definitions are used:

Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the patient signed the ICF

Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable as final outcome of an event if the patient has completed the trial or has died from another AE

Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE

Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known

Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with fatal outcome must be reported as an SAE

Unknown: This term is only applicable if the patient is lost to follow-up.

11.1.5. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose results in any of the following:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is otherwise medically important, that may not result in death, be life threatening or require hospitalization may be considered an SAE when (based on appropriate medical judgement) it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples could be emergency room or home treatment of allergic bronchospasm or convulsion

11.1.6. Other Important Events

The following events must always be reported in the electronic data capture (EDC) system on a dedicated form, regardless of whether it is related to an AE:

- suspicion of transmission of infectious agents via the trial product
- overdose of the trial product
- medication error involving the trial product
- inadvertent or accidental exposure to the trial product

11.1.7. Non-serious Adverse Events

A non-serious AE is any AE that does not fulfill the definition of an SAE.

11.1.8. Adverse Events of Special Interest

For this trial, the following events are to be regarded as AEs of special interest (AESI events or AESI), with data collected under a specific eCRF form:

- Suspicion of NME
- Risk of liver injury defined as ALT or AST >3 x ULN AND total bilirubin >2 x ULN, where no alternative etiology exists (Hy's law)
- Loss of consciousness, partial and generalized seizures
- Clinically significant changes in blood pressure or heart rate

11.1.9. Suspected Unexpected Serious Adverse Reactions

An AE is considered a suspected unexpected serious adverse reaction (SUSAR) if the nature or severity is not consistent with the applicable product Reference Safety Information (RSI). For dasiglucagon, the expectedness of an AE will be determined by whether or not it is listed in the RSI section of the IB.

11.2. Collection, Recording, and Reporting of Adverse Events

All AEs, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until Trial Completion. In addition, patients will be observed for any signs or

symptoms. They or their parent(s)/guardian, depending on the patient's age, will be asked about their condition by open questioning, such as "How have you been feeling since you were last asked?" at each contact with the trial site (visit or telephone). Patients or their parent(s)/guardian, depending on the patient's age, will also be encouraged to spontaneously report AEs occurring at any other time during the trial. At site visits and during monthly telephone contacts, the investigator should ask the patient and their caregiver(s) about any possible signs and symptoms of seizures as described in Appendix D.

All AEs, regardless of seriousness, severity, or presumed relationship to trial drug, must be recorded and evaluated by the investigator. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. If no diagnosis can be made, the investigator should record each sign and symptom as individual AEs. Investigators must record their opinion concerning the relationship of the AE to the trial drug. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

Each AE must be reported on the AE eCRF within 5 calendar days of the investigator becoming aware of the event.

All AE information should at a minimum include the following:

- Date and time of onset
- Date and time of investigator's first information about the AE
- Seriousness
- Severity
- Causal relationship with trial product
- Measures taken due to AE
- Interruption or discontinuation of treatment with trial product
- Date and time of resolution and final outcome

Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

All SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of trial drug, must be reported within 24 hours after obtaining knowledge about the event by completing the SAE form in the EDC system. A separate SAE form should be completed for each SAE.

All SAEs will be reported in EDC, and for each reported event a system-generated email will be sent to the safety CRO [redacted]), the medical monitor, sponsor medical director, and trial manager.

Specific information about AESIs will be collected via SAE form (if qualifying for serious adverse events [SAEs]) as well as via dedicated AESI eCRF page(s). Reporting requirements for serious and non-serious AEs as described above also apply for serious and non-serious AESIs.

Other important events (Section 11.1.6) will be reported via a dedicated eCRF page. Reporting timelines will be within 24 hours if related to an SAE and 5 calendar days for all other events.

It is the responsibility of [redacted] to report all SUSARs that occur in this trial to competent authorities, the IRB, or IEC in accordance with the local requirements in force and the ICH guideline for GCP. SUSARs will be coded using the latest version of MedDRA.

11.2.1. Contact Information

Pharmacovigilance for this trial is outsourced to [redacted]; refer to Appendix A for contact details.

11.3. Follow-up of Adverse Events

The investigator must record follow-up information on the eCRF for non-serious AEs and on the SAE form for SAEs. Follow-up questions to investigators regarding SAEs are queried directly by [redacted] to the investigator.

Follow-up information must be reported according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the events is "recovered/resolved," "recovered/resolved with sequelae," or "fatal," and until all queries have been resolved. Cases of chronic conditions, cancer, or AEs that are ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved." Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g., corrections or additions) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovered/resolved," or "recovered/resolved with sequelae" or until the patient has reached Trial Completion, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer, or AEs that are ongoing at time of death (where death is due to another AE) may be closed with the outcome of "recovering/resolving" or "not recovered/not resolved." Cases can be closed with the outcome of "recovering/resolving" when a patient has reached Trial Completion.

If a potential hypersensitivity reaction is observed, additional blood samples may be required to further characterize the potential hypersensitivity reaction. If an anaphylactic shock is suspected, samples may be taken for the measurement of tryptase. In this case, a blood sample should be taken 3-4 hours after the event and again approximately 1-2 weeks later to determine tryptase baseline levels. In addition, assessments for elevated histamine levels may be considered.

The investigator must ensure that the worst-case severity and seriousness of an event is kept throughout the trial, i.e., if the severity of an AE changes over time then it should be reported as 1 AE with the most severity. A worsening of an unresolved AE must be reported as follow-up with re-assessment of severity and/or seriousness of the event.

If an AE is resolved and re-appears later then it should be reported as a new AE.

Queries or follow-up requests must be responded within 14 calendar days from the date of receipt of the request, unless otherwise specified in the follow-up request.

11.4. Pregnancy

Parent(s)/guardian of female patients who are of childbearing potential must be instructed to notify the investigator immediately if their child becomes pregnant or if they suspect she is pregnant during the trial. All initial reports of pregnancy in female patients must be reported by trial site personnel using the appropriate pregnancy form in EDC within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs and must be reported using the SAE form. If a patient becomes pregnant during the trial, treatment must be discontinued.

The investigator must follow the pregnancy until its outcome is known and the newborn infant is 1 month of age. The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the fetus and newborn infant.

11.5. Precautions

Normal precautions taken for a clinical trial, including the provision of emergency equipment, will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct patients and parent(s)/guardian. During a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to patients for any AEs, including clinically significant laboratory values related to the trial. The investigator should inform the patient's parent(s)/guardian when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

For further information on safety precautions for dasiglucagon, refer to the current version of the IB.

11.6. Safety Committee

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

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

11.7. Independent Data Monitoring Committee

An independent data monitoring committee (DMC) will be established for this trial and will work according to written procedures, e.g., the DMC charter.

12. STATISTICS

12.1. Sample Size Determination

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

12.2. Analysis Populations

Three analysis populations have been defined for this trial:

- The Safety Set: defined as all patients administered any trial drug. This population will be used to provide descriptive summaries of safety data.
- The Full Analysis Set (FAS): defined as all patients in the Safety Set who complete at least 1 day of trial drug. This population will be used to analyze efficacy data.
- The Pharmacokinetic Analysis Set (PK): defined as all patients in the Safety Set who have at least one measurement with quantifiable plasma concentration of dasiglucagon. This population will be used to provide descriptive summaries of PK data.

Inclusion in the analysis populations will be determined prior to database lock.

12.3. Statistical Analyses

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be 2 sided with a significance level of $\alpha = 0.05$.

For analyses involving trial site, if the number of patients per site is small, sites may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively; the exception to this is the time of PG within pre-specified ranges, which will not have a baseline value. For categorical endpoints, descriptive summaries will include counts and percentages.

All data will be presented in the data listings.

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

12.3.1. Trial Patients and Demographics

12.3.1.1. Disposition and Withdrawals

The numbers of patients randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall. The number of patients in each analysis population will be reported.

12.3.1.2. Protocol Deviations

Protocol deviations will be provided in a listing and summarized if appropriate.

12.3.1.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, ethnicity, weight, and length/height) at baseline will be summarized using descriptive statistics. No formal statistical analyses will be performed.

Prior and concomitant medications and procedures will be summarized by the number and percentage of patients taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes, and preferred term (PT).

12.3.2. Duration of Exposure and Compliance

Trial drug administration (i.e., amount administered) will be summarized in terms of each patient's mean, mode, and final dose, and in terms of duration of exposure. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided.

12.3.3. Efficacy Analyses

All efficacy endpoints will be analyzed using average weekly results over the 3-month period between visits.
Due to the impact of pancreatectomy on efficacy endpoints, primary analysis for all endpoints will not handle any endpoint assessment after any pancreatectomy (endpoints set to missing after pancreatectomy). A sensitivity analysis will be run on key secondary efficacy endpoint without censoring data after any pancreatectomy.

12.3.3.1. Key Secondary Analysis

The first key secondary endpoint, total amount of carbohydrates administered to treat hypoglycemia, will be analyzed by using a mixed-model for repeated measures using restricted maximum likelihood (REML). The model will include time period, region as fixed effects, baseline as covariate and patient as random effect. Baseline is defined as the total amount of carbohydrates administered to treat hypoglycemia during the last 2 weeks of the lead-in trial. Time period is defined as up to Month 1, Month 1 to Month 3 and then 3-month period of time for the first year and 6-month period of time for subsequent years. This endpoint will also be described by region and on a sub-group of patients with gastrostomy or NG-tube at entry in extension trial.

Time to event data (including time to remove of NG tube/gastrostomy and time to pancreatic surgery) will be analyzed using Kaplan-Meier methods. Those analysis will be performed on subgroup of patient from FAS with an NG tube or gastrostomy at the time of entry into the extension study/without any pancreatic surgery at the time of entry into the extension study respectively. Time to pancreatic surgery will also be analyzed by region.

The secondary endpoint of CGM percent time <70 mg/dL (3.3 mmol/L), where percent time is calculated as (number of minutes in hypoglycemia / total number of minutes patient is wearing CGM) * 100%, will be analyzed by using a mixed-model for repeated measures using REML. The model will include time period, region as fixed effects, baseline as covariate and patient as

random effect. Baseline is defined as the CGM percent time <70 mg/dL during the last 2 weeks of the lead-in trial.

The endpoints of Rate of CGM-detected hypoglycemic episodes (<70 mg/dL [3.9 mmol/L]) and Rate of clinically significant CGM-detected hypoglycemic episodes (<54 mg/dL [3.0 mmol/L] for 15 minutes or more) will be analyzed using generalized linear mixed-model (GLMM) regression approach assuming a negative binomial distribution, with time period and region as fixed effects and patients as a random effect. Baseline hypoglycemic rate is defined as the rate in the last 2 weeks of the lead-in trial.

12.3.3.2. Secondary and Other Efficacy Analysis

The endpoint of reduction in concomitant medication usage from start of lead-in trial, namely diaxozide and somatostatin analogs, will be summarized on subgroup of patients with diazoxide / somatostain dose at start of lead-in trial respectively.

Number of gastric carbohydrate administrations (NG tube or gastrostomy) to treat hypoglycemia will also be described by region.

For all other efficacy endpoints, continuous and categorical endpoints will be presented using summary statistics or frequencies, respectively. If warranted, continuous measures will be analyzed using a paired t-test or mixed model with region as a fixed effect and baseline value as a covariate; categorical measures will be analyzed using a Chi-square goodness-of-fit test or binomial test for proportions, as data permit, to determine whether there is a difference from the previous time point.

An interim analysis will be performed as appropriate to support the application for approval of dasiglucagon.

Quality of Life

Quality of life will be assessed by the PedsQL and a CHI disease-specific questionnaire (Appendix B).

For each item of the PedsQL instrument (parent), a 5-point response scale is used (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always). Items are reverse-scored and linearly transformed to a 0-100 scale (0 → 100, 1 → 75, 2 → 50, 3 → 25, 4 → 0) so that higher scores indicate better health-related QoL (less negative impact). Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed. Change from baseline for PedsQL for each of the scales (physical functioning, emotional functioning, social functioning, and school functioning) and summary scores (total scale score, physical health summary score, and psychosocial health summary score) will be summarized.

Answers to each question on the CHI disease-specific questionnaire will be summarized using frequencies at each relevant visit.

Resource Utilization

The number and percentage of patients with admissions/emergency department visits for glycemia, hospitalizations caused by CHI, visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and need for home visits by parameters will be summarized. Additionally, number and length (in days) of hospitalizations caused by

CHI, number of visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and number of home visits by paramedics will be summarized.

12.3.4. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 12.2). Safety assessments will include the evaluation of AEs; clinical laboratory assessments (hematology, biochemistry, and ADAs); vital signs, physical examinations; ECGs, and local tolerability issues. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

12.3.4.1. Primary Endpoint: Adverse Events

The primary endpoint of number of AEs will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis.

Adverse events will be coded using the latest version of MedDRA.

A treatment-emergent AE is defined as an AE with an onset at the time of or following the start of treatment with the trial drug until the patient has reached Trial Completion, and no longer than 12 weeks after treatment discontinuation, whichever occurs first.

The number and percentage of patients with AEs will be displayed by system organ class and PT. The incidence of AEs will also be presented by severity and relationship to the trial drug. Serious AEs and AEs resulting in discontinuation of trial drug will be summarized separately in a similar manner. Patient listings of AEs, SAEs, and AEs causing discontinuation of trial drug will be produced.

12.3.4.2. Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values by time point.

The number of patients with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte.

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

12.3.4.3. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and SpO_2.

The number of patients with vital signs values categorized Abnormal, Clinically Significant or Abnormal, Not Clinically Significant will be tabulated showing change from baseline (shift tables) for each parameter.

12.3.4.4. Twelve-lead Electrocardiograms

The number and percentage of patients with normal and abnormal ECG findings will be summarized for each time point. Abnormal results will be grouped as Abnormal, Clinically Significant; or Abnormal, Not Clinically Significant.

12.3.4.5. Physical Examination Findings

The number and percentage of patients with normal and abnormal findings in the complete physical examination will be displayed.

12.3.4.6. Local Tolerability

The number and percentage of patients with local tolerability findings, collected separately from AEs, will be summarized.

12.3.5. Interim Analysis

An interim analysis may be performed as appropriate to support a possible New Drug Application.

13. TRIAL CONDUCT

The accuracy and reliability of data is ensured, among others, by the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and associated personnel before the trial, periodic monitoring visits, and meticulous data management.

13.1. Sponsor and Investigator Responsibilities

13.1.1. Sponsor Responsibilities

The sponsor is obligated to conduct the trial in accordance with strict ethical principles (Section 15). The sponsor reserves the right to terminate participation of a trial site at any time (Section 13.7), and/or to discontinue the trial (Section 13.6 for US trials and Section 13.6.2 for trials conducted outside of the US).

The sponsor agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the trial according to the trial protocol.

13.1.2. Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.2), the investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the trial in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this trial in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the November 2016 ICH Guidance for Industry E6(R2) GCP, and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the trial to subinvestigators and trial coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the trial and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated

trial-related responsibilities (e.g., subinvestigators and trial coordinators) and their specific trial-related duties.

Investigators should ensure that all persons who have been delegated trial-related responsibilities are adequately qualified and trained in the protocol, trial drug handling, and their specific duties within the context of the trial. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the trial may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all trial documentation by authorized individuals.

13.2. Site Initiation

Trial personnel may not screen or enroll patients into the trial until after receiving notification from the sponsor or its designee that the trial can be initiated at the trial site. The trial site will not be authorized for trial initiation until:

1. The trial site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The trial site has a Clinical Trial Agreement in place.
4. Trial site personnel, including the investigator, have participated in a trial initiation meeting.

The regulatory documents must be received from the investigator before the sponsor will authorize shipment of trial drug to the trial site, Regulatory Green Light. Copies of the investigator's regulatory documents must be retained at the trial site in a secure location in the ISF. Additional documents, including a copy of the protocol and applicable amendment(s), the dasiglucagon IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and trial drug accountability records should also be retained in the ISF. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

13.3. Screen Failures

Only patients completing trials ZP4207-17103 or ZP4207-17109 are eligible for inclusion, upon confirmation of a positive benefit-risk balance for continued dasiglucagon treatment and meeting the inclusion/exclusion criteria. There is no Screening Period for entry into this trial.

13.4. Trial Documents

All documentation and material provided by the sponsor for this trial are to be retained in a secure location and treated as confidential material.

13.4.1. Investigator's Regulatory Documents

The regulatory documents will be maintained by the investigator in the ISF.

13.4.2. Case Report Forms

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the trial to ensure that the trial information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRF must be signed by the investigator or a subinvestigator when all data are entered and cleaned. These signatures serve to attest that the information contained in the eCRF is accurate and true.

13.4.3. Source Documents

Information recorded in the eCRF should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be entered into the eCRF at the site.

The investigator should permit trial-related monitoring, IEC review, regulatory inspections, and sponsor audit by providing direct access to source data and documents.

13.5. Data Quality Control

The sponsor and its designees will perform quality control checks on this clinical trial.

13.5.1. Monitoring Procedures

The sponsor and/or its designee will conduct site visits to monitor the trial and ensure (i) the safety and rights of the patients are respected, (ii) compliance with the protocol, GCP, and applicable regulations and guidelines and (iii) that accurate, valid, and complete data are collected. The assigned CRA(s) will visit the investigator and trial site at periodic intervals and maintain periodic communication; this is described in detail in the Monitoring Plan. The investigator agrees to allow the CRA(s) and other authorized sponsor personnel access to ISF and source data (original documents, data, and records). The CRA(s) will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the investigator and staff. While on site, the CRA(s) will review:

- regulatory documents
- entries in the EDC system compared with the source documents
- consents
- adherence to the inclusion/exclusion criteria

- AE records
- storage and accountability of trial drug and trial materials
- adherence to the protocol and ICH-GCP

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs are described in the Trial Reference Manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to meet with the CRA(s) during trial site visits; to ensure that trial staff is available to the CRA(s) as needed; to provide the CRA(s) access to all trial documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

13.5.2. Data Management

The sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and Premier standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the trial manual.A partial database lock is planned for interim analyses prior to NDA submission. Additional partial database locks may be performed for analyses to support the NDA process.

13.5.3. Quality Assurance/Audit

This trial will be subject to audit by the sponsor/its designee or national/international regulatory authorities. Audits may be performed to check compliance with GCP guidelines, and can include:

- Site audits
- Trial master file (TMF) audits
- Database audits
- Document audits (e.g., protocol and/or the clinical trial report [CTR])

The sponsor or its designee may conduct additional audits on a selection of trial sites, requiring access to patient notes, trial documentation, and facilities or laboratories used for the trial.

The trial site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify the sponsor immediately.

13.6. Trial Termination

The trial may be terminated at the sponsor's discretion at any time and for any reason.

13.6.1. Regular Trial Termination

The end of the trial period is defined as the time all patients have reached Trial Completion as described in Section 7.2. Monitoring of treatment-induced or treatment-boosted ADA-positive patients at Trial Completion will continue until the ADA levels return to baseline or until 2 years after end of the trial period, whichever occurs first. Trial Finalization is the time of finalization of all trial activities (LPLV). Within 90 days of the end of the clinical trial (Trial Finalization), the sponsor or its designee and/or the site will notify the IRBs and IECs and regulatory authorities on the regular termination of the trial by submitting the End of Trial Declaration, as required according to national laws and regulations as depicted in Figure 2.

13.6.2. Premature Trial Termination

The trial may be terminated prematurely for any reason and at any time by the sponsor, the IRBs/IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to terminate the trial prematurely is binding to all investigators at all trial sites.

Within 15 days of premature termination of a clinical trial, the sponsor or its designee and/or the site will notify the IRBs/IECs and regulatory authorities on the premature termination as required according to national laws and regulations. The sponsor or its designee must clearly explain the reasons for premature termination.

If the trial is terminated prematurely, all investigators must inform their patients and take care of their appropriate follow-up and further treatment to ensure protection of their interests. Trial sites may be asked to have all patients currently participating in the trial complete all of the assessments for an Early Termination Visit.

13.7. Trial Site Closure

At the end of the trial period, trial sites with no treatment-induced or treatment-boosted ADA-positive patients will be closed. Sites with treatment-induced or treatment-boosted ADA-positive patients will remain open until the ADA level of their last ADA-positive patient has returned to baseline or until 2 years after end of the trial period, whichever occurs first.

The sponsor may terminate participation of a trial site at any time. Examples of conditions that may require premature termination of a trial site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate patient enrollment

13.7.1. Record Retention

After trial finalization at sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the trial, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the trial drug has been approved or the sponsor has discontinued its research with the trial drug, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the trial drug

However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After trial finalization at sites in Europe, the sponsor will receive a copy of their data in electronic format (e.g., CD) and retain them for at least 25 years.

One copy will remain with the investigator. The investigator shall arrange for the retention of the patient identification codes, patient files, and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

The investigator shall keep copies of these trial records (and all trial-related documents, including source data) for the maximum period of time permitted by the hospital, institution, or private practice.

13.7.2. Sample Retention

Samples will only be used for purposes related to this trial.

All blood samples will be destroyed upon completion of the CTR, except for residual ADA samples, which will be stored until approval of market authorization because further characterization of the antibody response may be requested by the health authorities. Identifiable samples can be destroyed at any time at the request of the patient.

13.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB/IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the trial.

13.9. Use of Information and Publication

All information concerning dasiglucagon, the sponsor's operations, patent applications, formulae, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or its designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of trial execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this trial will be used by the sponsor in connection with the continued development of dasiglucagon and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this trial is the property of the sponsor. Publication or other public presentation of dasiglucagon data resulting from this trial requires prior review and written approval of the sponsor. Abstracts, manuscripts, and presentation materials should be provided to the sponsor for review and approval at least 30 days prior to the relevant submission deadline. Data from individual trial sites must not be published separately.

It is agreed that the results of the trial will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until the sponsor has reviewed and commented on such a presentation or manuscript for publication.

14. FINAL CLINICAL TRIAL REPORT

The sponsor will retain ownership of the data.

The final CTR will be reported on the trial period and will be prepared and reviewed in cooperation with the signatory investigator. The coordinating investigator will be appointed by the sponsor to review and sign the CTR on behalf of all participating investigators. This report will include a summary of the trial results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints. The results from the neutralizing antibody assay may be included or reported separately pending availability of the results. The results of the ADA follow-up samples will be reported separately after completion of the ADA Follow-up Period (Trial Finalization).

The final CTR may be submitted to the regulatory authorities.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki and Good Clinical Practice

This trial will be conducted in compliance with the November 2016 ICH Guidance for Industry E6(R2) GCP (including archiving of essential trial documents), the 2013 version of the Declaration of Helsinki, and the applicable regulations of the country(ies) in which the trial is conducted.

See Appendix C for regulation and guidelines.

15.2. Patient Information and Informed Consent

According to the Declaration of Helsinki and ICH GCP, patients' parent(s)/guardian must provide their written informed consent (and the child must provide assent, depending on local IRB/IEC requirements) prior to enrollment in a clinical trial and before any protocol-specified procedures are performed. Patients' parent(s)/guardian (and the patient, depending on local IRB/IEC requirements) must declare their consent by personally signing and dating the ICF.

France, Germany, Israel: *The consent must correspond to the patient's presumed will where such a will can be ascertained.*

The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each patient's parent(s)/guardian (and patient, depending on local IRB/IEC requirements) should be made aware by the investigator of the nature of the trial (objectives, methods, and potential hazards and benefits) and the procedures involved using the information on the ICF.

France, Germany, Israel: *Additionally, the patient will be informed about the nature, significance, risks, and implications of the trial with age-appropriate information, and his or her assent will be obtained in accordance with local regulations, as applicable.*

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Patients, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the trial.

Patient information and the ICF must be in a language fully comprehensible to the prospective patient's parent(s)/guardian (and patient, depending on local IRB/IEC requirements). The written information must be provided to the patient's parent(s)/guardian (and the patient, depending on local IRB/IEC requirements) to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent (and assent). The investigator must confirm that the text was understood by the patient's parent(s)/guardian (and patient where applicable). The patient's parent(s)/guardian (and patient, where applicable) will then sign and date the IRB/IEC-approved consent (and assent) form indicating that he or she has given his or her consent for his or her child to participate in the trial. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the trial patient number. Each signed ICF and assent must be kept on file by the investigator for possible inspection by regulatory authorities, the sponsor, and/or the sponsor's designee. Collection of informed consent has to be documented on the eCRF.

Furthermore, the patient's parent(s)/guardian will be informed that if he or she wishes to withdraw his or her child (see Section 8.3) at any time during the trial, this will not have any negative consequences. Patients may be withdrawn by the investigator if any change related to

safety or ethics precludes further participation in the trial. Patients' parent(s)/guardian (and patient, where applicable) will be asked to agree to a final assessment in the event of an early termination of the trial.

If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patients' parent(s)/guardian in a timely manner, and a revised written informed consent must be obtained.

Patients' parent(s)/guardian (and patient where applicable) will be informed that data from their child's case may be stored in a computer without inclusion of his or her name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

15.3. Approval by Institutional Review Board and Independent Ethics Committee

For Investigational New Drug studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB/IEC must review and approve this protocol before trial initiation. Written notification of approval is to be provided by the investigator to the sponsor's monitor and project manager before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor form, IRB/IEC Approval Form, or written documentation from the IRB/IEC containing the same information.

Until written approval by the IRB/IEC has been received by the investigator, no patient may undergo any procedure not part of routine care for the patient's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by the sponsor before implementation. This written approval will consist of a completed IRB Approval Form or written documentation from the IRB/IEC containing the same information.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCES

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17. ATTACHMENTS

17.1. Schedule of Events

Table 1 Schedule of Events

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

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

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

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

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

17.2. Investigator's Agreement

PROTOCOL NUMBER:	ZP4207-17106
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
FINAL PROTOCOL:	Version 21.0, 15-Jan-2025

The undersigned acknowledges possession of and has read the product information (e.g., IB) on the trial drug and has discussed these data with the trial monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the trial drug to selected patients in his/her care, according to the trial protocol.

- He or she agrees to use the trial material, including trial drug, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of the sponsor.
- He or she understands that any deviation from the protocol may lead to early termination of the trial.
- He or she agrees to report to the sponsor within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of trial drug.
- He or she agrees to comply with the sponsor and regulatory requirements for the monitoring and auditing of this trial.

In addition, he/she agrees that the trial will be carried out in accordance with the revised Declaration of Helsinki (2013) and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the trial.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

18. APPENDICES

A. Contact Information
B. List of Quality of Life Questionnaires
C. Regulations and Good Clinical Practice Guidelines
D. Seizure Checklist

A. Contact Information

Safety CRO:

Name:	[redacted]
Address:	[redacted]
	[redacted]
E-mail:	[redacted]
Telephone:	[redacted]

B. List of Quality of Life Questionnaires

- Infants 1-12 Months: "PedsQL™ Pediatric Quality of Life Inventory Infant Scales – Version 1 - Parent Report for Infants (ages 1-12 months)"
- Infants 13-24 Months: "PedsQL™ Pediatric Quality of Life Inventory Infant Scales – Version 1 - Parent Report for Infants (ages 13-24 months)"
- Parent Report for Teens 13-18 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Teens (ages 13-18 yrs)"
- Parent Report for Children 8-12 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Children (ages 8-12 yrs)"
- Parent Report for Children 5-7 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Young Children (ages 5-7 yrs)"
- Parent Report for Toddlers 2-4 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Toddlers (ages 2-4 yrs)"
- CHI Disease-Specific Questionnaire Developed by the Patient Association, Congenital Hyperinsulinism International, and Taken from the Patient-Reported Registry, the HI Global Registry

C. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives [and applicable regulations/guidances]:

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
https://www.ich.org/page/efficacy-guidelines

D. Seizure Checklist

At site visits and during monthly telephone contacts, the investigator should ask the patient and their caregiver(s), about any possible signs and symptoms of seizures. The below listed symptoms should be reviewed during the interview:

- Staring episodes
- Temporary confusion
- Not responding to noise or words for brief periods
- Appearing confused or in a daze
- Nodding the head rhythmically, when associated with loss of awareness or even loss of consciousness
- Periods of rapid eye blinking, jerky eye movements, or forced eye deviation.
- Jerking movements of the arms and legs (myoclonus or clonic movements)
- Stiffening of the body (entire body or one arm/leg)
- Loss of consciousness or awareness, fainting
- Falling suddenly for no apparent reason, especially when associated with loss of consciousness
- Breathing problems (abnormal breathing pattern or interruption of breathing)
- Loss of bowel or bladder control
- Auditory/visual aura (episodic hallucinations or distortions of perception
- Myoclonus
- Automatism
- Biting of tongue

An episode of partial or generalized seizure should be reported as an AESI, as described in Section 11.1.8.

Any single signs or symptoms observed by the patient/caregiver(s) and evaluated by the investigator to not be a seizure should be reported as an AE(s).

PROTOCOL

PRODUCT NAME/NUMBER:	Dasiglucagon
PROTOCOL NUMBER:	ZP4207-17106
IND NUMBER:	135869
EUDRACT NUMBER:	2017-004546-15
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
PROTOCOL DATE:	Original Protocol Version 1.0, 14-Dec-2017 Amended protocol final version 19.0 (All countries except Germany and UK), 08-Nov-2024
SPONSORED BY:	Zealand Pharma A/S Sydmarken 11 2860 Soeborg (Copenhagen) Denmark Telephone: +45 88 77 36 00
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive Suite 150 Durham, NC 27709 USA

REVISION HISTORY

PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
PROTOCOL DATE:	Original Protocol Version 1.0, 14-Dec-2017
	This updated global protocol version 19.0 includes:
AMENDMENT No. 1	Final Version 2.0, 31-May-2018 (All countries)
AMENDMENT No. 2	Final Version 3.0, 24-Jul-2018 (United Kingdom)
AMENDMENT No. 3	Final Version 4.0, 25-Jul-2019 (France, Germany, Israel)
AMENDMENT No. 4	Final Version 5.0, 03-Jun-2019 (Germany)
AMENDMENT No. 5	Final Version 6.0, 03-Jun-2019 (All countries)
AMENDMENT No. 7	Final Version 8.0, 11-Oct-2019 (All countries except Germany)
AMENDMENT No. 8	Final Version 9.0, 29-Jan-2020 (Germany)
AMENDMENT No. 9	Final Version 10.0, 01-Oct-2021 (All countries except Germany)
AMENDMENT No. 10	Final Version 11.0, 11-Oct-2021 (Germany)
AMENDMENT No. 11	Final Version 12.0, 28-Sep-2022 (All countries except Germany)
AMENDMENT No. 12	Final Version 13.0, 28-Sep-2022 (Germany)
AMENDMENT No. 13	Final Version 14.0, 22-May-2023 (All countries except Germany)
AMENDMENT No. 14	Final Version 16.0, 09-Apr-2024 (All countries except Germany)
AMENDMENT No. 15	Final Version 17.0, 09-Apr-2024 (Germany)
AMENDMENT No. 16	Final Version 18.0, 02-Sep-2024 (UK)

1. APPROVAL SIGNATURES

PROTOCOL NUMBER:	ZP4207-17106
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the trial.

[redacted]

Senior Clinical Trial Manager
Zealand Pharma A/S

[redacted]

Senior Medical Director
Zealand Pharma A/S

[redacted]

Senior Biostatistician
Premier Research

2. SYNOPSIS

PRODUCT NAME/NUMBER	Dasiglucagon
PROTOCOL NUMBER	ZP4207-17106
EUDRACT NUMBER	2017-004546-15
DEVELOPMENT PHASE	Phase 3
PROTOCOL TITLE	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
INDICATION	Congenital hyperinsulinism (CHI)
OBJECTIVES	Primary: To evaluate the long-term safety of dasiglucagon administered as subcutaneous (SC) infusion in children with CHI Secondary: • To evaluate the long-term efficacy of dasiglucagon in reducing hypoglycemia • To evaluate the long-term efficacy of dasiglucagon in reducing glucose requirements • To evaluate the long-term tolerability of dasiglucagon administered as SC infusion in children with CHI • To investigate quality of life and resource utilization
TRIAL DESIGN	This is an open-label, multinational, multicenter, long-term safety and efficacy extension trial in patients with CHI who completed either ZP4207-17103 or ZP4207-17109 (defined as a lead-in trial). The investigator is allowed to change the standard of care (SOC) medication for CHI at his or her discretion in order to optimize the treatment of each patient. To use a minimally invasive yet objective method of assessing the frequency of hypoglycemia, patients will be required to wear a continuous glucose monitoring (CGM) device throughout the entire trial period. Pauses are allowed; however, CGM should be used for the 30 days leading up to each visit, and families will also be asked to perform self-monitored plasma glucose (SMPG). Parent(s)/guardian will be trained on the use of the meters. The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial. Any post-treatment follow-up scheduled for patients in the lead-in trial will be redundant if they are enrolled in the present trial by the time of the scheduled Follow-up Visit. Patients will be seen at Months 1, 3, and 6 and every 3 months thereafter and contacted by the investigator monthly by telephone in between site visits. At site visits, patients and their parent(s)/guardian will receive a paper diary to record potential adverse events (AEs) and concomitant medication, among other information, which will be reviewed regularly by site staff at each visit. Patients will be allowed to remain in the trial until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP) or until approximately Q3 2024 (treatment period), whichever occurs first. An interim analysis may be performed as appropriate to support a marketing application/ new drug application.
PLANNED NUMBER OF PATIENTS	A maximum of 44 patients are expected to be enrolled in the lead-in trials, and approximately 30-44 of those patients are expected to be enrolled in this trial.

TRIAL ENTRY CRITERIA	Eligible patients are those who have completed treatment in either trial ZP4207-17103 or ZP4207-17109 and are expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon, with an investigator statement documenting the positive benefit-risk assessment (based on considerations of glycemic effect, tolerability, and nature and frequency of AEs experienced in the lead-in trial).
INVESTIGATIONAL PRODUCT	Dasiglucagon injection 4 mg/mL in a 3 mL vial containing 1 mL
REFERENCE PRODUCT	None
TREATMENT REGIMENS	Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with an option to further titrate the dose to meet the needs of each patient. During the trial, SMPG assessments will be performed as instructed by the investigator. For patients using the Dexcom G5 CGM, SMPG assessments will at least be performed 2 times per day for CGM calibration. Patients will continue their SOC treatment for CHI. The combined treatment of SOC and dasiglucagon should aim to reduce gastric dextrose infusions and glucose fortified meals as much as possible, maintaining the patient's plasma glucose within 70 and 120 mg/dL at all times on normal feedings.
PLANNED TRIAL SITES	Up to 14 sites in the United States, Europe, and Israel with all sites having been involved in the lead-in trials.
CRITERIA FOR EVALUATION	Primary endpoint: • AEs Key secondary efficacy endpoints: • Total amount of gastric carbohydrates administered (nasogastric [NG] tube or gastrostomy) to treat hypoglycemia • Time to removal of NG tube or gastrostomy • Time to pancreatic surgery (sub-total or total pancreatectomy) • CGM percent time <70 mg/dL (3.9 mmol/L) • Rate of CGM-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more • Rate of clinically significant CGM-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more The primary endpoint will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and then in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis. All efficacy endpoints will be analyzed using average weekly results over Month 1, Month 1 to Month 3 and then each 3-month period between visits.
STATISTICAL METHODS	Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively; the exception to this is the time of plasma glucose (PG) within pre-specified ranges, which will not have a baseline value. For categorical endpoints, descriptive summaries will include counts and percentages. All data will be presented in the data listings.

	Analysis Populations Three analysis populations have been defined for this trial: The Safety Set: defined as all patients administered any trial drug. This population will be used to provide descriptive summaries of safety data. The Full Analysis Set (FAS): defined as all patients in the Safety Set who complete at least 1 day of trial drug. This population will be used to analyze efficacy data. The Pharmacokinetic Analysis Set (PK): defined as all patients in the Safety Set who have at least one measurement with quantifiable plasma concentration of dasiglucagon. This population will be used to provide descriptive summaries of PK data. Primary Analysis For the primary endpoint, the number of AEs will be summarized by time period (up to Month 1, Month 1 to Month 3, Month 3 to Month 6, Month 6 to Month 9, Month 9 to Month 12, etc.). Efficacy Analyses For the first and fourth key secondary endpoints, total amount of carbohydrates administered to treat hypoglycemia and CGM percent time <70 mg/dL, respectively, will be analyzed using a mixed-model for repeated measures using restricted maximum likelihood (REML). Time to event data will be analyzed using Kaplan-Meier methods. For the two last key secondary endpoints, the rate of CGM-detected hypoglycemic episodes, will be analyzed using a generalized linear mixed-model (GLMM) regression approach assuming a negative binomial distribution. For all other efficacy endpoints, continuous and categorical endpoints will be presented using summary statistics or frequencies, respectively. If warranted, continuous measures will be analyzed using a paired t-test or mixed model with region as a fixed effect and baseline value as a covariate; categorical measures will be analyzed using a Chi-square goodness-of-fit test or binomial test for proportions, as data permit, to determine whether there is a difference from the previous time point. An interim analysis will be performed as appropriate to support the application for approval of dasiglucagon. Safety Analyses Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with an onset at the time of or following the start of treatment with the trial drug through the Follow-up Visit or Early Termination Visit, whichever occurs first, and no longer than 12 weeks after treatment discontinuation will be defined as treatment emergent. The overall incidence of AEs will be displayed by system organ class, preferred term, and treatment. The incidence of AEs will also be presented by severity and by relationship to the trial drug. Vital signs, clinical laboratory measures (including hematology, biochemistry, and incidence of anti-drug antibodies [ADAs]), ECGs, physical examinations, and local tolerability data will be summarized by treatment, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. A formal statistical analysis plan (SAP) will be prepared to provide further details on the methods for statistical analysis.
SAMPLE SIZE DETERMINATION	The sample size is based upon patients rolling over from the lead-in trials; no sample size calculation was performed.

TRIAL AND TREATMENT DURATION	The sequence and maximum duration of the trial periods will be as follows: **Trial Period (from last visit in lead-in trial until Trial Completion, as defined below):** 1. Baseline: defined as the End of Treatment (EoT) Visit from lead-in trials ZP4207-17103 or ZP4207-17109. 2. Treatment Period: treatment will continue until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP), or until approximately Q3 2024, whichever occurs first, at which time an EoT Visit will be scheduled. 3. EoT Visit: see above. 4. Follow-up Visits: will occur at 4 weeks and 12 weeks after the EoT Visit. 5. Trial Completion: completion of the final Follow-up Visit or the EoT Visit if the patient continues treatment with dasiglucagon commercially or through an EAP. **ADA Follow-up Period (from Trial Completion until last patient's last visit [LPLV]):** 6. Monitoring of treatment-induced or treatment-boosted ADA-positive patients: monitoring of ADA-positive patients will continue until the ADA levels return to baseline (defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial) or until 2 years after End of Trial, whichever occurs first. **End of Trial:** defined as the time all patients have reached Trial Completion (completed the Follow-up Period, or the EoT Visit if continuing treatment with dasiglucagon commercially or through an EAP, whichever occurs first). **LPLV:** last visit of the last patient in the ADA Follow-up Period

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4. LIST OF ABBREVIATIONS

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
$AOC_{glucose}$	area over the glucose curve
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time zero to infinity
CE	Conformité Européene
CGM	continuous glucose monitoring
CHI	congenital hyperinsulinism
C_{max}	maximum concentration
CRA	clinical research associate
CRO	contract research organization
CTR	clinical trial report
DMC	data monitoring committee
EAP	early access program
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ER/A&E	emergency room/accident & emergency department
EoT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GI	gastrointestinal
GLMM	generalized linear mixed-model
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
IB	investigator's brochure
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IM	intramuscular(ly)
IRB	institutional review board
ISF	Investigator Site File
IV	intravenous(ly)
LAR	legally authorized representative
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	necrolytic migratory erythema
NG	nasogastric
NME	necrolytic migratory erythema
PD	pharmacodynamics(s)
PedsQL	Pediatric Quality of Life Inventory
PG	plasma glucose
PK	pharmacokinetic(s)
PT	preferred term
QoL	quality of life
RBC	red blood cell
REML	restricted maximum likelihood
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SMPG	self-monitored plasma glucose
SOC	standard of care
SpO_2	blood oxygen saturation level
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
TMM	trial materials manual
ULN	upper limit of normal

Zealand	Zealand Pharma A/S

5. INTRODUCTION

5.1. Background and Rationale

Congenital hyperinsulinism (CHI) is a rare and challenging disorder in which β-cells in the pancreas secrete insulin irrespective of plasma glucose (PG) concentration, resulting in persistent and often severe hypoglycemia.[1] Congenital hyperinsulinism affects up to 1 in 50,000 newborns. It is typically diagnosed on the basis of signs and symptoms of hypoglycemia during the neonatal period or in infancy; however, the diagnosis may be made later in childhood. Several different genetic mutations have been described to cause CHI, which can be either focal (only a small area of the pancreas is affected) or diffuse (most of the pancreas is affected). The condition can persist into adulthood; however, the severity generally decreases with age due to the increased insulin requirements and/or reduced insulin resistance, and CHI is thus primarily a pediatric disease with regard to medical treatment needs. Hypoglycemia that results from CHI is of particular concern because it is an important cause of brain injury in neonates, infants, and children with this disease, which leads to long-term neurological impairments.[1,2] Up to approximately 50% of children with CHI experience neurodevelopmental abnormalities caused by severe hypoglycemia that results from inadequate treatment and/or delays in diagnosis.[1,3] Severe brain damage is the consequence of severe hypoglycemia, which presents as coma and/or long-lasting epileptic seizures in neonates. Major intellectual disability is, therefore, most frequent in neonatal patients with initial onset, whereas hypoglycemia is usually less severe and brain damage less frequent in children with CHI diagnosed later in childhood.[1] Since symptoms and severity of hypoglycemia can vary and pose a diagnostic challenge in neonates, infants, and children with CHI, prompt recognition and treatment of hypoglycemia is critical to reduce the risk of long-term neurological consequences.

5.2. Current Treatment and Unmet Medical Need

Medical treatment for CHI is focused on chronic therapies to avoid hypoglycemia, as well as on rescue therapy during acute episodes of severe hypoglycemia. Available medical therapies (mainly diazoxide/octreotide/glucagon for reconstitution alone or in combination with glucose infusion) are inadequate and accompanied by inability to control plasma glucose, as reflected in a large proportion of patients requiring sub-total pancreatectomy.[4,5,6] With the exception of surgery for focal CHI, which is curative in the vast majority of patients, sub-total pancreatectomy for diffuse CHI has substantial inadequacies. A recent trial[7] showed that 60% of patients who underwent near-total pancreatectomy had persistent hypoglycemia after surgery. Moreover, 96% had developed insulin-dependent diabetes within 11 years after surgery, indicating the serious and long-term consequences of the procedure.

First-line medical treatment is diazoxide, which is the only EU- and US-approved drug for treatment of hyperinsulinemic hypoglycemia. Diazoxide acts to open K_{ATP} channels of the pancreatic β-cells, thereby inhibiting insulin secretion. Unfortunately, many patients with CHI are resistant to diazoxide because of mutations in the genes encoding the K_{ATP} channel of the pancreatic β-cells.[6] For those who respond to diazoxide treatment, the more common side effects comprise hypertrichosis, fluid retention, and gastrointestinal (GI) symptoms; however, side effects are usually not severe. In diazoxide non-responders, second-line (and off-label) treatment is a somatostatin analog (octreotide or lanreotide [long acting]), which (among other effects) inhibits secretion of insulin and glucagon from the pancreas and suppresses glucagon-like

peptide-1 (GLP-1) secretion. Factors that limit their use comprise tachyphylaxis, as well as possible side effects, including necrotizing enterocolitis, gallstones, and hepatitis.[6]

Glucagon has been shown to be effective in the treatment of CHI. The glycogenolytic effect of glucagon and its ability to increase plasma glucose levels has been confirmed in children with CHI or neonatal hypoglycemia,[8,9] and administration of reconstituted glucagon (via intravenous [IV] infusion or as repeated subcutaneous [SC] injection) is often used in the initial phase during the establishment of CHI diagnosis and to stabilize patients with CHI before surgery or initiation of other medical treatments.[10] Furthermore, glucagon is administered as single SC doses to treat severe hypoglycemic episodes. While IV administration of glucagon to patients with CHI is used short-term in the hospital setting, e.g., before pancreatectomy,[2,10,11] long-term glucagon treatment is complicated by the fact that currently available glucagon products are unstable in nature and form fibrils within hours after reconstitution.[12] This fibril formation may lead to infusion set clotting, catheter obstruction, and dosing errors that may cause acute severe hypoglycemia. Catheter obstruction and occlusion because of glucagon fibril formation and aggregation were observed daily to 2 to 3 times weekly in a retrospective review of 9 patients with CHI receiving continuous SC infusion of glucagon for weeks or months.[11] In another series of patients, 60% of the patients treated with SC glucagon experienced catheter occlusion.[6] In a home-care setting, this fibril formation and associated risk of dosing errors carry the risk of hypoglycemic events, which is a major barrier for using currently marketed glucagon products for long-term treatment of patients with CHI.

With respect to long-term glucagon treatment in CHI, there are a few reports on home treatment with subcutaneously infused glucagon in children with CHI over extended periods (years) that suggest benefit in patient care with a potentially good safety profile as compared to diazoxide and octreotide.[6,11,13] While this attests to the potential clinical relevance of long-term glucagon treatment in CHI, the use of SC infusion of currently marketed glucagon is severely limited by the issues with fibril formation and solution instability of recombinant glucagon as described previously.

5.3. Dasiglucagon for the Treatment of Congenital Hyperinsulinism

5.3.1. Dasiglucagon

Dasiglucagon is a peptide analog of human glucagon that has been developed for the treatment and prevention of hypoglycemia in patients with diabetes mellitus via SC or IV administration. Dasiglucagon is under development for prevention and treatment of hypoglycemia in children with CHI and for the following other indications: Improving glycemic control in insulin-treated patients with type 1 diabetes mellitus, as part of a bihormonal artificial pancreas system, treatment of post-bariatric hypoglycemia and glycemic control during exercise and physical activity in patients with diabetes.

Dasiglucagon is a stable analog of glucagon that has been specifically designed to overcome the issues with fibril formation and instability in solution observed with marketed glucagon products. Compared to glucagon, dasiglucagon also comprises 29 amino acids. As a result of chemical modifications (7 amino acid substitutions compared to human glucagon), the pronounced tendency of glucagon to form fibrils and aggregate has been effectively prevented in dasiglucagon. In addition, the chemical stability in aqueous media at physiological pH has been improved.

To support the use of dasiglucagon in the pump, compatibility/in-use studies have been performed with dasiglucagon 4 mg/mL in the Hoffman-La Roche Accu-Chek Combo infusion pump using the Accu-Chek Spirit 3.15 mL cartridge system and the Accu-Chek Flexlink infusion set. The studies support an in-use time for up to 6 days at 37ºC.

Dasiglucagon was granted orphan drug designation by the European Commission on 20 June 2017 for the '*treatment of congenital hyperinsulinism.*' Furthermore, the Food and Drug Administration (FDA) granted an orphan drug designation for the '*treatment of hypoglycemia in patients with congenital hyperinsulinism (CHI)*' on 10 August 2017.

5.3.2. Nonclinical Experience

The completed nonclinical pharmacology program has determined that dasiglucagon is a specific glucagon receptor agonist with comparable in vitro potency to glucagon, promoting a rapid onset of PG increase in both normal and insulin-induced hypoglycemic animals, similar to that of glucagon. The effects of dasiglucagon and glucagon were investigated in an insulin-induced hypoglycemic rat model, which is considered particularly relevant to characterize the use of dasiglucagon for the treatment of CHI because it mimics the inappropriate insulin to PG levels in CHI and resultant hypoglycemia. The onset of PG increase with dasiglucagon was rapid and similar to that observed for glucagon, confirming comparable pharmacodynamics.

Results of the toxicity studies with dasiglucagon are comparable to what has been reported for glucagon. Those from chronic toxicity studies with dasiglucagon in rats and dogs are in line with the results of short-term toxicity studies, indicating that long-term treatment with dasiglucagon is safe and that the pharmacodynamic (PD) effects noted do not adversely affect organ function following chronic use.

5.3.3. Clinical Experience

Dasiglucagon is being developed to manage patients with CHI 1) as an initial short-term therapy to stabilize PG levels and reduce glucose infusion needs, and 2) as a long-term treatment to help maintain euglycemia.

Within the indication of prevention and treatment of hypoglycemia in children with CHI, efficacy and safety results are available from two completed trials.

Efficacy

Phase 2/3, two-period efficacy and safety trial ZP4207-17103

In this trial, 12 CHI patients (aged 7 days to 12 months) who needed continuous IV glucose administration to manage hypoglycemia completed a randomized clinical trial that consisted of a double-blind placebo-controlled crossover Part 1 followed by an open-label Part 2. Dosing of dasiglucagon approximated continuous SC infusion by delivering small doses at frequent intervals via an infusion pump according to a predefined algorithm. The focus in this trial was on the clinically relevant reduction and eventually elimination of the need for continuous IV glucose infusion, while avoiding hypoglycemia.

Compared to placebo, a statistically significant reduction in mean IV glucose infusion rate was obtained during the last 12 hours after dasiglucagon treatment (treatment difference

[95% CI]: -5.21 mg/kg/min [-8.29 to -2.13], p = 0.0037). This corresponded to a 55% reduction of weighted mean IV glucose infusion rate compared to placebo.

The total amount (g) of carbohydrates administered (regardless of the route) per day during Part 1 of the trial was statistically significantly lower after dasiglucagon treatment compared with placebo (treatment difference [95% CI]: -30.93 g/day [-56.80 to -5.05], p = 0.0238).

Phase 3, two-period efficacy and safety trial ZP4207-17109

In this phase 3 trial in 32 CHI patients aged 3 months to 12 years, dasiglucagon treatment added to standard of care (SOC) did not significantly reduce the number of intermittent SMPG-measured hypoglycemia events per week when compared to SOC alone (primary endpoint).

CGM metrics are not validated for use in patients with CHI. However, a post hoc analysis showed that dasiglucagon treatment resulted in clinically meaningful reductions in all measures of hypoglycemia assessed by blinded CGM (including number of events and time in hypoglycemia) compared to SOC treatment alone.

Safety

Phase 2/3, two-period efficacy and safety trial ZP4207-17103

A total of 12 patients aged from ≥7 days to <12 months were exposed to dasiglucagon in trial ZP4207-17103. The total duration of dasiglucagon exposure was 0.67 patient-years. Two SAEs (respiratory distress and acute respiratory failure) in the same patient were reported; both events were reported in the open-label period (where patients received dasiglucagon), and none were considered related to treatment with dasiglucagon.

Adverse events, other safety parameters, and immunogenicity

The most frequently reported AEs with dasiglucagon during Part 1 + Part 2 of the trial were anemia, vomiting, and rash papular (each reported by 3 patients). None of these AEs were reported more frequently with dasiglucagon as compared to placebo during the cross-over period (Part 1).

No confirmed cases of necrolytic migratory erythema (NME) were reported. Two hemodynamic events were reported: 2 AEs of tachycardia (1 during placebo and 1 during dasiglucagon treatment), which were both mild, intermittent, and not related to trial treatment.

No remarkable abnormalities were found in the biochemistry, hematology, vital signs, electrocardiogram (ECG), echocardiography, and physical and neurological exams. A few cases of clinically significant changes in hemoglobin, electrolytes, ALT, and AST were noted. None indicated any trends in aggregated change from baseline.

Local tolerability reactions, assessed only for patients in dasiglucagon + standard of care group, were mostly mild and attributed to the adhesive dressing. None of the local reactions were severe, and none were attributed to the trial intervention.

None of the children were tested positive for treatment-boosted or treatment-induced ADA (10 out of 12 children were tested for ADA at baseline and 8 were tested during trial).

Phase 3, two-period efficacy and safety trial ZP4207-17109

A total of 32 patients ages ≥3 months to ≤12 years were randomized and exposed to dasiglucagon in the completed ZP4207-17109 trial; total duration of dasiglucagon exposure was 3.8 patient-years. Overall, dasiglucagon treatment appeared well-tolerated in the trial. A total of 5 SAEs in 3 patients were reported in the dasiglucagon plus SOC group (central line infection, localized infection, folliculitis, influenza H1N1, and hyperglycemia); none of these were considered related to dasiglucagon treatment.

Adverse events, other safety parameters, and immunogenicity

In trial ZP4207-17109, vomiting was reported more frequently in the dasiglucagon treatment group as compared with those receiving SOC treatment, consistent with these gastrointestinal events being well-known side effects of glucagon treatment. More cases of skin and subcutaneous tissue disorders (including two confirmed events of necrolytic migratory erythema NME) were reported for dasiglucagon relative to SOC treatment, but no skin-related events led to discontinuation of dosing. Also, a minor imbalance of events was noted within the system organ class of infections and infestations during the initial 4-week trial period (12 with dasiglucagon versus 4 with SOC only).

No remarkable abnormalities were found in the biochemistry, hematology, vital signs, ECG, echocardiography, or physical and neurological examinations. A few cases of transient increases in ALT and AST were noted for dasiglucagon; of those reported as AEs, all were assessed as not/unlikely related to the trial product. No hemodynamic events were reported.

With respect to dasiglucagon antibody development, 7 out of 30 children (23.3%) with ADA assessments were ADA-positive during the trial (1 with treatment-boosted and 6 with treatment-induced ADA). Of these 7 children, 1 (14.3%) had cross-reactivity to glucagon and another (14.3%) had dasiglucagon in vitro neutralizing antibodies at the follow-up visit. In vitro neutralizing antibodies were not detected for the remaining 5 children with treatment-induced ADA.

QT prolongation

A comprehensive evaluation of the effect of dasiglucagon on cardiac repolarization and its proarrhythmic potential has been made based on 1) nonclinical data, 2) data from trial ZP4207-17144 in healthy subjects, in which potential ECG effects were evaluated through serial ECG monitoring and concentration-QTc analysis, and 3) data from phase 2/3 clinical trials to support the indication of treatment of severe hypoglycemia. It is concluded that there is no indication of dasiglucagon exerting a clinically relevant effect on QTcF interval or having a proarrhythmic potential.

The above conclusion is supported by the data from the completed CHI trials.

5.3.4. Literature Data

In a retrospective review of 223 cases of diffuse or focal CHI, glucagon was reported to be used in 55% of patients with diffuse CHI and in 31% of patients with focal CHI.[10] In an observational trial of 55 newborns who received glucagon because of hypoglycemia after birth, applied doses were mainly in the range of 0.5 to 1.0 mg/day, and results indicated an increase in PG from a mean of 36.3 md/dL to a mean of 93.0 mg/dL, observed within 4 hours after the start of glucagon

infusion.[9] The frequency of hypoglycemic episodes was significantly reduced, and no further episodes of severe hypoglycemia were observed.

The long-term use of glucagon in patients with CHI is limited by the instability of marketed glucagon after reconstitution. A literature review on the long-term medical treatment of CHI revealed that only 1% of 619 patients identified received glucagon as part of their medical management.[6] A retrospective review of 9 children with CHI who received continuous SC infusion of glucagon for weeks or months showed that introduction of glucagon allowed the reduction or discontinuation of central glucose infusion in all patients.[11] Six of 9 patients were discharged with continued glucagon therapy that their parents were able to continue without further symptomatic hypoglycemia, convulsions, or unconsciousness. In 3 children, glucagon therapy was continued for 1 to 4 years, which led to stable euglycemia.

The data reported on marketed glucagon use in patients with CHI indicate that continuous SC infusion of a glucagon agonist could provide therapeutic benefit to patients by stabilizing PG levels and reducing the frequency of hypoglycemic episodes.[5,6,9,10,11]

5.3.5. Anticipated Medical Benefit of Dasiglucagon in the Treatment of Congenital Hyperinsulinism

With its physio-chemical stability in liquid formulation, dasiglucagon could provide significant added benefit in the treatment of CHI relative to currently marketed glucagon by enabling long-term reliable IV infusion to control blood glucose. Long-term subcutaneous infusion of dasiglucagon through a pump may be an attractive alternative or addition to diazoxide and octreotide, as it may reduce the dependency on intensive nutritional support whilst maintaining euglycemia by harnessing physiological mechanisms for combating hypoglycemia. It is anticipated that reduced need for frequent tube feedings or continuous gastric infusion of nutrients, and increased fasting tolerance will be demonstrated, together with improvements in the quality of life of the patients and their families/guardians. If long-term euglycemia is achieved with medical therapy, pancreatectomy for the treatment of diffuse CHI could eventually be avoided, or at least postponed beyond the neonatal or very young infant period. In 1 cohort of non-surgically treated children, the mean clinical remission rate was 5 (1.5-12) years for diffuse CHI.[5] This suggests that a significant proportion of infants with CHI could avoid surgery if medical treatment allowed for the effective long-term control of hyperinsulinism.

5.3.6. Anticipated Risks of Dasiglucagon in the Treatment of CHI

Overall, in the two completed trials, the most commonly reported types of AEs in patients with CHI were skin disorders (various rashes and eczema), gastrointestinal disorders (including vomiting), and infections.

Glucagon exerts positive inotropic and chronotropic effects and may, therefore, cause tachycardia and hypertension. Across completed trials supporting the CHI indication, one event of tachycardia was reported with dasiglucagon, and one with placebo. Both events were mild and transient and considered not related to trial treatment.

Accidental overdose may occur due to inappropriate handling of the infusion pump or due to pump malfunction. Overdose may result in nausea, vomiting, inhibition of GI tract motility, short-term increase in heart rate or blood pressure, and/or hypokalemia. Symptomatic care for

nausea and vomiting, as well as monitoring of heart rate, blood pressure, and hypokalemia, is advised.

Administration site reactions are seen with many injectable peptides. Administration site reactions occurred sporadically in completed trials supporting pump use, as well as in a previously published trial with marketed glucagon delivered by pump. For the CHI indication, local tolerability reactions were mostly mild and attributed to the adhesive dressing. None of the local reactions were severe.

As with all therapeutic peptides and proteins, there is an inherent risk for the induction of an ADA response against dasiglucagon. In the completed CHI trials, no ADA formation was observed in trial ZP4207-17103; in ZP4207-17109 23.3% of the patients developed ADA. The impact of ADA on safety or efficacy of dasiglucagon treatment in children with CHI remains to be established.

Administration of glucagon or dasiglucagon may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins.

From sporadic reports of extended SC/IV infusion of marketed glucagon and in glucagonoma patients,[14] sustained exposure to high levels of glucagon may lead to development of skin condition necrolytic migratory erythema (NME), a highly specific migrating, erythematous rash with predilection for perioral, perianal, and lower leg distribution.[11] In the ZP4207-17109 trial, two confirmed events of NME were reported for dasiglucagon relative to SOC treatment, but no skin-related events led to discontinuation of dosing. No confirmed cases of NME were reported in the ZP4207-17103 trial.

For further information on risks, please refer to the current version of the investigator's brochure (IB).

5.3.7. Summary of Potential Benefits and Risks

As with all treatment interventions, the anticipated benefits to trial patients should be balanced against the potential risks. The accumulated experience from nonclinical studies and clinical trials with dasiglucagon supports that dasiglucagon is a specific glucagon receptor agonist and is well tolerated. Glucagon and its analogs belong to a well-known drug class with known mode of action. The clinical investigators involved in the trial will all have had experience with use of glucagon in patients with CHI.

The investigator will inform the patients/parent(s)/guardian of the potential risks of dasiglucagon treatment and other trial-related procedures before they enter the trial. The investigator must become familiar with all sections of the dasiglucagon IB before the start of the trial.

In summary, with its marked improvements in stability in solution and solubility in aqueous media compared to currently marketed glucagon products, dasiglucagon is expected to have significant clinical benefits in the treatment of CHI and to substantially reduce the disease burden in these patients. This includes enabling convenient and reliable long-term treatment via a pump device in a home setting, which holds the potential to delay and ultimately avoid pancreatectomy and its related exo/endocrine complications, particularly the development of insulin-dependent diabetes.

Dasiglucagon may overall provide significant added benefit in the treatment of CHI relative to currently marketed glucagon products by enabling long-term reliable SC infusion to control PG.

The proposed trial population is still experiencing hypoglycemia despite medical treatments being escalated to the highest therapeutically permissible or tolerated doses, or despite having undergone subtotal pancreatectomy. Therefore, these patients are dependent on continuous or very frequent delivery of carbohydrates, often through invasive routes (NG tube or gastrostomy). This limits their ability to lead normal lives, including participating in everyday activities, and therefore, impacts their development. For this trial population, the major and clinically relevant benefit is the expected reduction in number and volume of nutritional interventions while avoiding hypoglycemia. The reduced volume of nutritional interventions should limit the risk of volume overload, especially in patients treated with significant doses of diazoxide. Achievement of euglycemia could lead to reduction of other CHI medication, further limiting the potential for adverse events associated with those treatments. In addition, the need for pancreatectomy, or re-surgery in those who already underwent pancreatic surgery is reduced and potentially eliminated.

Overall, the benefit to risk ratio for patients entering the ZP4207-17106 trial is considered acceptable.

6. OBJECTIVES

6.1. Objectives

6.1.1. Primary Objective

To evaluate the long-term safety of dasiglucagon administered as SC infusion in children with CHI.

6.1.2. Secondary Objectives

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

6.2. Endpoints

The primary endpoint will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and then in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis. All efficacy endpoints will be analyzed using average weekly results over Month 1, Month 1 to Month 3 and then the 3-month period between visits.

6.2.1. Primary Endpoint

- Adverse events

6.2.2. Key Secondary Efficacy Endpoints

- Total amount of gastric carbohydrates administered (nasogastric [NG] tube or gastrostomy) to treat hypoglycemia
- Time to removal of NG tube or gastrostomy

- Time to pancreatic surgery (sub-total or total pancreatectomy)
- Continuous glucose monitoring (CGM) percent time <70 mg/dL (3.9 mmol/L)
- Rate of CGM-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more
- Rate of clinically significant CGM-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more

6.2.3. Secondary Efficacy Endpoints

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

6.2.4. Other Efficacy Endpoints

- CGM percent time in range 70-180 mg/dL (3.9-10.0 mmol/L)
- CGM percent time >180 mg/dL (10 mmol/L)
- CGM percent time <54 mg/dL (3.0 mmol/L)
- Number of parent reported hypoglycemic events pr. week that required an intervention AND with PG <70 mg/dL (3.9 mmol/L) as detected by self-monitored plasma glucose (SMPG) or CGM
- Number of SMPG-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) per week based on SMPG measurements as captured in patient device
- Number of clinically significant SMPG-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) per week based on SMPG measurements as captured in patient device
- Number of emergency department visits for hypoglycemia
- Number and length of hospitalizations caused by CHI or CHI-related events
- Number of outpatient visits to health care providers (family doctors, specialist, etc.) caused by CHI or CHI-related events

- Number of home visits by paramedics due to hypoglycemia
- Quality-of-life (Pediatric Quality of Life Inventory [PedsQL™][Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score] and CHI-specific questionnaire)

6.2.5. Other Safety Endpoints

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

7. TRIAL DESIGN

7.1. Overall Trial Design and Plan

This is a phase 3, open-label, multinational, multicenter, long-term safety and efficacy extension trial in patients with CHI who completed either ZP4207-17103 or ZP4207-17109 (defined as a lead-in trial). To qualify for participation, patients are expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon due to CHI, with an investigator statement documenting the positive benefit-risk assessment.

The primary objective of this trial is to assess the long-term safety of dasiglucagon administered as SC infusion.

Informed consent (and assent as applicable) for participation in this trial will be obtained from eligible patients. Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with possible further dose adjustments to optimize treatment to each patient's needs.

The investigator is allowed to change the standard of care (SOC) medication for CHI at his or her discretion in order to optimize the treatment of each patient. To use a minimally invasive yet objective method of assessing the frequency of hypoglycemia, patients will be required to wear a CGM device throughout the entire trial period. Pauses are allowed; however, CGM must be used for the 30 days leading up to each visit, and families will also be asked to perform SMPG.

The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial. Any post-treatment follow-up scheduled for patients in the lead-in trial will be redundant if they are enrolled in the present trial by the time of the scheduled Follow-up Visit.

Patients will be seen at the trial site at Months 1, 3, and 6, and every 3 months thereafter, and contacted by the investigator monthly by telephone in between site visits. At site visits, patients and their parent(s)/guardian will receive a paper diary to record potential AEs and concomitant

medication, among other information, which will be reviewed regularly by site staff at each visit. Patients will be allowed to remain in the trial until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP), or until approximately Q3 2024 (Treatment Period), whichever occurs first. Any post-treatment Follow-up Visits will be redundant for the patients who are continuing treatment with dasiglucagon commercially or through an EAP, and they will end trial participation at their End of Treatment (EoT) Visit. Figure 1 depicts the trial design.

Patients who are treatment-induced or treatment-boosted ADA-positive at Trial Completion will be offered continued ADA monitoring until the ADA levels return to baseline or until 2 years after End of Trial, whichever occurs first. Baseline is defined as the ADA level prior to dasiglucagon dosing in the lead-in trial.

Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.

An interim analysis may be performed as appropriate to support a possible marketing authorization application/new drug application (NDA).

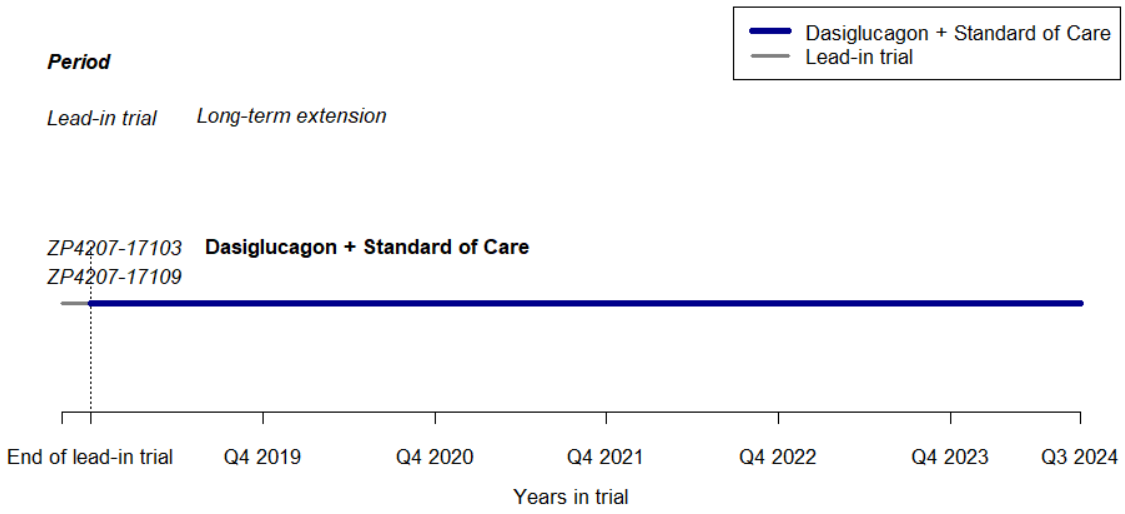

Figure 1 Trial Design

7.2. Trial Duration

The sequence and maximum duration of the trial periods will be as follows:

Trial Period (from last visit in lead-in trial until Trial Completion, as defined below):

1. Baseline: defined as the EoT Visit from lead-in trials ZP4207-17103 or ZP4207-17109.

2. Treatment Period: treatment will continue until approval and commercial availability of dasiglucagon in the country of participation or through an EAP, or until approximately Q3 2024, whichever occurs first, at which time an EoT Visit will be scheduled.

3. EoT Visit: see above.

4. Follow-up Visits: will occur at 4 weeks and 12 weeks after the EoT Visit.

5. **Trial Completion**: completion of the final Follow-up Visit or the EoT Visit if the patient continues treatment with dasiglucagon commercially or through an EAP.

ADA Follow-up Period (from Trial Completion until last patient last visit [LPLV]):

6. Monitoring of treatment-induced or treatment-boosted ADA-positive patients after trial completion: monitoring of ADA-positive patients will continue until the ADA levels return to baseline (as defined in Section 10.1.3.1) or until 2 years after end of trial, whichever occurs first.

End of Trial: defined as the the time all patients have reached Trial Completion (completed the Follow-up Period or the EoT Visit if continuing treatment with dasiglucagon commercially or through an EAP), whichever occurs first.

LPLV: last visit of the last patient in the ADA Follow-up Period

7.3. Discussion of Trial Design

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

The open-label treatment from the last treatment period of lead-in trials ZP4207-17103 and ZP4207-17109 was chosen because the added treatment burden of a blinded trial design was not considered ethically justified.

Investigators will be required to reaffirm and document a positive benefit/risk assessment of continued treatment with dasiglucagon at each site visit, in close collaboration with the parent(s)/legally authorized representative (LAR) to ensure that patients are not unnecessarily exposed to the trial product. Treatment should be stopped if continued benefit is not evident or if safety issues overweigh the benefit of treatment.

A hypoglycemia threshold of PG <70 mg/dL (3.9 mmol/L) was chosen as an alert value for the key secondary hypoglycemia endpoints in alignment with the metabolic disease field experts, although clinicians might use lower thresholds for guiding treatment decisions for treatment of hypoglycemia in patients with CHI.

7.4. Trial Sites

The trial will take place at up to 14 sites experienced in the treatment of CHI in the United States and Europe, all of which will have been involved in the lead-in trials. A maximum of 44 patients are expected to be enrolled in the lead-in trials, and approximately 30-44 of those patients are expected to be enrolled in this trial.

7.5. Point of Contact

A point of contact will be identified to provide information to each patient's parent(s)/guardian about where to obtain information on the trial, the patient's rights, and whom to contact in case of trial-related injury. This information will be provided in the patient information and informed consent form (ICF).

8. PATIENT POPULATION

8.1. Selection of Trial Population

A screening log of potential trial candidates must be maintained at each trial site.

8.2. Trial Entry Criteria

8.2.1. Inclusion Criteria

A patient will be eligible for trial participation if he or she meets all of the following criteria:

1. Completed treatment in either Trial ZP4207-17103 or ZP4207-17109
2. Expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon (based on considerations of glycemic effect, tolerability, and nature and frequency of AEs experienced in the lead-in trial), with signed investigator statement documenting the positive benefit-risk assessment made
3. Has a negative serum pregnancy test at baseline (only for females of child-bearing potential)
4. Sexually active female patients and their partners must use acceptable contraception or refrain from sexual activity from baseline until 30 days after the last dose of trial drug. Females must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception. Abstinence can only be accepted if this is true abstinence in line with the preferred and usual lifestyle of the patient.

   Acceptable methods of contraception are:

   a) Hormonal contraceptives (e.g., oral contraceptive pill, depot, patch, intramuscular implant or injection, sponge, or vaginal ring), stabilized for at least 30 days if first use

   or

   b) Barrier method, e.g., (i) condom (male or female) and (ii) diaphragm with spermicide

Germany: *Only highly effective methods of birth control are accepted (i.e., one that results in less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices), or sexual abstinence.*

5. Able and willing to comply with trial procedures
6. Following receipt of oral and written information about the trial, the patient (depending on local institutional review board [IRB]/independent ethics committee [IEC] requirements) must provide assent and one or both parents* or guardian of the patient must provide signed informed consent before any trial-related activity is carried out. ***France, Germany, Israel:*** *The consent must correspond to the patient's presumed will where such a will can be ascertained.*

* If required by local regulations, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

8.2.2. Exclusion Criteria

A patient will be excluded from the trial if he or she meets any of the following criteria:

1. The patient developed any conditions prohibited by the lead-in trial, requires medication prohibited by the lead-in trial, or has other new complications that preclude participation in the investigator's opinion.
2. Has participated in an interventional clinical trial (investigational or marketed product) within 3 months before baseline or 5 half-lives of the drug under investigation (whichever comes first) or plans to participate in another clinical trial. Excluded from this is participation in Trial ZP4207-17103, Trial ZP4207-17109, and/or 18F-Dopa positron emission tomography computed tomography/magnetic resonance imaging investigation (when performed as a part of a clinical trial) for diagnosis of focal CHI.

8.3. Patient Participation Stopping Criteria

8.3.1. Efficacy Reasons

Treatment should be discontinued if there is no longer any evidence of beneficial effect of dasiglucagon due to inadequate or complete lack of response, or in case continuation of treatment is not considered needed any longer due to natural course of the disease, i.e. improvement or full resolution.

The decision should be taken at the discretion of the investigator and involve the parents/LAR in the decision making. The decision should be based on all efficacy and safety assessments performed during participation in the trial. A temporary treatment interruption can be applied in order to inform the decision. If deemed needed, the patient can be admitted to the hospital during the treatment interruption.

8.3.2. Safety Reasons

Treatment should be permanently discontinued in case risk outweighs the benefit, i.e. unacceptable safety issues related to the treatment that are life-threatening, or associated with significant comorbidity.

8.4. Premature Patient Withdrawal

Patients' parent(s)/guardian will be advised that they are free to withdraw their children from participation in this trial at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep patients in the trial. However, patients must be withdrawn from the trial if their parent(s)/guardian withdraw consent to participate.

Investigators must attempt to contact patients' parent(s)/guardian who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Attempts to contact the patient must be documented. At least 3 phone calls and 3 written attempts to contact the patient will be made prior to considering them lost to follow-up. Should an AE be the cause of withdrawal, it must be documented, reported, and followed as described in Section 11.2.

If a patient/parent(s)/guardian withdraws consent, the reason for withdrawal and the date of withdrawal will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the trial should be performed at the time of premature withdrawal.

8.5. Treatment Discontinuation

To prevent missing data, patients should to the extent possible be kept in the trial. Therefore, treatment discontinuation is often the preferred option in case of, e.g., substantial non-compliance with trial procedures or initiation of prohibited treatment that interferes with the efficacy and safety evaluation. If it is an investigator decision to discontinue the patient's treatment, the investigator should, whenever possible, discuss the potential discontinuation of the treatment with the medical monitor. If the patient is discontinued from trial treatment by the investigator or by parent(s)/guardian's decision, the reason and date of treatment discontinuation will be recorded on the appropriate page of the eCRF. The patient should be asked to continue in the trial by following the planned visit schedule. At a minimum, the patient will be asked to attend the Follow-up Visits at 4 weeks and 12 weeks (± 7 days) after discontinuation of trial treatment. If the patient is treatment-induced or treatment-boosted ADA-positive at Trial Completion the patient will be offered continued ADA monitoring until their ADA levels return to baseline (defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial) or until 2 years after End of Trial, whichever occurs first. See Section 10.1.3.1 and Section 17.1.

8.6. Patient Replacement Criteria

Patients who withdraw from the trial prematurely will not be replaced.

Enrolled patients who are subsequently withdrawn from the trial may not reenter. The patient number for a withdrawn patient will not be reassigned to another patient.

8.7. Trial Stopping Criteria

In case of 2 or more serious safety concerns of similar nature potentially related to treatment, that are either life-threatening or associated with significant comorbidity and/or permanent disability, the trial will be temporarily paused. If relationship between the concerns and IMP is confirmed or there is reasonable evidence that the concerns are probably or possibly related to the IMP and overall benefit of dasiglucagon is outweighed, the trial will be permanently stopped.

9. TREATMENTS

9.1. Identification of Investigational Product

Dasiglucagon injection 4 mg/mL will be supplied by the sponsor in a 3 mL vial containing 1 mL.

Dasiglucagon will be provided in the form of solution for injection for subcutaneous administration through an infusion pump.

Trial drug products, as applicable, must be transferred from the vial to an Accu-Chek® Spirit Cartridge. The amount of drug product dosed via the pump will vary between patients.

Cartridges and infusion sets should be replaced as indicated in the instructions for use.

9.1.1. Packaging and Labeling

Trial drug products will be packaged and labeled by the sponsor.

Dispensing unit configuration: 6 vials containing dasiglucagon, 4 mg/mL, packaged in an outer carton. The vial and carton will be packaged and labeled in local language indicating the content (open label).

The storage conditions for trial drug products will be described on the trial drug product label. The labels will supply no information about the patients. Each treatment unit (containing 6 vials) will have a unique Dispensing Unit Number for drug allocation, drug accountability, and traceability purposes.

Labelling will be performed according to Annex 13 of the Good Manufacturing Practice guidelines of the European Commission, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, local laws, and regulations.

9.2. Treatments Administered

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

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

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

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

The combined treatment of SOC and dasiglucagon should aim to reduce gastric dextrose infusions and glucose fortified meals as much as possible, maintaining the patient's PG within 70 and 120 mg/dL (3.9-6.7 mmol/L) at all times.

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

Plasma glucose assessments will be performed throughout the trial as instructed by the investigator.

For patients using the Dexcom G5 CGM, SMPG assessments will be performed at least 2 times per day for CGM calibration.

For PG monitoring, the same hand-held PG meter as in the lead-in trials will be used.

Details on the administration instructions and guidelines for preparation and handling of the trial drug product are in the pharmacy manual/trial materials manual (TMM).

9.3. Trial Supplies

The device and ancillaries listed in the following table will be supplied by the sponsor throughout the trial. Trained trial personnel will train parent(s)/guardian on the use of the devices.

Instructions for the use of all these supplies will be provided in a separate manual.

Item	Name	Manufacturer
Pump	Accu-Chek Spirit Combo	Hoffman-La Roche AG, Basel, Switzerland
Cartridge	Accu-Chek Spirit 3.15 mL Cartridge system	Hoffman-La Roche AG, Basel, Switzerland
Infusion sets	Accu-Chek FlexLink Infusion set (Accu-Check® UltraFlex Infusion set in US) and Accu-Chek Rapid-D Link Infusion set	Hoffman-La Roche AG, Basel, Switzerland
Infusion set inserter	Accu-Chek LinkAssist Insertion device (can be used with FlexLink & UltraFlex)	Hoffman-La Roche AG, Basel, Switzerland
PG monitoring	StatStrip Xpress2	Nova Biomedical, Waltham, MA, USA
CGM	Dexcom G5 Dexcom G6	Dexcom Inc., San Diego, CA, USA

The infusion pump system is Conformité Européene (CE)-marked for the management of diabetes mellitus in persons requiring insulin, as prescribed by a physician. In this trial, the pump system is used outside the CE-marked intended use since the pump system will be delivering dasiglucagon to patients with CHI. The PG meter is used as intended according to the CE mark, except for the use by a lay person in a home care setting. The CGM devices are used as intended according to the CE mark, except for the age group and the disease.

The pump, the SMPG, and the CGM will be packaged and labeled for use in investigational trials.

9.4. Dispensing and Storage

The trial drug product supplied by the sponsor is to be dispensed exclusively to patients in this clinical trial according to the instructions of this protocol and the pharmacy manual/TMM. The investigator is responsible for dispensing the trial drug product according to the dosage scheme.

Dasiglucagon for injection 4 mg/mL must be stored at 2–8°C in a refrigerator.

The investigator must ensure the availability of proper storage conditions. All trial drug product provided for this trial will be stored in a secure area with restricted access at the trial site.

The temperature should be monitored by recording the actual, minimum, and maximum temperatures using a calibrated thermometer or thermocouple, or by continuous recording using a qualified temperature monitoring system. The temperature should be evaluated and documented at least on working days on a temperature log. This log must be included in the Investigator Site File (ISF) upon trial termination.

The investigator must contact the clinical research associate (CRA) in case of temperature deviations outside the acceptable range.

Please refer to the pharmacy manual/TMM for additional information on handling of the trial drug.

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the trial drug product, including the date, quantity, batch or code number, and identification of patients (patient number) who received the trial drug. The investigator will not supply the trial drug product to any person except subinvestigators, designated trial personnel, and patients in this trial. The trial drug product may not be relabeled or reassigned for use by other patients. If any of the trial drug product is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and the appropriate regulatory agencies as required.

9.5. Method of Assigning Patients to Treatment Groups

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

9.6. Blinding and Unblinding Treatment Assignment

This is an open-label trial.

9.7. Selection of Doses in the Trial

Both the starting dose and the maximum allowed doses are based on experience with glucagon products in this patient population.[11]

At the time of protocol development, no pediatric PK data were available for dasiglucagon. An approximate estimation of expected drug concentration in a 3 kg patient was made by extrapolation of a previously made PK model for pediatric patients with weights between 25 and 45 kg.[15]

The predicted plasma concentration is expected to give a low PD response in the lowest dose level and be above maximum effect at the highest dose level. The maximum expected plasma

concentrations of dasiglucagon is in the range of what is achieved following a rescue dose to adults. The doses of dasiglucagon will be titrated to meet the needs of the individual patient. The titration will stop when no additional PD effects are observed as the infusion rate is increased. The infusion rate of dasiglucagon will be monitored and adjusted to meet the needs of the individual patient throughout the trial period. Since the dasiglucagon dose is titrated individually based on the desired PD response, it does not need to be related to any measure of the patient's size.

9.8. Selection of Timing of Dose for Each Patient

Dosing details are provided in Section 9.2.

9.9. Dose Adjustment Criteria

Dosing details are presented in Section 9.2.

9.10. Treatment Compliance

Compliance data will be collected. Infusion details will be recorded in the patient's eCRF, and drug accountability will be performed as detailed in the pharmacy manual/TMM.

9.11. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.11.1. Permitted Therapies

Concomitant CHI treatments (e.g., somatostatin analogs) that were initiated prior to trial entry are permitted throughout the trial. Somatostatin analogs may also be added throughout the trial at the investigator's discretion if the maximum dose level of dasiglucagon (70 µg/hr) has been reached or if further titration is not possible due to undesirable side effects.

Other CHI-specific treatments to be added during the trial need to be discussed with the medical monitor.

Caution is advised when beta-blockers, indomethacin, anticholinergic drugs, and warfarin are prescribed, due to reports of interaction with marketed glucagon products.

9.11.2. Prohibited Therapies

The following therapies are prohibited during the trial:

- Systemic corticosteroids, e.g., hydrocortisone >20 mg/m^2 body surface area (or equivalent)
- Anti-inflammatory biological agents, kinase inhibitors, or other immune-modulating agents
- Exogenous insulin
- Use of paracetamol/acetaminophen is strongly discouraged for the duration of trial when patients are using the Dexcom G5 CGM because it interferes with the accuracy of the device. Parent(s)/guardian should contact the trial site before dosing child with paracetamol/acetaminophen. Both the site staff and the parent(s)/guardian should explore

other options of treating fever and mild pain before deciding paracetamol/acetaminophen is needed.
When patients are using the Dexcom G6 CGM the use of paracetamol/acetaminophen is allowed.

- Other investigational agents
- Marketed glucagon products throughout the trial unless necessary for rescue therapy to treat severe hypoglycemia, as per local standard of care
- Prescription or non-prescription medications known to cause QT prolongation

Continuation in the trial after the patient received excluded therapies will be at the discretion of the investigator after consultation with the medical monitor.

10. TRIAL PROCEDURES

The patient (depending on local IRB/IEC requirements) must provide assent and one or both parent(s)/guardian (according to local law) must provide written informed consent before any trial-related procedures are initiated, including the cessation of prohibited concomitant therapy. ***France, Germany, Israel:*** *The consent must correspond to the patient's presumed will where such a will can be ascertained. Depending on local IRB/IEC requirements, the patient should also provide assent before any trial-related procedures are initiated.*

For the timing of assessments and procedures throughout the trial, refer to the Schedule of Events (Section 17.1). Throughout the trial, trial personnel should make every reasonable effort to follow the timing of assessments and procedures in Section 17.1 for each patient. If a patient misses a trial visit for any reason, the visit should be rescheduled as soon as possible.

At enrollment and throughout the trial, the investigator will ensure:

- Appropriate re-training of patient's parent(s)/guardian in the use of dasiglucagon in the Accu-Chek Spirit Combo pump based on the training material provided
- Parent(s)/guardian are trained appropriately on the use of CGM device
- Parent(s)/guardian are trained appropriately on how to perform SMPG measurements and on how to complete the diary. They will check their child's SMPG as instructed by the investigator. When the patient is using the Dexcom G5 CGM, the SMPG should be measured at least 2 times per day for calibration of the CGM device.
- Parent(s)/guardian are instructed not to change the dose of trial drug without prior consultation with the investigator
- Parent(s)/guardian are instructed how to recognize and handle signs of hypoglycemia
- Parent(s)/guardian are instructed to call the investigator/site staff in case of questions

10.1. Assessments

Quality of life should be the first assessment performed at each visit according to the Schedule of Events (Section 17.1).

10.1.1. Efficacy

10.1.1.1. Plasma Glucose Monitoring

Plasma glucose assessments will be performed regularly throughout the trial. During the trial, SMPG assessments (using StatStrip Xpress2) will be performed as instructed by the investigator. When a patient is using the Dexcom G5 CGM, SMPG assessments will be performed at least 2 times per day for CGM calibration.

At each visit the investigator will ensure that SMPG data are downloaded from the patient's device. The investigator will check for patient compliance in SMPG measurements. The procedure for download of SMPG data will be described in the pharmacy manual/TMM.

10.1.1.2. Continuous Glucose Monitoring

Both the Dexcom G5 and Dexcom G6 can be used for continuous glucose monitoring during the trial. The Dexcom G5 will be taken off the market by the supplier during 2020 and all patients should be shifted to the Dexcom G6 CGM device.

The CGMs (Dexcom G5 and Dexcom G6), supplied for use throughout the trial, will be used to guide treatment decisions, as well as to evaluate efficacy after trial completion. Continuous glucose monitoring should be used for the entire trial period. Pauses are allowed, but CGM must be used for the 30 days leading up to each site visit (see Section 17.1).

At each visit, the investigator will ensure that CGM data are downloaded from the patient's device. The procedure for download of CGM data will be described in the pharmacy manual/TMM.

The CGM devices should be calibrated and used according to the manufacturer's instructions; the Dexcom G5 should be calibrated 2 times per day, the Dexcom G6 does not require calibration.

The contract research organization (CRO) or delegate will handle the device sourcing, configuration for use in the trial, procedures for data extraction, device service, and return handling.

10.1.1.3. Quality of Life

Quality of life (Appendix B) will be assessed using the PedsQL and additional CHI disease-specific QoL questions (parent-reported versions) according to the Schedule of Events (Section 17.1).

The PedsQL Measurement Model is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL Measurement Model integrates seamlessly both generic core scales and disease-specific modules into one measurement system.

The 23-item PedsQL Generic Core Scales was designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. The 4 Multidimensional Scales and 3 Summary Scores are:

Scales	Summary Scores
• Physical Functioning (8 items)	• Total Scale Score (23 items)
• Emotional Functioning (5 items)	• Physical Health Summary Score (8 items)
• Social Functioning (5 items)	• Psychosocial Health Summary Score (15 items)
• School Functioning (5 items)	

The CHI disease-specific questions were developed by the patient association Congenital Hyperinsulinism International and taken from the patient-reported registry, the HI Global Registry. The HI Global Registry questions are grouped mostly under general QoL; however, some questions relate specifically to diet and feeding, surgical management, glucose monitoring, and child development. The HI Global Registry is governed by a Global Steering Committee, including key global clinical experts.

10.1.1.4. Other Assessments

Resource Utilization:

- Emergency department visits for hypoglycemia
- Number and length of hospitalizations caused by CHI or CHI-related events
- Number of visits to health care providers (family doctors, specialist, etc.) caused by CHI or CHI-related events
- Number of home visits by paramedics due to hypoglycemia

Diary:

The patient's parent(s)/guardian will be provided with a paper diary at all visits, except at the End of Treatment and Follow-up Visits. The investigator will instruct the patient's parent(s)/guardian on how to complete the diary. The diary should be completed throughout the trial until the end of treatment. The following information should be recorded in the diary:

- Hypoglycemic events for which there was an intervention, regardless whether the event was detected via SMPG or CGM
- Concomitant medications
- AEs
- Hospitalizations, visits to health care providers or emergency room/ accident & emergency department (ER/A&E), and visits by paramedics
- Data regarding suspicion of NME and neurological findings

Diary entries should be reviewed at each visit and the review be documented in the diary. Data from the diary entries should be transcribed to the eCRF on an ongoing basis.

Prescribed continuous gastric carbohydrates:

Total amount of prescribed carbohydrates as part of continuous gastric infusion and infusion duration as listed in this section will be collected on the 7 days prior to the the following visits: Start of the lead-in trial (ZP4207-17103 or ZP4207-17109), Visit 1, Visit 4, Visit 6 and at End of Treatment.

In ZP4207-17103 start of trial is defined as the 7 days prior to the run-in period and in ZP4207-17109 start of trial is defined as the 7 days prior to the randomization visit.

- Total amount (g) of prescribed carbohydrates as part of continuous gastric infusion
- Total duration (h) of prescribed continuous gastric infusion
- Total duration (h) of prescribed nightly (8 pm – 8 am) continuous gastric infusion

10.1.2. Pharmacokinetics/Drug Exposure

Blood samples will be collected to measure dasiglucagon levels at steady-state (Schedule of Events; Section 17.1).

Details on sampling/collection, shipment, and analysis will be provided in the laboratory manual.

10.1.3. Safety

Safety assessments will include the evaluation of AEs, clinical laboratory assessments (hematology, biochemistry, and ADAs), vital signs, physical examination, ECGs, echocardiography, and local tolerability.

10.1.3.1. Laboratory Safety Assessments

Trial procedures require a maximum total of approximately 4 mL blood per visit. No more than 1 mL blood per kg body weight should be sampled per visit day. Where this limit is exceeded,[16,17] safety laboratory tests (2 mL per sampling) will be prioritized over immunogenicity (1 mL) and drug exposure (0.4 mL) samples.

All measurements described in this section are recognized standard methods.

Hematology and Biochemistry

Samples for hematology and biochemistry will be collected at the time points specified in the Schedule of Events (Section 17.1).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count, including differential
Biochemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine, sodium, potassium, chloride, estimated glomerular filtration rate (eGFR), urea, insulin, ketones (measured at the local laboratory or with PG meter), free fatty acids, and hemoglobin A1c (HbA1c)

Laboratory specimens will be analyzed at local laboratories.

Immunogenicity

Blood samples will be collected to test for antibodies against dasiglucagon at Visits 1, 3, 4, 6; in intervals of 6 months throughout the Treatment Period, at final drug administration, and at the Follow-up Visits (Section 17.1); and processed and shipped according to instructions provided in the laboratory manual.

Patients who are treatment-induced or treatment-boosted ADA-positive at Trial Completion will be offered continued ADA monitoring until the ADA levels return to baseline or until 2 years after end of trial, whichever occurs first. The patients will be invited to come to the site for ADA blood sampling visits 1 to 3 times a year with a minimum of 4 months between the visits. Baseline is defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial.

Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.

Samples for ADA measurement will be analyzed in batches during the trial. The ADA samples will be analyzed at a special laboratory.

The clinical ADA assays have been validated in accordance with existing guidelines and recommendations.[18,19]

Samples will be measured in anti-dasiglucagon antibody screening and confirmatory assays. Due to the limited sample volume, in the CHI pediatric patients, the ADA characterization of confirmed positive samples will be conducted according to the following priority:

- Cross-reactivity against endogenous glucagon (cross-reactivity Yes/No)
- Establishment of anti-dasiglucagon binding titer
- Dasiglucagon in-vitro neutralizing potential of the antibodies
- Glucagon in-vitro neutralizing potential of the antibodies (only if positive for crossreactivity)
- Neutralizing antibody titers, in case of a positive result in the in-vitro neutralizing antibody assays

The in vitro neutralizing effects of antibodies will be measured using an assay based on glucagon receptor-transfected human embryonic kidney cells. The sensitivity in the 1st generation NAb assay initially used was approximately 51.8 ng/mL. In the recently developed 2nd generation NAb assay, the sensitivity is 89.8 ng/mL. The assays were also validated for recombinant glucagon with similar results. The cell-based neutralizing antibody analyses will be performed by a special laboratory (BioAgilytix, Durham, NC, USA). No further serum sampling will be needed since the ADA samples can be used for neutralizing antibody analysis.

The neutralizing potential in samples from ADA-positive patients will be evaluated on the basis of drug exposure/PD data (steady-state exposure and plasma glucose) if the assessment for NAb activity in confirmed ADA-positive samples is not possible due to the limited sample volume.

The ADA samples will be analyzed in batches during the trial, and patients who developed treatment induced anti-dasiglucagon antibodies (treatment induced or treatment boosted, titer increase above 4 fold) will be offered follow up until the ADA level is back to baseline or until the outcomes related to anti-drug antibodies are no longer detected.

For patients with a body weight <10 kg, it will not be possible to collect back-up ADA samples. However, any residual serum samples may be stored until approval of market authorization by the health authorities.

For patients with a body weight ≥10 kg, a back-up ADA sample and residual serum samples may be stored until approval of market authorization since further characterization of the antibody response may be requested.

Pregnancy Testing

A serum pregnancy test will be performed every 3 months in females of child-bearing potential.

Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all trial personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of patient samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the laboratory manual. The investigator is responsible for ensuring that all trial samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

Evaluation of Laboratory Values

The normal ranges of values for the laboratory assessments in this trial will be provided by the responsible laboratory and submitted to the sponsor before the beginning of the trial. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, the investigator must evaluate if the value is clinically significant and record his or her assessment in the appropriate eCRF.

All laboratory values that in the investigator's opinion are clinically relevant during or after termination of the treatment have to be reported as AEs and followed, as described in Section 11.2.

10.1.3.2. Clinical Examinations

Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and blood oxygen saturation level (SpO_2) will be measured according to the Schedule of Events (Section 17.1).

Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed while the child is in a sleeping or calm state according to the time points specified in the Schedule of Events (Section 17.1). If it is not practical or possible, then a 2-lead ECG may be used.[20] If arrhythmia is detected on a 2-lead ECG, this should be followed by 12-lead ECG. All ECG recordings will be identified with the patient number, date, and time of the recording and will be attached to his or her medical record.

The ECG parameters (heart rate, PQ, QRS, QT, and QTcF) and any abnormality will be recorded and described in the eCRF, including the investigator's assessment of clinical significance (Abnormal, Clinically Significant; or Abnormal, Not Clinically Significant). At subsequent visits, any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant findings, will be recorded as AEs.

Echocardiogram

An echocardiogram will be performed according to the time points specified in the Schedule of Events (Section 17.1).

Physical Examination and Neurological Examination

A complete physical examination of body systems (excluding breast and genitourinary, nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait, all as applicable for the patient's age) will be performed according to the Schedule of Events (Section 17.1).

Local Tolerability

Local tolerability data will be collected separately from AEs. Within the eCRF, data will be collected on the nature of any reaction (erythema, pain, swelling, etc.), the severity (mild, moderate, severe), and any action take (e.g., no action, interruption of infusion). The likely cause of the reaction will also be collected (e.g., insertion site, drug, adhesive dressing).

Other skin findings will be collected along with other AEs. If clinical suspicion of NME is made, data describing the lesion(s) will be collected as an AE of special interest (AESI, see Section 11.1.8), together with a photograph or series of photographs of the lesion(s) uploaded to a central repository.

10.1.3.3. Reporting of Hypoglycemia Events

Hypoglycemic episodes (below 70 mg/dL / 3.9 mmol/L) that require intervention are to be reported via the dedicated hypoglycemia eCRF form. Hypoglycemic episodes that fulfill the definition of an SAE should furthermore be recorded as an SAE. The following information should be collected:

- Date, start time, source (SMPG/CGM)
- Selected symptoms (e.g., unconsciousness, seizures)
- Intervention:
  - type and amount of food, route of administration (oral vs. NG tube/gastrostomy)
  - use of marketed glucagon as rescue therapy
  - contact with trial doctor or emergency services, paramedic visit, ER/A&E admission, hospitalization

10.1.3.4. Technical Complaints

Reporting of Technical Complaints

Technical complaints should be reported to the sponsor on any of the following products, if technical issues occur between their first and last use:

- Dasiglucagon 4 mg/mL-vial containing 1 mL
- Accu-Chek Spirit pump
- Accu-Chek Spirit 3.15 mL Cartridge system, Accu-Chek Flex-link Infusion set (Accu-Check UltraFlex Infusion set in the US), and Accu-Check Rapid-D Link infusion set
- Accu-Chek Link-Assist Insertion device

- SMPG meter, StatStrip Xpress2
- Dexcom G5/G6 system

The investigator must report whether the technical complaint is associated with any AEs or SAEs. Any AE/SAE associated with a technical complaint must be reported in accordance with Section 11.2; the relationship between the technical complaint and the AE/SAE must be assessed by the investigator.

Technical complaints must be reported on a dedicated technical complaint form.

The investigator must complete the technical complaint form in the eCRF according to the following timelines, starting from the time the trial site becomes aware of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- All other technical complaints within **5 calendar days**

Use the paper technical complaint form when reporting a technical complaint for an item that is not yet allocated to a patient. The form should be sent by email to the safety CRO, refer to Appendix A for contact details.

Collection, Storage, and Shipment of Technical Complaint Item(s)

The investigator must collect and store the item(s) and notify the CRA (including photo documentation) **within 5 calendar days** of obtaining the item at trial site. Upon request, the CRA must coordinate the shipment as per instruction from the sponsor.

10.1.3.5. Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 11 and in Appendix D.

11. ADVERSE EVENTS AND PREGNANCIES

Timely, accurate, and complete reporting and analysis of safety information from clinical trials are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical trial patient administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not related to the product.

AEs include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory AE: a clinical abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires

active management. Active management includes active treatment or further investigations, e.g., change of dose or more frequent follow-up due to the abnormality

The following should **not** be considered as AEs:

- Pre-existing conditions, including those found as a result of baseline procedures (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the patient has signed the informed consent

11.1.2. Severity

When assessing the severity of an AE, the following definitions are used:

Mild: No or transient symptoms, no interference with the patient's daily activities

Moderate: Marked symptoms, moderate interference with the patient's daily activities

Severe: Considerable interference with the patient's daily activities, which the patient find unacceptable. A severe reaction does not necessarily deem the AE as serious (SAE) and an SAE is not always severe in nature.

11.1.3. Causality

When assessing the cause of an AE, the following definitions are used:

Probable: Good reason and sufficient documentation to assume a causal relationship

Possible: A causal relationship is conceivable and cannot be dismissed

Unlikely: The event is most likely related to etiology other than the product

Not related: No relationship to product

Causality will take into consideration whether the cause of the AE was related to the trial drug. For SAEs it will additionally be reported if the event is at least possibly related to any concomitant drug/therapy, study procedure or other (including any device).

11.1.4. Outcome

When assessing the outcome of an AE, the following definitions are used:

Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the patient signed the ICF

Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable as final outcome of an event if the patient has completed the trial or has died from another AE

Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE

Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known

Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with fatal outcome must be reported as an SAE

Unknown: This term is only applicable if the patient is lost to follow-up.

11.1.5. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose results in any of the following:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is otherwise medically important, that may not result in death, be life threatening or require hospitalization may be considered an SAE when (based on appropriate medical judgement) it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples could be emergency room or home treatment of allergic bronchospasm or convulsion

11.1.6. Other Important Events

The following events must always be reported in the electronic data capture (EDC) system on a dedicated form, regardless of whether it is related to an AE:

- suspicion of transmission of infectious agents via the trial product
- overdose of the trial product
- medication error involving the trial product
- inadvertent or accidental exposure to the trial product

11.1.7. Non-serious Adverse Events

A non-serious AE is any AE that does not fulfill the definition of an SAE.

11.1.8. Adverse Events of Special Interest

For this trial, the following events are to be regarded as AEs of special interest (AESI events or AESI), with data collected under a specific eCRF form:

- Suspicion of NME
- Risk of liver injury defined as ALT or AST >3 x ULN AND total bilirubin >2 x ULN, where no alternative etiology exists (Hy's law)
- Loss of consciousness, partial and generalized seizures
- Clinically significant changes in blood pressure or heart rate

11.1.9. Suspected Unexpected Serious Adverse Reactions

An AE is considered a suspected unexpected serious adverse reaction (SUSAR) if the nature or severity is not consistent with the applicable product Reference Safety Information (RSI). For dasiglucagon, the expectedness of an AE will be determined by whether or not it is listed in the RSI section of the IB.

11.2. Collection, Recording, and Reporting of Adverse Events

All AEs, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until patient's Trial Completion. In addition, patients will be observed for any signs or symptoms. They or their parent(s)/guardian, depending on the patient's age, will be asked about their condition by open questioning, such as "How have you been feeling since you were last asked?" at each contact with the trial site (visit or telephone). Patients or their parent(s)/guardian, depending on the patient's age, will also be encouraged to spontaneously report AEs occurring at any other time during the trial. At site visits and during monthly telephone contacts, the investigator should ask the patient and their caregiver(s) about any possible signs and symptoms of seizures as described in Appendix D.

All AEs, regardless of seriousness, severity, or presumed relationship to trial drug, must be recorded and evaluated by the investigator. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. If no diagnosis can be made, the investigator should record each sign and symptom as individual AEs. Investigators must record their opinion concerning the relationship of the AE to the trial drug. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

Each AE must be reported on the AE eCRF within 5 calendar days of the investigator becoming aware of the event.

All AE information should at a minimum include the following:

- Date and time of onset
- Date and time of investigator's first information about the AE
- Seriousness
- Severity
- Causal relationship with trial product
- Measures taken due to AE
- Interruption or discontinuation of treatment with trial product
- Date and time of resolution and final outcome

Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

All SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of trial drug, must be reported within 24 hours after obtaining knowledge about the event by completing the SAE form in the EDC system. A separate SAE form should be completed for each SAE.

All SAEs will be reported in EDC, and for each reported event a system-generated email will be sent to the safety CRO ([redacted]), the medical monitor, sponsor medical director, and trial manager.

Specific information about AESIs will be collected via SAE form (if qualifying for serious adverse events [SAEs]) as well as via dedicated AESI eCRF page(s). Reporting requirements for serious and non-serious AEs as described above also apply for serious and non-serious AESIs.

Other important events (Section 11.1.6) will be reported via a dedicated eCRF page. Reporting timelines will be within 24 hours if related to an SAE and 5 calendar days for all other events.

It is the responsibility of [redacted] to report all SUSARs that occur in this trial to competent authorities, the IRB, or IEC in accordance with the local requirements in force and the ICH guideline for GCP. Suspected unexpected serious adverse reactions will be coded using the latest version of MedDRA.

11.2.1. Contact Information

Pharmacovigilance for this trial is outsourced to [redacted]; refer to Appendix A for contact details.

11.3. Follow-up of Adverse Events

The investigator must record follow-up information on the eCRF for non-serious AEs and on the SAE form for SAEs. Follow-up questions to investigators regarding SAEs are queried directly by [redacted] to the investigator.

Follow-up information must be reported according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the events is "recovered/resolved," "recovered/resolved with sequelae," or "fatal," and until all queries have been resolved. Cases of chronic conditions, cancer, or AEs that are ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved." Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g., corrections or additions) information and must be reported within 24 hours of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovered/resolved," or "recovered/resolved with sequelae" or until the patient has completed the trial, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer, or AEs that are ongoing at time of death (where death is due to another AE) may be closed with the outcome of "recovering/resolving" or "not recovered/not resolved." Cases can be closed with the outcome of "recovering/resolving" when a patient has completed the trial.

If a potential hypersensitivity reaction is observed, additional blood samples may be required to further characterize the potential hypersensitivity reaction. If an anaphylactic shock is suspected, samples may be taken for the measurement of tryptase. In this case, a blood sample should be

taken 3-4 hours after the event and again approximately 1-2 weeks later to determine tryptase baseline levels. In addition, assessments for elevated histamine levels may be considered.

The investigator must ensure that the worst-case severity and seriousness of an event is kept throughout the trial, i.e., if the severity of an AE changes over time then it should be reported as 1 AE with the most severity. A worsening of an unresolved AE must be reported as follow-up with re-assessment of severity and/or seriousness of the event.

If an AE is resolved and re-appears later then it should be reported as a new AE.

Queries or follow-up requests must be responded within 14 calendar days from the date of receipt of the request, unless otherwise specified in the follow-up request.

11.4. Pregnancy

Parent(s)/guardian of female patients who are of childbearing potential must be instructed to notify the investigator immediately if their child becomes pregnant or if they suspect she is pregnant during the trial. All initial reports of pregnancy in female patients must be reported by trial site personnel using the appropriate pregnancy form in EDC within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs and must be reported using the SAE form. If a patient becomes pregnant during the trial, treatment must be discontinued.

The investigator must follow the pregnancy until its outcome is known and the newborn infant is 1 month of age. The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the fetus and newborn infant.

11.5. Precautions

Normal precautions taken for a clinical trial, including the provision of emergency equipment, will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct patients and parent(s)/guardian. During a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to patients for any AEs, including clinically significant laboratory values related to the trial. The investigator should inform the patient's parent(s)/guardian when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

For further information on safety precautions for dasiglucagon, refer to the current version of the IB.

11.6. Safety Committee

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

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

11.7. Independent Data Monitoring Committee

An independent data monitoring committee (DMC) will be established for this trial and will work according to written procedures, e.g., the DMC charter.

12. STATISTICS

12.1. Sample Size Determination

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

12.2. Analysis Populations

Three analysis populations have been defined for this trial:

- The Safety Set: defined as all patients administered any trial drug. This population will be used to provide descriptive summaries of safety data.
- The Full Analysis Set (FAS): defined as all patients in the Safety Set who complete at least 1 day of trial drug. This population will be used to analyze efficacy data.
- The Pharmacokinetic Analysis Set (PK): defined as all patients in the Safety Set who have at least one measurement with quantifiable plasma concentration of dasiglucagon. This population will be used to provide descriptive summaries of PK data.

Inclusion in the analysis populations will be determined prior to database lock.

12.3. Statistical Analyses

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be 2 sided with a significance level of $\alpha = 0.05$.

For analyses involving trial site, if the number of patients per site is small, sites may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively; the exception to this is the time of PG within pre-specified ranges, which will not have a baseline value. For categorical endpoints, descriptive summaries will include counts and percentages.

All data will be presented in the data listings.

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

any samples available after drug administration. Titers will be reported as median and interquartile range.

12.3.1. Trial Patients and Demographics

12.3.1.1. Disposition and Withdrawals

The numbers of patients randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall. The number of patients in each analysis population will be reported.

12.3.1.2. Protocol Deviations

Protocol deviations will be provided in a listing and summarized if appropriate.

12.3.1.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, ethnicity, weight, and length/height) at baseline will be summarized using descriptive statistics. No formal statistical analyses will be performed.

Prior and concomitant medications and procedures will be summarized by the number and percentage of patients taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes, and preferred term (PT).

12.3.2. Duration of Exposure and Compliance

Trial drug administration (i.e., amount administered) will be summarized in terms of each patient's mean, mode, and final dose, and in terms of duration of exposure. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided.

12.3.3. Efficacy Analyses

All efficacy endpoints will be analyzed using average weekly results over the 3-month period between visits.

Due to the impact of pancreatectomy on efficacy endpoints, primary analysis for all endpoints will not handle any endpoint assessment after any pancreatectomy (endpoints set to missing after pancreatectomy). A sensitivity analysis will be run on key secondary efficacy endpoint without censoring data after any pancreatectomy.

12.3.3.1. Key Secondary Analysis

The first key secondary endpoint, total amount of carbohydrates administered to treat hypoglycemia, will be analyzed by using a mixed-model for repeated measures using restricted maximum likelihood (REML). The model will include time period, region as fixed effects, baseline as covariate and patient as random effect. Baseline is defined as the total amount of carbohydrates administered to treat hypoglycemia during the last 2 weeks of the lead-in trial. Time period is defined as up to Month 1, Month 1 to Month 3 and then 3-month period of time for the first year and 6-month period of time for subsequent years. This endpoint will also be

described by region and on a sub-group of patients with gastrostomy or NG-tube at entry in extension trial.

Time to event data (including time to remove of NG tube/gastrostomy and time to pancreatic surgery) will be analyzed using Kaplan-Meier methods. Those analysis will be performed on subgroup of patient from FAS with an NG tube or gastrostomy at the time of entry into the extension study/without any pancreatic surgery at the time of entry into the extension study respectively. Time to pancreatic surgery will also be analyzed by region.

The secondary endpoint of CGM percent time <70 mg/dL (3.3 mmol/L), where percent time is calculated as (number of minutes in hypoglycemia / total number of minutes patient is wearing CGM) * 100%, will be analyzed by using a mixed-model for repeated measures using REML. The model will include time period, region as fixed effects, baseline as covariate and patient as random effect. Baseline is defined as the CGM percent time <70 mg/dL during the last 2 weeks of the lead-in trial.

The endpoints of Rate of CGM-detected hypoglycemic episodes (<70 mg/dL [3.9 mmol/L]) and Rate of clinically significant CGM-detected hypoglycemic episodes (<54 mg/dL [3.0 mmol/L] for 15 minutes or more) will be analyzed using generalized linear mixed-model (GLMM) regression approach assuming a negative binomial distribution, with time period and region as fixed effects and patients as a random effect. Baseline hypoglycemic rate is defined as the rate in the last 2 weeks of the lead-in trial.

12.3.3.2. Secondary and Other Efficacy Analysis

The endpoint of reduction in concomitant medication usage from start of lead-in trial, namely diaxozide and somatostatin analogs, will be summarized on subgroup of patients with diazoxide / somatostain dose at start of lead-in trial respectively.

Number of gastric carbohydrate administrations (NG tube or gastrostomy) to treat hypoglycemia will also be described by region.

For all other efficacy endpoints, continuous and categorical endpoints will be presented using summary statistics or frequencies, respectively. If warranted, continuous measures will be analyzed using a paired t-test or mixed model with region as a fixed effect and baseline value as a covariate; categorical measures will be analyzed using a Chi-square goodness-of-fit test or binomial test for proportions, as data permit, to determine whether there is a difference from the previous time point.

An interim analysis will be performed as appropriate to support the application for approval of dasiglucagon.

Quality of Life

Quality of life will be assessed by the PedsQL and a CHI disease-specific questionnaire (Appendix B).

For each item of the PedsQL instrument (parent), a 5-point response scale is used (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always). Items are reverse-scored and linearly transformed to a 0-100 scale (0 → 100, 1 → 75, 2 → 50, 3 → 25, 4 → 0) so that higher scores indicate better health-related QoL (less negative impact). Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If

more than 50% of the items in the scale are missing, the scale score is not computed. Change from baseline for PedsQL for each of the scales (physical functioning, emotional functioning, social functioning, and school functioning) and summary scores (total scale score, physical health summary score, and psychosocial health summary score) will be summarized.

Answers to each question on the CHI disease-specific questionnaire will be summarized using frequencies at each relevant visit.

Resource Utilization

The number and percentage of patients with admissions/emergency department visits for glycemia, hospitalizations caused by CHI, visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and need for home visits by parameters will be summarized. Additionally, number and length (in days) of hospitalizations caused by CHI, number of visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and number of home visits by paramedics will be summarized.

12.3.4. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 12.2). Safety assessments will include the evaluation of AEs; clinical laboratory assessments (hematology, biochemistry, and ADAs); vital signs, physical examinations; ECGs, and local tolerability issues. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

12.3.4.1. Primary Endpoint: Adverse Events

The primary endpoint of number of AEs will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis.

Adverse events will be coded using the latest version of MedDRA.

A treatment-emergent AE is defined as an AE with an onset at the time of or following the start of treatment with the trial drug until the patient has completed the trial, and no longer than 12 weeks after treatment discontinuation, whichever occurs first.

The number and percentage of patients with AEs will be displayed by system organ class and PT. The incidence of AEs will also be presented by severity and relationship to the trial drug. Serious AEs and AEs resulting in discontinuation of trial drug will be summarized separately in a similar manner. Patient listings of AEs, SAEs, and AEs causing discontinuation of trial drug will be produced.

12.3.4.2. Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values by time point.

The number of patients with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte.

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

12.3.4.3. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and SpO_2.

The number of patients with vital signs values categorized Abnormal, Clinically Significant or Abnormal, Not Clinically Significant will be tabulated showing change from baseline (shift tables) for each parameter.

12.3.4.4. Twelve-lead Electrocardiograms

The number and percentage of patients with normal and abnormal ECG findings will be summarized for each time point. Abnormal results will be grouped as Abnormal, Clinically Significant; or Abnormal, Not Clinically Significant.

12.3.4.5. Physical Examination Findings

The number and percentage of patients with normal and abnormal findings in the complete physical examination will be displayed.

12.3.4.6. Local Tolerability

The number and percentage of patients with local tolerability findings, collected separately from AEs, will be summarized.

12.3.5. Interim Analysis

An interim analysis may be performed as appropriate to support a possible New Drug Application.

13. TRIAL CONDUCT

The accuracy and reliability of data is ensured, among others, by the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and associated personnel before the trial, periodic monitoring visits, and meticulous data management.

13.1. Sponsor and Investigator Responsibilities

13.1.1. Sponsor Responsibilities

The sponsor is obligated to conduct the trial in accordance with strict ethical principles (Section 15). The sponsor reserves the right to terminate participation of a trial site at any time (Section 13.7), and/or to discontinue the trial (Section 13.6 for US trials and Section 13.6.2 for trials conducted outside of the US).

The sponsor agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the trial according to the trial protocol.

13.1.2. Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.2), the investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the trial in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this trial in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the November 2016 ICH Guidance for Industry E6(R2) GCP, and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the trial to subinvestigators and trial coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the trial and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated trial-related responsibilities (e.g., subinvestigators and trial coordinators) and their specific trial-related duties.

Investigators should ensure that all persons who have been delegated trial-related responsibilities are adequately qualified and trained in the protocol, trial drug handling, and their specific duties within the context of the trial. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the trial may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all trial documentation by authorized individuals.

13.2. Site Initiation

Trial personnel may not screen or enroll patients into the trial until after receiving notification from the sponsor or its designee that the trial can be initiated at the trial site. The trial site will not be authorized for trial initiation until:

1. The trial site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The trial site has a Clinical Trial Agreement in place.
4. Trial site personnel, including the investigator, have participated in a trial initiation meeting.

The regulatory documents must be received from the investigator before the sponsor will authorize shipment of trial drug to the trial site, Regulatory Green Light. Copies of the investigator's regulatory documents must be retained at the trial site in a secure location in the ISF. Additional documents, including a copy of the protocol and applicable amendment(s), the dasiglucagon IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and trial drug accountability records should also be retained in the ISF. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

13.3. Screen Failures

Only patients completing trials ZP4207-17103 or ZP4207-17109 are eligible for inclusion, upon confirmation of a positive benefit-risk balance for continued dasiglucagon treatment and meeting the inclusion/exclusion criteria. There is no Screening Period for entry into this trial.

13.4. Trial Documents

All documentation and material provided by the sponsor for this trial are to be retained in a secure location and treated as confidential material.

13.4.1. Investigator's Regulatory Documents

The regulatory documents will be maintained by the investigator in the ISF.

13.4.2. Case Report Forms

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the trial to ensure that the trial information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRF must be signed by the investigator or a subinvestigator when all data are entered and cleaned. These signatures serve to attest that the information contained in the eCRF is accurate and true.

13.4.3. Source Documents

Information recorded in the eCRF should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be entered into the eCRF at the site.

The investigator should permit trial-related monitoring, IEC review, regulatory inspections, and sponsor audit by providing direct access to source data and documents.

13.5. Data Quality Control

The sponsor and its designees will perform quality control checks on this clinical trial.

13.5.1. Monitoring Procedures

The sponsor and/or its designee will conduct site visits to monitor the trial and ensure (i) the safety and rights of the patients are respected, (ii) compliance with the protocol, GCP, and applicable regulations and guidelines and (iii) that accurate, valid, and complete data are

collected. The assigned CRA(s) will visit the investigator and trial site at periodic intervals and maintain periodic communication; this is described in detail in the Monitoring Plan. The investigator agrees to allow the CRA(s) and other authorized sponsor personnel access to ISF and source data (original documents, data, and records). The CRA(s) will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the investigator and staff. While on site, the CRA(s) will review:

- regulatory documents
- entries in the EDC system compared with the source documents
- consents
- adherence to the inclusion/exclusion criteria
- AE records
- storage and accountability of trial drug and trial materials
- adherence to the protocol and ICH-GCP

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs are described in the Trial Reference Manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to meet with the CRA(s) during trial site visits; to ensure that trial staff is available to the CRA(s) as needed; to provide the CRA(s) access to all trial documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

13.5.2. Data Management

The sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and Premier standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the trial manual.A partial database lock is planned for interim analyses prior to NDA submission. Additional partial database locks may be performed for analyses to support the NDA process.

13.5.3. Quality Assurance/Audit

This trial will be subject to audit by the sponsor/its designee or national/international regulatory authorities. Audits may be performed to check compliance with GCP guidelines, and can include:

- Site audits
- Trial master file (TMF) audits
- Database audits
- Document audits (e.g., protocol and/or the clinical trial report [CTR])

The sponsor or its designee may conduct additional audits on a selection of trial sites, requiring access to patient notes, trial documentation, and facilities or laboratories used for the trial.

The trial site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify the sponsor immediately.

13.6. Trial Termination

The trial may be terminated at the sponsor's discretion at any time and for any reason.

13.6.1. Regular Trial Termination

The end of this trial is defined as the date of the last visit of the last patient completing the Trial Period as described in Section 7.2. Monitoring of treatment-induced or treatment-boosted ADA-positive patients at Trial Completion will continue until the ADA levels return to baseline or until 2 years after End of Trial, whichever occurs first. Within 90 days of the end of the clinical trial, the sponsor or its designee and/or the site will notify the IRBs and IECs and regulatory authorities on the regular termination of the trial, as required according to national laws and regulations.

13.6.2. Premature Trial Termination

The trial may be terminated prematurely for any reason and at any time by the sponsor, the IRBs/IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to terminate the trial prematurely is binding to all investigators at all trial sites.

Within 15 days of premature termination of a clinical trial, the sponsor or its designee and/or the site will notify the IRBs/IECs and regulatory authorities on the premature termination as required according to national laws and regulations. The sponsor or its designee must clearly explain the reasons for premature termination.

If the trial is terminated prematurely, all investigators must inform their patients and take care of their appropriate follow-up and further treatment to ensure protection of their interests. Trial sites

may be asked to have all patients currently participating in the trial complete all of the assessments for an Early Termination Visit.

13.7. Trial Site Closure

At the end of the trial, trial sites with no treatment-induced or treatment-boosted ADA-positive patients will be closed. Sites with treatment-induced or treatment-boosted ADA-positive patients will remain open until the ADA level of their last ADA-positive patient has returned to baseline or until 2 years after End of Trial, whichever occurs first.

The sponsor may terminate participation of a trial site at any time. Examples of conditions that may require premature termination of a trial site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate patient enrollment

13.7.1. Record Retention

After trial completion at sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the trial, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the trial drug has been approved or the sponsor has discontinued its research with the trial drug, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the trial drug

However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After trial completion at sites in Europe, the sponsor will receive a copy of their data in electronic format (e.g., CD) and retain them for at least 25 years.

One copy will remain with the investigator. The investigator shall arrange for the retention of the patient identification codes, patient files, and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

The investigator shall keep copies of these trial records (and all trial-related documents, including source data) for the maximum period of time permitted by the hospital, institution, or private practice.

13.7.2. Sample Retention

Samples will only be used for purposes related to this trial.

All blood samples will be destroyed upon completion of the CTR, except for residual ADA samples, which will be stored until approval of market authorization because further characterization of the antibody response may be requested by the health authorities. Identifiable samples can be destroyed at any time at the request of the patient.

13.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB/IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the trial.

13.9. Use of Information and Publication

All information concerning dasiglucagon, the sponsor's operations, patent applications, formulae, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or its designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of trial execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this trial will be used by the sponsor in connection with the continued development of dasiglucagon and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this trial is the property of the sponsor. Publication or other public presentation of dasiglucagon data resulting from this trial requires prior review and written approval of the sponsor. Abstracts, manuscripts, and presentation materials should be provided to the sponsor for review and approval at least 30 days prior to the relevant submission deadline. Data from individual trial sites must not be published separately.

It is agreed that the results of the trial will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until the sponsor has reviewed and commented on such a presentation or manuscript for publication.

14. FINAL CLINICAL TRIAL REPORT

The sponsor will retain ownership of the data.

The final CTR will be reported on the Trial Period and will be prepared and reviewed in cooperation with the signatory investigator. The coordinating investigator will be appointed by the sponsor to review and sign the CTR on behalf of all participating investigators. This report will include a summary of the trial results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints. The results from the neutralizing antibody assay may be included or reported separately pending availability of the results. The results of the ADA follow-up samples will be reported separately after completion of the ADA Follow-up Period.

The final CTR may be submitted to the regulatory authorities.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki and Good Clinical Practice

This trial will be conducted in compliance with the November 2016 ICH Guidance for Industry E6(R2) GCP (including archiving of essential trial documents), the 2013 version of the Declaration of Helsinki, and the applicable regulations of the country(ies) in which the trial is conducted.

See Appendix C for regulation and guidelines.

15.2. Patient Information and Informed Consent

According to the Declaration of Helsinki and ICH GCP, patients' parent(s)/guardian must provide their written informed consent (and the child must provide assent, depending on local IRB/IEC requirements) prior to enrollment in a clinical trial and before any protocol-specified procedures are performed. Patients' parent(s)/guardian (and the patient, depending on local IRB/IEC requirements) must declare their consent by personally signing and dating the ICF.

France, Germany, Israel: *The consent must correspond to the patient's presumed will where such a will can be ascertained.*

The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each patient's parent(s)/guardian (and patient, depending on local IRB/IEC requirements) should be made aware by the investigator of the nature of the trial (objectives, methods, and potential hazards and benefits) and the procedures involved using the information on the ICF.

France, Germany, Israel: *Additionally, the patient will be informed about the nature, significance, risks, and implications of the trial with age-appropriate information, and his or her assent will be obtained in accordance with local regulations, as applicable*.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Patients, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the trial.

Patient information and the ICF must be in a language fully comprehensible to the prospective patient's parent(s)/guardian (and patient, depending on local IRB/IEC requirements). The written information must be provided to the patient's parent(s)/guardian (and the patient, depending on local IRB/IEC requirements) to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent (and assent). The investigator must confirm that the text was understood by the patient's parent(s)/guardian (and patient where applicable). The patient's parent(s)/guardian (and patient, where applicable) will then sign and date the IRB/IEC-approved consent (and assent) form indicating that he or she has given his or her consent for his or her child to participate in the trial. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the trial patient number. Each signed ICF and assent must be kept on file by the investigator for possible inspection by regulatory authorities, the sponsor, and/or the sponsor's designee. Collection of informed consent has to be documented on the eCRF.

Furthermore, the patient's parent(s)/guardian will be informed that if he or she wishes to withdraw his or her child (see Section 8.3) at any time during the trial, this will not have any negative consequences. Patients may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the trial. Patients' parent(s)/guardian (and patient, where applicable) will be asked to agree to a final assessment in the event of an early termination of the trial.

If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patients' parent(s)/guardian in a timely manner, and a revised written informed consent must be obtained.

Patients' parent(s)/guardian (and patient where applicable) will be informed that data from their child's case may be stored in a computer without inclusion of his or her name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

15.3. Approval by Institutional Review Board and Independent Ethics Committee

For Investigational New Drug studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB/IEC must review and approve this protocol before trial initiation. Written notification of approval is to be provided by the investigator to the sponsor's monitor and project manager before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor form, IRB/IEC Approval Form, or written documentation from the IRB/IEC containing the same information.

Until written approval by the IRB/IEC has been received by the investigator, no patient may undergo any procedure not part of routine care for the patient's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by the sponsor before implementation. This written approval will consist of a completed IRB Approval Form or written documentation from the IRB/IEC containing the same information.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

16. REFERENCES

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17. ATTACHMENTS

17.1. Schedule of Events

Table 1 Schedule of Events

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

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

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

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

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

17.2. Investigator's Agreement

PROTOCOL NUMBER:	ZP4207-17106
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
FINAL PROTOCOL:	Version 19.0, 08-Nov-2024

The undersigned acknowledges possession of and has read the product information (e.g., IB) on the trial drug and has discussed these data with the trial monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the trial drug to selected patients in his/her care, according to the trial protocol.

- He or she agrees to use the trial material, including trial drug, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of the sponsor.
- He or she understands that any deviation from the protocol may lead to early termination of the trial.
- He or she agrees to report to the sponsor within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of trial drug.
- He or she agrees to comply with the sponsor and regulatory requirements for the monitoring and auditing of this trial.

In addition, he/she agrees that the trial will be carried out in accordance with the revised Declaration of Helsinki (2013) and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the trial.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

18. APPENDICES

A. Contact Information
B. List of Quality of Life Questionnaires
C. Regulations and Good Clinical Practice Guidelines
D. Seizure Checklist

A. Contact Information

Safety CRO:

Name: [redacted]
Address: [redacted]
[redacted]
E-mail: [redacted]
Telephone: [redacted]

B. List of Quality of Life Questionnaires

- Infants 1-12 Months: "PedsQL™ Pediatric Quality of Life Inventory Infant Scales – Version 1 - Parent Report for Infants (ages 1-12 months)"
- Infants 13-24 Months: "PedsQL™ Pediatric Quality of Life Inventory Infant Scales – Version 1 - Parent Report for Infants (ages 13-24 months)"
- Parent Report for Teens 13-18 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Teens (ages 13-18 yrs)"
- Parent Report for Children 8-12 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Children (ages 8-12 yrs)"
- Parent Report for Children 5-7 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Young Children (ages 5-7 yrs)"
- Parent Report for Toddlers 2-4 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Toddlers (ages 2-4 yrs)"
- CHI Disease-Specific Questionnaire Developed by the Patient Association, Congenital Hyperinsulinism International, and Taken from the Patient-Reported Registry, the HI Global Registry

C. Regulations and Good Clinical Practice Guidelines

1. Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives [and applicable regulations/guidances]:

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents

2. Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
https://www.ich.org/page/efficacy-guidelines

D. Seizure Checklist

At site visits and during monthly telephone contacts, the investigator should ask the patient and their caregiver(s), about any possible signs and symptoms of seizures. The below listed symptoms should be reviewed during the interview:

- Staring episodes
- Temporary confusion
- Not responding to noise or words for brief periods
- Appearing confused or in a daze
- Nodding the head rhythmically, when associated with loss of awareness or even loss of consciousness
- Periods of rapid eye blinking, jerky eye movements, or forced eye deviation.
- Jerking movements of the arms and legs (myoclonus or clonic movements)
- Stiffening of the body (entire body or one arm/leg)
- Loss of consciousness or awareness, fainting
- Falling suddenly for no apparent reason, especially when associated with loss of consciousness
- Breathing problems (abnormal breathing pattern or interruption of breathing)
- Loss of bowel or bladder control
- Auditory/visual aura (episodic hallucinations or distortions of perception
- Myoclonus
- Automatism
- Biting of tongue

An episode of partial or generalized seizure should be reported as an AESI, as described in Section 11.1.8.

Any single signs or symptoms observed by the patient/caregiver(s) and evaluated by the investigator to not be a seizure should be reported as an AE(s).

PROTOCOL

PRODUCT NAME/NUMBER:	Dasiglucagon
PROTOCOL NUMBER:	ZP4207-17106
IND NUMBER:	135869
EUDRACT NUMBER:	2017-004546-15
DEVELOPMENT PHASE:	Phase 3
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
PROTOCOL DATE:	Original Protocol Version 1.0, 14-Dec-2017 Amended local German protocol final version 17.0, 09-Apr-2024
SPONSORED BY:	Zealand Pharma A/S Sydmarken 11 2860 Soeborg (Copenhagen) Denmark Telephone: +45 88 77 36 00
CONTRACT RESEARCH ORGANIZATION:	Premier Research One Park Drive Suite 150 Durham, NC 27709 USA

REVISION HISTORY

PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
PROTOCOL DATE:	Original Protocol Version 1.0, 14-Dec-2017
	This updated local (Germany) protocol version 15.0 includes:
AMENDMENT No. 1	Final Version 2.0, 31-May-2018 (All countries)
AMENDMENT No. 2	Final Version 3.0, 24-Jul-2018 (United Kingdom)
AMENDMENT No. 3	Final Version 4.0, 25-Jul-2019 (France, Germany, Israel)
AMENDMENT No. 4	Final Version 5.0, 03-Jun-2019 (Germany)
AMENDMENT No. 5	Final Version 6.0, 03-Jun-2019 (All countries)
AMENDMENT No. 7	Final Version 8.0, 11-Oct-2019 (All countries except Germany)
AMENDMENT No. 8	Final Version 9.0, 29-Jan-2020 (Germany)
AMENDMENT No. 9	Final Version 10.0, 01-Oct-2021 (All countries except Germany)
AMENDMENT No. 10	Final Version 11.0, 11-Oct-2021 (Germany)
AMENDMENT No. 11	Final Version 12.0, 28-Sep-2022 (All countries except Germany)
AMENDMENT No. 12	Final Version 13.0, 28-Sep-2022 (Germany)
AMENDMENT No. 13	Final Version 14.0, 22-May-2023(All countries except Germany)
AMENDMENT No. 14	Final Version 15.0, 22-May-2023 (Germany)
AMENDMENT No. 15	Final Version 16.0, 09-Apr-2024 (All countries except Germany)
AMENDMENT No. 16	Final Version 17.0, 09-Apr-2024 (Germany)

1. APPROVAL SIGNATURES

PROTOCOL NUMBER:	ZP4207-17106
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the trial.

[redacted]

Senior Clinical Trial Manager
Zealand Pharma A/S

[redacted]

Senior Medical Director
Zealand Pharma A/S

[redacted]

Senior Biostatistician
Premier Research

2. SYNOPSIS

PRODUCT NAME/NUMBER	Dasiglucagon
PROTOCOL NUMBER	ZP4207-17106
EUDRACT NUMBER	2017-004546-15
DEVELOPMENT PHASE	Phase 3
PROTOCOL TITLE	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
INDICATION	Congenital hyperinsulinism (CHI)
OBJECTIVES	Primary: To evaluate the long-term safety of dasiglucagon administered as subcutaneous (SC) infusion in children with CHI Secondary: • To evaluate the long-term efficacy of dasiglucagon in reducing hypoglycemia • To evaluate the long-term efficacy of dasiglucagon in reducing glucose requirements • To evaluate the long-term tolerability of dasiglucagon administered as SC infusion in children with CHI • To investigate quality of life and resource utilization
TRIAL DESIGN	This is an open-label, multinational, multicenter, long-term safety and efficacy extension trial in patients with CHI who completed either ZP4207-17103 or ZP4207-17109 (defined as a lead-in trial). The investigator is allowed to change the standard of care (SOC) medication for CHI at his or her discretion in order to optimize the treatment of each patient. To use a minimally invasive yet objective method of assessing the frequency of hypoglycemia, patients will be required to wear a continuous glucose monitoring (CGM) device throughout the entire trial period. Pauses are allowed; however, CGM should be used for the 30 days leading up to each visit, and families will also be asked to perform self-monitored plasma glucose (SMPG). Parent(s)/guardian will be trained on the use of the meters. The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial. Any post-treatment follow-up scheduled for patients in the lead-in trial will be redundant if they are enrolled in the present trial by the time of the scheduled Follow-up Visit. Patients will be seen at Months 1, 3, and 6 and every 3 months thereafter and contacted by the investigator monthly by telephone in between site visits. At site visits, patients and their parent(s)/guardian will receive a paper diary to record potential adverse events (AEs) and concomitant medication, among other information, which will be reviewed regularly by site staff at each visit. Patients will be allowed to remain in the trial until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP) or until approximately Q3 2024 (treatment period), whichever occurs first. An interim analysis may be performed as appropriate to support a marketing application/ new drug application.
PLANNED NUMBER OF PATIENTS	A maximum of 44 patients are expected to be enrolled in the lead-in trials, and approximately 30-44 of those patients are expected to be enrolled in this trial.

TRIAL ENTRY CRITERIA	Eligible patients are those who have completed treatment in either trial ZP4207-17103 or ZP4207-17109 and are expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon, with an investigator statement documenting the positive benefit-risk assessment (based on considerations of glycemic effect, tolerability, and nature and frequency of AEs experienced in the lead-in trial).
INVESTIGATIONAL PRODUCT	Dasiglucagon injection 4 mg/mL in a 3 mL vial containing 1 mL
REFERENCE PRODUCT	None
TREATMENT REGIMENS	Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with an option to further titrate the dose to meet the needs of each patient. During the trial, SMPG assessments will be performed as instructed by the investigator. For patients using the Dexcom G5 CGM, SMPG assessments will be performed at least 2 times per day for CGM calibration. Patients will continue their SOC treatment for CHI. The combined treatment of SOC and dasiglucagon should aim to reduce gastric dextrose infusions and glucose fortified meals as much as possible, maintaining the patient's plasma glucose within 70 and 120 mg/dL at all times on normal feedings.
PLANNED TRIAL SITES	Up to 14 sites in the United States, Europe, and Israel with all sites having been involved in the lead-in trials.
CRITERIA FOR EVALUATION	Primary endpoint: • AEs Key secondary efficacy endpoints: • Total amount of gastric carbohydrates administered (nasogastric [NG] tube or gastrostomy) to treat hypoglycemia • Time to removal of NG tube or gastrostomy • Time to pancreatic surgery (sub-total or total pancreatectomy) • CGM percent time <70 mg/dL (3.9 mmol/L) • Rate of CGM-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) for 15 minutes or more • Rate of clinically significant CGM-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) for 15 minutes or more The primary endpoint will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and then in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis. All efficacy endpoints will be analyzed using average weekly results over Month 1, Month 1 to Month 3 and then each 3-month period between visits.
STATISTICAL METHODS	Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively; the exception to this is the time of plasma glucose (PG) within pre-specified ranges, which will not have a baseline value. For categorical endpoints, descriptive summaries will include counts and percentages. All data will be presented in the data listings.

	Analysis Populations Three analysis populations have been defined for this trial: The Safety Set: defined as all patients administered any trial drug. This population will be used to provide descriptive summaries of safety data. The Full Analysis Set (FAS): defined as all patients in the Safety Set who complete at least 1 day of trial drug. This population will be used to analyze efficacy data. The Pharmacokinetic Analysis Set (PK): defined as all patients in the Safety Set who have at least one measurement with quantifiable plasma concentration of dasiglucagon. This population will be used to provide descriptive summaries of PK data. Primary Analysis For the primary endpoint, the number of AEs will be summarized by time period up to Month 1, Month 1 to Month 3, Month 3 to Month 6, Month 6 to Month 9, Month 9 to Month 12, etc.). Efficacy Analyses For the first and fourth key secondary endpoints, total amount of carbohydrates administered to treat hypoglycemia and CGM percent time <70 mg/dL, respectively, will be analyzed using a mixed-model for repeated measures using restricted maximum likelihood (REML). Time to event data will be analyzed using Kaplan-Meier methods. For the two last key secondary endpoints, the rate of CGM-detected hypoglycemic episodes will be analyzed using a generalized linear mixed-model (GLMM) regression approach assuming a negative binomial distribution. For all other efficacy endpoints, continuous and categorical endpoints will be presented using summary statistics or frequencies, respectively. If warranted, continuous measures will be analyzed using a paired t-test or mixed model with region as a fixed effect and baseline value as a covariate; categorical measures will be analyzed using a Chi-square goodness-of-fit test or binomial test for proportions, as data permit, to determine whether there is a difference from the previous time point. An interim analysis will be performed as appropriate to support the application for approval of dasiglucagon. Safety Analyses Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Adverse events with an onset at the time of or following the start of treatment with the trial drug through the Follow-up Visit or Early Termination Visit, whichever occurs first, and no longer than 12 weeks after treatment discontinuation will be defined as treatment emergent. The overall incidence of AEs will be displayed by system organ class, preferred term, and treatment. The incidence of AEs will also be presented by severity and by relationship to the trial drug. Vital signs, clinical laboratory measures (including hematology, biochemistry, and incidence of anti-drug antibodies [ADAs]), ECGs, physical examinations, and local tolerability data will be summarized by treatment, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. A formal statistical analysis plan (SAP) will be prepared to provide further details on the methods for statistical analysis.
SAMPLE SIZE DETERMINATION	The sample size is based upon patients rolling over from the lead-in trials; no sample size calculation was performed.

TRIAL AND TREATMENT DURATION	The sequence and maximum duration of the trial periods will be as follows **Trial Period (from last visit in lead-in trial until Trial Completion, as defined below):** 1. Baseline: defined as the End of Treatment (EoT) Visit from lead-in trials ZP4207-17103 or ZP4207-17109. 2. Treatment Period: treatment will continue until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP) or until approximately Q3 2024, whichever occurs first, at which time an EoT Visit will be scheduled. 3. EoT Visit: see above 4. Follow-up Visits: will occur 4 weeks and 12 weeks after the EoT Visit. 5. Trial Completion: completion of the final Follow-up Visit or the EoT Visit if the patient continues treatment with dasiglucagon commercially or through an EAP. **ADA Follow-up Period (from Trial Completion until last patient's last visit [LPLV]):** 6. Monitoring of treatment-induced or treatment-boosted ADA-positive patients after Trial Completion: will continue until the ADA levels return to baseline (defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial) or until 2 years after End of Trial, whichever occurs first. **End of Trial:** defined as the time all patients have reached Trial Completion (completed the Follow-up Period or the EoT Visit if continuing treatment with dasiglucagon commercially or through an EAP, whichever occurs first). **LPLV**: last visit of the last patient in the ADA Follow-up Period.

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4. LIST OF ABBREVIATIONS

ADA	antidrug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
$AOC_{glucose}$	area over the glucose curve
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time zero to infinity
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CE	Conformité Européene
CGM	continuous glucose monitoring
CHI	congenital hyperinsulinism
C_{max}	maximum concentration
CRA	clinical research associate
CRO	contract research organization
CTR	clinical trial report
DMC	data monitoring committee
EAP	early access program
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ER/A&E	emergency room/accident & emergency department
EoT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GI	gastrointestinal
GLMM	generalized linear mixed-model

GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IM	intramuscular(ly)
IRB	institutional review board
ISF	Investigator Site File
IV	intravenous(ly)
LAR	legally authorized representative
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NG	nasogastric
NME	necrolytic migratory erythema
PD	pharmacodynamics(s)
PedsQL	Pediatric Quality of Life Inventory
PG	plasma glucose
PK	pharmacokinetic(s)
PT	preferred term
QoL	quality of life
RBC	red blood cell
REML	restricted maximum likelihood
RSI	Reference Safety Information
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	standard deviation
SMPG	self-monitored plasma glucose
SOC	standard of care

SpO_2	blood oxygen saturation level
SUSAR	suspected unexpected serious adverse reaction
TMF	trial master file
TMM	trial materials manual
ULN	upper limit of normal
USADE	unanticipated serious adverse device effect
Zealand	Zealand Pharma A/S

5. INTRODUCTION

5.1. Background and Rationale

Congenital hyperinsulinism (CHI) is a rare and challenging disorder in which β-cells in the pancreas secrete insulin irrespective of plasma glucose (PG) concentration, resulting in persistent and often severe hypoglycemia.[1] Congenital hyperinsulinism affects up to 1 in 50,000 newborns. It is typically diagnosed on the basis of signs and symptoms of hypoglycemia during the neonatal period or in infancy; however, the diagnosis may be made later in childhood. Several different genetic mutations have been described to cause CHI, which can be either focal (only a small area of the pancreas is affected) or diffuse (most of the pancreas is affected). The condition can persist into adulthood; however, the severity generally decreases with age due to the increased insulin requirements and/or reduced insulin resistance, and CHI is thus primarily a pediatric disease with regard to medical treatment needs. Hypoglycemia that results from CHI is of particular concern because it is an important cause of brain injury in neonates, infants, and children with this disease, which leads to long-term neurological impairments.[1,2] Up to approximately 50% of children with CHI experience neurodevelopmental abnormalities caused by severe hypoglycemia that results from inadequate treatment and/or delays in diagnosis.[1,3] Severe brain damage is the consequence of severe hypoglycemia, which presents as coma and/or long-lasting epileptic seizures in neonates. Major intellectual disability is, therefore, most frequent in neonatal patients with initial onset, whereas hypoglycemia is usually less severe and brain damage less frequent in children with CHI diagnosed later in childhood.[1] Since symptoms and severity of hypoglycemia can vary and pose a diagnostic challenge in neonates, infants, and children with CHI, prompt recognition and treatment of hypoglycemia is critical to reduce the risk of long-term neurological consequences.

5.2. Current Treatment and Unmet Medical Need

Medical treatment for CHI is focused on chronic therapies to avoid hypoglycemia, as well as on rescue therapy during acute episodes of severe hypoglycemia. Available medical therapies (mainly diazoxide/octreotide/glucagon for reconstitution alone or in combination with glucose infusion) are inadequate and accompanied by inability to control plasma glucose, as reflected in a large proportion of patients requiring sub-total pancreatectomy.[4,5,6] With the exception of surgery for focal CHI, which is curative in the vast majority of patients, sub-total pancreatectomy for diffuse CHI has substantial inadequacies. A recent trial[7] showed that 60% of patients who underwent near-total pancreatectomy had persistent hypoglycemia after surgery. Moreover, 96% had developed insulin-dependent diabetes within 11 years after surgery, indicating the serious and long-term consequences of the procedure.

First-line medical treatment is diazoxide, which is the only EU- and US-approved drug for treatment of hyperinsulinemic hypoglycemia. Diazoxide acts to open K_{ATP} channels of the pancreatic β-cells, thereby inhibiting insulin secretion. Unfortunately, many patients with CHI are resistant to diazoxide because of mutations in the genes encoding the K_{ATP} channel of the pancreatic β-cells.[6] For those who respond to diazoxide treatment, the more common side effects comprise hypertrichosis, fluid retention, and gastrointestinal (GI) symptoms; however, side effects are usually not severe. In diazoxide non-responders, second-line (and off-label) treatment is a somatostatin analog (octreotide or lanreotide [long acting]), which (among other effects) inhibits secretion of insulin and glucagon from the pancreas and suppresses glucagon-like

peptide-1 (GLP-1) secretion. Factors that limit their use comprise tachyphylaxis, as well as possible side effects, including necrotizing enterocolitis, gallstones, and hepatitis.[6]

Glucagon has been shown to be effective in the treatment of CHI. The glycogenolytic effect of glucagon and its ability to increase plasma glucose levels has been confirmed in children with CHI or neonatal hypoglycemia,[8,9] and administration of reconstituted glucagon (via intravenous [IV] infusion or as repeated subcutaneous [SC] injection) is often used in the initial phase during the establishment of CHI diagnosis and to stabilize patients with CHI before surgery or initiation of other medical treatments.[10] Furthermore, glucagon is administered as single SC doses to treat severe hypoglycemic episodes. While IV administration of glucagon to patients with CHI is used short-term in the hospital setting, e.g., before pancreatectomy,[2,10,11] long-term glucagon treatment is complicated by the fact that currently available glucagon products are unstable in nature and form fibrils within hours after reconstitution.[12] This fibril formation may lead to infusion set clotting, catheter obstruction, and dosing errors that may cause acute severe hypoglycemia. Catheter obstruction and occlusion because of glucagon fibril formation and aggregation were observed daily to 2 to 3 times weekly in a retrospective review of 9 patients with CHI receiving continuous SC infusion of glucagon for weeks or months.[11] In another series of patients, 60% of the patients treated with SC glucagon experienced catheter occlusion.[6] In a home-care setting, this fibril formation and associated risk of dosing errors carry the risk of hypoglycemic events, which is a major barrier for using currently marketed glucagon products for long-term treatment of patients with CHI.

With respect to long-term glucagon treatment in CHI, there are a few reports on home treatment with subcutaneously infused glucagon in children with CHI over extended periods (years) that suggest benefit in patient care with a potentially good safety profile as compared to diazoxide and octreotide.[6,11,13] While this attests to the potential clinical relevance of long-term glucagon treatment in CHI, the use of SC infusion of currently marketed glucagon is severely limited by the issues with fibril formation and solution instability of recombinant glucagon as described previously.

5.3. Dasiglucagon for the Treatment of Congenital Hyperinsulinism

5.3.1. Dasiglucagon

Dasiglucagon is a peptide analog of human glucagon that has been developed for the treatment and prevention of hypoglycemia in patients with diabetes mellitus via SC or IV administration. Dasiglucagon is under development for prevention and treatment of hypoglycemia in children with CHI and for the following other indications: Improving glycemic control in insulin-treated patients with type 1 diabetes mellitus, as part of a bihormonal artificial pancreas system, treatment of post-bariatric hypoglycemia and glycemic control during exercise and physical activity in patients with diabetes.

Dasiglucagon is a stable analog of glucagon that has been specifically designed to overcome the issues with fibril formation and instability in solution observed with marketed glucagon products. Compared to glucagon, dasiglucagon also comprises 29 amino acids. As a result of chemical modifications (7 amino acid substitutions compared to human glucagon), the pronounced tendency of glucagon to form fibrils and aggregate has been effectively prevented in dasiglucagon. In addition, the chemical stability in aqueous media at physiological pH has been improved.

To support the use of dasiglucagon in the pump, compatibility/in-use studies have been performed with dasiglucagon 4 mg/mL in the Hoffman-La Roche Accu-Chek Combo infusion pump using the Accu-Chek Spirit 3.15 mL cartridge system and the Accu-Chek Flexlink infusion set. The studies support an in-use time for up to 6 days at 37ºC.

Dasiglucagon was granted orphan drug designation by the European Commission on 20 June 2017 for the '*treatment of congenital hyperinsulinism.*' Furthermore, the Food and Drug Administration (FDA) granted an orphan drug designation for the '*treatment of hypoglycemia in patients with congenital hyperinsulinism (CHI)*' on 10 August 2017.

5.3.2. Nonclinical Experience

The completed nonclinical pharmacology program has determined that dasiglucagon is a specific glucagon receptor agonist with comparable in vitro potency to glucagon, promoting a rapid onset of PG increase in both normal and insulin-induced hypoglycemic animals, similar to that of glucagon. The effects of dasiglucagon and glucagon were investigated in an insulin-induced hypoglycemic rat model, which is considered particularly relevant to characterize the use of dasiglucagon for the treatment of CHI because it mimics the inappropriate insulin to PG levels in CHI and resultant hypoglycemia. The onset of PG increase with dasiglucagon was rapid and similar to that observed for glucagon, confirming comparable pharmacodynamics.

Results of the toxicity studies with dasiglucagon are comparable to what has been reported for glucagon. Those from chronic toxicity studies with dasiglucagon in rats and dogs are in line with the results of short-term toxicity studies, indicating that long-term treatment with dasiglucagon is safe and that the pharmacodynamic (PD) effects noted do not adversely affect organ function following chronic use.

5.3.3. Clinical Experience

Dasiglucagon is being developed to manage patients with CHI 1) as an initial short-term therapy to stabilize PG levels and reduce glucose infusion needs, and 2) as a long-term treatment to help maintain euglycemia

Within the indication of prevention and treatment of hypoglycemia in children with CHI, efficacy and safety results are available from two completed trials.

Efficacy

Phase 2/3, two-period efficacy and safety trial ZP4207-17103

In this trial, 12 CHI patients (aged 7 days to 12 months) who needed continuous IV glucose administration to manage hypoglycemia completed a randomized clinical trial that consisted of a double-blind placebo-controlled crossover Part 1 followed by an open-label Part 2. Dosing of dasiglucagon approximated continuous SC infusion by delivering small doses at frequent intervals via an infusion pump according to a predefined algorithm. The focus in this trial was on the clinically relevant reduction and eventually elimination of the need for continuous IV glucose infusion, while avoiding hypoglycemia.

Compared to placebo, a statistically significant reduction in mean IV glucose infusion rate was obtained during the last 12 hours after dasiglucagon treatment (treatment difference [95% CI]: -5.21 mg/kg/min [-8.29 to -2.13], p = 0.0037). This corresponded to a 55% reduction of weighted mean IV glucose infusion rate compared to placebo.

The total amount (g) of carbohydrates administered (regardless of the route) per day during Part 1 of the trial was statistically significantly lower after dasiglucagon treatment compared with placebo (treatment difference [95% CI]: -30.93 g/day [-56.80 to -5.05], p = 0.0238).

Phase 3, two-period efficacy and safety trial ZP4207-17109

In this phase 3 trial in 32 CHI patients aged 3 months to 12 years, dasiglucagon treatment added to standard of care (SOC) did not significantly reduce the number of intermittent SMPG-measured hypoglycemia events per week when compared to SOC alone (primary endpoint).

CGM metrics are not validated for use in patients with CHI. However, a post hoc analysis showed that dasiglucagon treatment resulted in clinically meaningful reductions in all measures of hypoglycemia assessed by blinded CGM (including number of events and time in hypoglycemia) compared to SOC treatment alone.

Safety

Phase 2/3, two-period efficacy and safety trial ZP4207-17103

A total of 12 patients aged from ≥7 days to <12 months were exposed to dasiglucagon in trial ZP4207-17103. The total duration of dasiglucagon exposure was 0.67 patient-years. Two SAEs (respiratory distress and acute respiratory failure) in the same patient were reported; both events were reported in the open-label period (where patients received dasiglucagon), and none were considered related to treatment with dasiglucagon.

Adverse events, other safety parameters, and immunogenicity

The most frequently reported AEs with dasiglucagon during Part 1 + Part 2 of the trial were anemia, vomiting, and rash papular (each reported by 3 patients). None of these AEs were reported more frequently with dasiglucagon as compared to placebo during the cross-over period (Part 1).

No confirmed cases of necrolytic migratory erythema (NME) were reported. Two hemodynamic events were reported: 2 AEs of tachycardia (1 during placebo and 1 during dasiglucagon treatment), which were both mild, intermittent, and not related to trial treatment.

No remarkable abnormalities were found in the biochemistry, hematology, vital signs, electrocardiogram (ECG), echocardiography, and physical and neurological exams. A few cases of clinically significant changes in hemoglobin, electrolytes, ALT, and AST were noted. None indicated any trends in aggregated change from baseline.

Local tolerability reactions, assessed only for patients in dasiglucagon + standard of care group, were mostly mild and attributed to the adhesive dressing. None of the local reactions were severe, and none were attributed to the trial intervention.

None of the children were tested positive for treatment-boosted or treatment-induced ADA (10 out of 12 children were tested for ADA at baseline and 8 were tested during trial).

Phase 3, two-period efficacy and safety trial ZP4207-17109

A total of 32 patients ages ≥3 months to ≤12 years were randomized and exposed to dasiglucagon in the completed ZP4207-17109 trial; total duration of dasiglucagon exposure was 3.8 patient-years. Overall, dasiglucagon treatment appeared well-tolerated in the trial. A total of

5 SAEs in 3 patients were reported in the dasiglucagon plus SOC group (central line infection, localized infection, folliculitis, influenza H1N1, and hyperglycemia); none of these were considered related to dasiglucagon treatment.

Adverse events, other safety parameters, and immunogenicity

In trial ZP4207-17109, vomiting was reported more frequently in the dasiglucagon treatment group as compared with those receiving SOC treatment, consistent with these gastrointestinal events being well-known side effects of glucagon treatment. More cases of skin and subcutaneous tissue disorders (including two confirmed events of necrolytic migratory erythema NME) were reported for dasiglucagon relative to SOC treatment, but no skin-related events led to discontinuation of dosing. Also, a minor imbalance of events was noted within the system organ class of infections and infestations during the initial 4-week trial period (12 with dasiglucagon versus 4 with SOC only).

No remarkable abnormalities were found in the biochemistry, hematology, vital signs, ECG, echocardiography, or physical and neurological examinations. A few cases of transient increases in ALT and AST were noted for dasiglucagon; of those reported as AEs, all were assessed as not/unlikely related to the trial product. No hemodynamic events were reported.

With respect to dasiglucagon antibody development, 7 out of 30 children (23.3%) with ADA assessments were ADA-positive during the trial (1 with treatment-boosted and 6 with treatment-induced ADA). Of these 7 children, 1 (14.3%) had cross-reactivity to glucagon and another (14.3%) had dasiglucagon in vitro neutralizing antibodies at the follow-up visit. In vitro neutralizing antibodies were not detected for the remaining 5 children with treatment-induced ADA.

QT prolongation

A comprehensive evaluation of the effect of dasiglucagon on cardiac repolarization and its proarrhythmic potential has been made based on 1) nonclinical data, 2) data from trial ZP4207-17144 in healthy subjects, in which potential ECG effects were evaluated through serial ECG monitoring and concentration-QTc analysis, and 3) data from phase 2/3 clinical trials to support the indication of treatment of severe hypoglycemia. It is concluded that there is no indication of dasiglucagon exerting a clinically relevant effect on QTcF interval or having a proarrhythmic potential.

The above conclusion is supported by the data from the completed CHI trials.

5.3.4. Literature Data

In a retrospective review of 223 cases of diffuse or focal CHI, glucagon was reported to be used in 55% of patients with diffuse CHI and in 31% of patients with focal CHI.[10] In an observational trial of 55 newborns who received glucagon because of hypoglycemia after birth, applied doses were mainly in the range of 0.5 to 1.0 mg/day, and results indicated an increase in PG from a mean of 36.3 md/dL to a mean of 93.0 mg/dL, observed within 4 hours after the start of glucagon infusion.[9] The frequency of hypoglycemic episodes was significantly reduced, and no further episodes of severe hypoglycemia were observed.

The long-term use of glucagon in patients with CHI is limited by the instability of marketed glucagon after reconstitution. A literature review on the long-term medical treatment of CHI revealed that only 1% of 619 patients identified received glucagon as part of their medical

management.[6] A retrospective review of 9 children with CHI who received continuous SC infusion of glucagon for weeks or months showed that introduction of glucagon allowed the reduction or discontinuation of central glucose infusion in all patients.[11] Six of 9 patients were discharged with continued glucagon therapy that their parents were able to continue without further symptomatic hypoglycemia, convulsions, or unconsciousness. In 3 children, glucagon therapy was continued for 1 to 4 years, which led to stable euglycemia.

The data reported on marketed glucagon use in patients with CHI indicate that continuous SC infusion of a glucagon agonist could provide therapeutic benefit to patients by stabilizing PG levels and reducing the frequency of hypoglycemic episodes.[5,6,9,10,11]

5.3.5. Anticipated Medical Benefit of Dasiglucagon in the Treatment of Congenital Hyperinsulinism

With its physio-chemical stability in liquid formulation, dasiglucagon could provide significant added benefit in the treatment of CHI relative to currently marketed glucagon by enabling long-term reliable IV infusion to control blood glucose. Long-term subcutaneous infusion of dasiglucagon through a pump may be an attractive alternative or addition to diazoxide and octreotide, as it may reduce the dependency on intensive nutritional support whilst maintaining euglycemia by harnessing physiological mechanisms for combating hypoglycemia. It is anticipated that reduced need for frequent tube feedings or continuous gastric infusion of nutrients, and increased fasting tolerance will be demonstrated, together with improvements in the quality of life of the patients and their families/guardians. If long-term euglycemia is achieved with medical therapy, pancreatectomy for the treatment of diffuse CHI could eventually be avoided, or at least postponed beyond the neonatal or very young infant period. In 1 cohort of non-surgically treated children, the mean clinical remission rate was 5 (1.5-12) years for diffuse CHI.[5] This suggests that a significant proportion of infants with CHI could avoid surgery if medical treatment allowed for the effective long-term control of hyperinsulinism.

5.3.6. Anticipated Risks of Dasiglucagon in the Treatment of CHI

Overall, in the two completed trials the most commonly reported types of AEs in patients with CHI were skin disorders (various rashes, and eczema), gastrointestinal disorders (including vomiting), and infections.

Glucagon exerts positive inotropic and chronotropic effects and may, therefore, cause tachycardia and hypertension. Across completed trials supporting the CHI indication, one event of tachycardia was reported with dasiglucagon, and one with placebo. Both events were mild and transient and considered not related to trial treatment.

Accidental overdose may occur due to inappropriate handling of the infusion pump or due to pump malfunction. Overdose may result in nausea, vomiting, inhibition of GI tract motility, short-term increase in heart rate or blood pressure, and/or hypokalemia. Symptomatic care for nausea and vomiting, as well as monitoring of heart rate, blood pressure, and hypokalemia, is advised.

Administration site reactions are seen with many injectable peptides. Administration site reactions occurred sporadically in completed trials supporting pump use, as well as in a previously published trial with marketed glucagon delivered by pump. For the CHI indication, local tolerability reactions were mostly mild and attributed to the adhesive dressing. None of the local reactions were severe.

As with all therapeutic peptides and proteins, there is an inherent risk for the induction of an ADA response against dasiglucagon. In the completed CHI trials, no ADA formation was observed in trial ZP4207-17103; in ZP4207-17109 23.3% of the patients developed ADA. The impact of ADA on safety or efficacy of dasiglucagon treatment in children with CHI remains to be established.

Administration of glucagon or dasiglucagon may be associated with a risk of allergic reactions similar to those observed for other therapeutic peptides or proteins.

From sporadic reports of extended SC/IV infusion of marketed glucagon and in glucagonoma patients,[14] sustained exposure to high levels of glucagon may lead to development of skin condition necrolytic migratory erythema (NME), a highly specific migrating, erythematous rash with predilection for perioral, perianal, and lower leg distribution.[11] In the ZP4207-17109 trial, two confirmed events of NME were reported for dasiglucagon relative to SOC treatment, but no skin-related events led to discontinuation of dosing. No confirmed cases of NME were reported in the ZP4207-17103 trial.

For further information on risks, please refer to the current version of the investigator's brochure (IB).

5.3.7. Summary of Potential Benefits and Risks

As with all treatment interventions, the anticipated benefits to trial patients should be balanced against the potential risks. The accumulated experience from nonclinical studies and clinical trials with dasiglucagon supports that dasiglucagon is a specific glucagon receptor agonist and is well tolerated. Glucagon and its analogs belong to a well-known drug class with known mode of action. The clinical investigators involved in the trial will all have had experience with use of glucagon in patients with CHI.

The investigator will inform the patients/parent(s)/guardian of the potential risks of dasiglucagon treatment and other trial-related procedures before they enter the trial. The investigator must become familiar with all sections of the dasiglucagon IB before the start of the trial.

In summary, with its marked improvements in stability in solution and solubility in aqueous media compared to currently marketed glucagon products, dasiglucagon is expected to have significant clinical benefits in the treatment of CHI and to substantially reduce the disease burden in these patients. This includes enabling convenient and reliable long-term treatment via a pump device in a home setting, which holds the potential to delay and ultimately avoid pancreatectomy and its related exo/endocrine complications, particularly the development of insulin-dependent diabetes.

Dasiglucagon may overall provide significant added benefit in the treatment of CHI relative to currently marketed glucagon products by enabling long-term reliable SC infusion to control PG. The proposed trial population is still experiencing hypoglycemia despite medical treatments being escalated to the highest therapeutically permissible or tolerated doses, or despite having undergone subtotal pancreatectomy. Therefore, these patients are dependent on continuous or very frequent delivery of carbohydrates, often through invasive routes (NG tube or gastrostomy). This limits their ability to lead normal lives, including participating in everyday activities, and therefore, impacts their development. For this trial population, the major and clinically relevant benefit is the expected reduction in number and volume of nutritional interventions while avoiding hypoglycemia. The reduced volume of nutritional interventions should limit the risk of

volume overload, especially in patients treated with significant doses of diazoxide. Achievement of euglycemia could lead to reduction of other CHI medication, further limiting the potential for adverse events associated with those treatments. In addition, the need for pancreatectomy, or re-surgery in those who already underwent pancreatic surgery is reduced and potentially eliminated.

Overall, the benefit to risk ratio for patients entering the ZP4207-17106 trial is considered acceptable.

6. OBJECTIVES

6.1. Objectives

6.1.1. Primary Objective

To evaluate the long-term safety of dasiglucagon administered as SC infusion in children with CHI.

6.1.2. Secondary Objectives

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

6.2. Endpoints

The primary endpoint will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and then in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis. All efficacy endpoints will be analyzed using average weekly results over Month 1, Month 1 to Month 3 and then the 3-month period between visits.

6.2.1. Primary Endpoint

- Adverse events

6.2.2. Key Secondary Efficacy Endpoints

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

6.2.3. Secondary Efficacy Endpoints

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

6.2.4. Other Efficacy Endpoints

- CGM percent time in range 70-180 mg/dL (3.9-10.0 mmol/L)
- CGM percent time >180 mg/dL (10 mmol/L)
- CGM percent time <54 mg/dL (3.0 mmol/L)
- Number of parent reported hypoglycemic events pr. week that required an intervention AND with PG <70 mg/dL (3.9 mmol/L) as detected by self-monitored plasma glucose (SMPG) or CGM
- Number of SMPG-detected hypoglycemia episodes <70 mg/dL (3.9 mmol/L) per week based on SMPG measurements as captured in patient device
- Number of clinically significant SMPG-detected hypoglycemia episodes <54 mg/dL (3.0 mmol/L) per week based on SMPG measurements as captured in patient device
- Number of emergency department visits for hypoglycemia
- Number and length of hospitalizations caused by CHI or CHI-related events
- Number of outpatient visits to health care providers (family doctors, specialist, etc.) caused by CHI or CHI-related events
- Number of home visits by paramedics due to hypoglycemia
- Quality-of-life (Pediatric Quality of Life Inventory [PedsQL™][Total Scale Score, Physical Health Summary Score, and Psychosocial Health Summary Score] and CHI-specific questionnaire)

6.2.5. Other Safety Endpoints

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

7. TRIAL DESIGN

7.1. Overall Trial Design and Plan

This is a phase 3, open-label, multinational, multicenter, long-term safety and efficacy extension trial in patients with CHI who completed either ZP4207-17103 or ZP4207-17109 (defined as a lead-in trial). To qualify for participation, patients are expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon due to CHI, with an investigator statement documenting the positive benefit-risk assessment.

The primary objective of this trial is to assess the long-term safety of dasiglucagon administered as SC infusion.

Informed consent (and assent as applicable) for participation in this trial will be obtained from eligible patients. Eligible patients will continue with dasiglucagon at the dose level reached at the end of their participation in the lead-in trial, with possible further dose adjustments to optimize treatment to each patient's needs.

The investigator is allowed to change the standard of care (SOC) medication for CHI at his or her discretion in order to optimize the treatment of each patient. To use a minimally invasive yet objective method of assessing the frequency of hypoglycemia, patients will be required to wear a CGM device throughout the entire trial period. Pauses are allowed; however, CGM must be used for the 30 days leading up to each visit, and families will also be asked to perform SMPG.

The End of Treatment Visit from the lead-in trial (ZP4207-17103 or ZP4207-17109) will serve as the Baseline Visit for the present trial. Any post-treatment follow-up scheduled for patients in the lead-in trial will be redundant if they are enrolled in the present trial by the time of the scheduled Follow-up Visit.

Patients will be seen at the trial site at Months 1, 3, and 6, and every 3 months thereafter, and contacted by the investigator monthly by telephone in between site visits. At site visits, patients and their parent(s)/guardian will receive a paper diary to record potential AEs and concomitant medication, among other information, which will be reviewed regularly by site staff at each visit. Patients will be allowed to remain in the trial until approval and commercial availability of dasiglucagon in the country of participation or through an early access program (EAP) or until approximately Q3 2024 (treatment period), whichever occurs first. Any post-treatment Follow-up Visits will be redundant for the patients who are continuing treatment with

dasiglucagon commercially or through an EAP, and they will end trial participation at their End of Treatment (EoT) Visit. Figure 1 depicts the trial design.

Patients who are treatment-induced or treatment-boosted ADA-positive at Trial Completion will be offered continued ADA monitoring until the ADA levels return to baseline or until 2 years after End of Trial, whichever occurs first. Baseline is defined as the ADA level prior to dasiglucagon dosing in the lead-in trial.

Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.

An interim analysis may be performed as appropriate to support a possible marketing authorization application/new drug application (NDA).

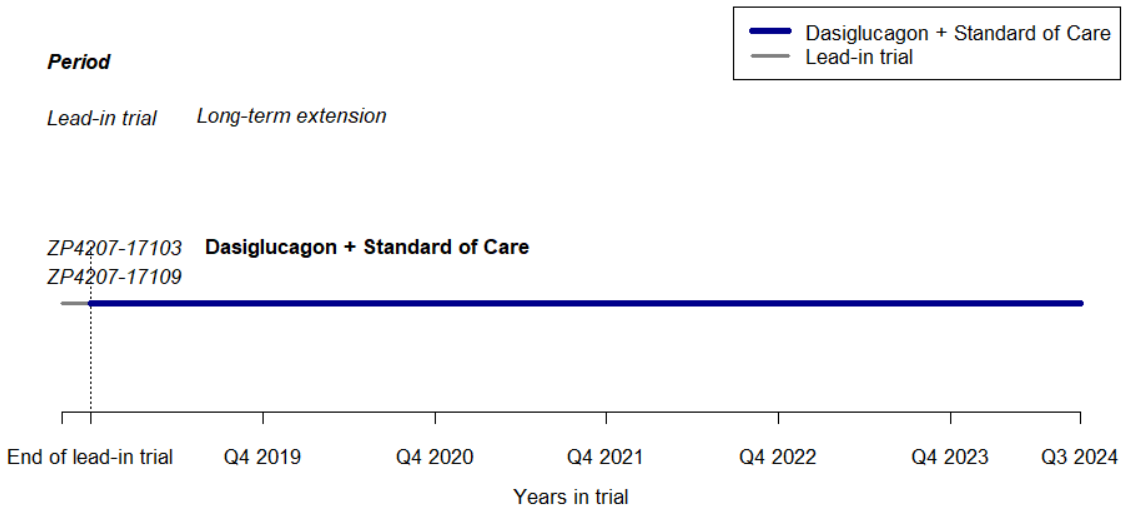

Figure 1 Trial Design

7.2. Trial Duration

The sequence and maximum duration of the trial periods will be as follows:

Trial Period (from last visit in lead-in trial until Trial Completion, as defined below):

1. Baseline: defined as the EoT Visit from lead-in trials ZP4207-17103 or ZP4207-17109.
2. Treatment Period: treatment will continue until approval and commercial availability of dasiglucagon in the country of participation or through an EAP or until approximately Q3 2024, whichever occurs first, at which time an EoT Visit will be scheduled.
3. EoT Visit: see above.
4. Follow-up Visits: will occur 4 weeks and 12 weeks after the EoT Visit.

5. **Trial Completion**: completion of the final Follow-up Visit or the EoT Visit if the patient continues treatment with dasiglucagon commercially or through an EAP.

ADA Follow-up Period (from Trial Completion until last patient last visit [LPLV]):

6. Monitoring of treatment-induced or treatment-boosted ADA-positive patients after Trial Completion: monitoring of ADA-positive patients will continue until the ADA levels return to baseline (as defined in Section 10.1.3.1) or until 2 years after End of Trial, whichever occurs first.

End of Trial: defined as the the time all patients have reached Trial Completion (completed the Follow-up Period, or the EoT Visit if continuing treatment with dasiglucagon commercially or through an EAP, whichever occurs first).

LPLV: last visit of the last patient in the ADA Follow-up Period

7.3. Discussion of Trial Design

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

The open-label treatment from the last treatment period of lead-in trials ZP4207-17103 and ZP4207-17109 was chosen because the added treatment burden of a blinded trial design was not considered ethically justified.

Investigators will be required to reaffirm and document a positive benefit/risk assessment of continued treatment with dasiglucagon at each site visit, in close collaboration with the parent(s)/ legally authorized representative (LAR) to ensure that patients are not unnecessarily exposed to the trial product. Treatment should be stopped if continued benefit is not evident or if safety issues overweigh the benefit of treatment.

A hypoglycemia threshold of PG <70 mg/dL (3.9 mmol/L) was chosen as an alert value for the key secondary hypoglycemia endpoints in alignment with the metabolic disease field experts, although clinicians might use lower thresholds for guiding treatment decisions for treatment of hypoglycemia in patients with CHI.

7.4. Trial Sites

The trial will take place at up to 14 sites experienced in the treatment of CHI in the United States and Europe, all of which will have been involved in the lead-in trials. A maximum of 44 patients are expected to be enrolled in the lead-in trials, and approximately 30-44 of those patients are expected to be enrolled in this trial.

7.5. Point of Contact

A point of contact will be identified to provide information to each patient's parent(s)/guardian about where to obtain information on the trial, the patient's rights, and whom to contact in case

of trial-related injury. This information will be provided in the patient information and informed consent form (ICF).

8. PATIENT POPULATION

8.1. Selection of Trial Population

A screening log of potential trial candidates must be maintained at each trial site.

8.2. Trial Entry Criteria

8.2.1. Inclusion Criteria

A patient will be eligible for trial participation if he or she meets all of the following criteria:

1. Completed treatment in either Trial ZP4207-17103 or ZP4207-17109
2. Expected to continue to have a positive benefit-risk assessment for treatment with dasiglucagon (based on considerations of glycemic effect, tolerability, and nature and frequency of AEs experienced in the lead-in trial), with signed investigator statement documenting the positive benefit-risk assessment made
3. Has a negative serum pregnancy test at baseline (only for females of child-bearing potential)
4. Sexually active female patients and their partners must use acceptable contraception or refrain from sexual activity from baseline until 30 days after the last dose of trial drug. Females must abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception. Abstinence can only be accepted if this is true abstinence in line with the preferred and usual lifestyle of the patient.

   Acceptable methods of contraception are:

   a) Hormonal contraceptives (e.g., oral contraceptive pill, depot, patch, intramuscular implant or injection, sponge, or vaginal ring), stabilized for at least 30 days if first use

   or

   b) Barrier method, e.g., (i) condom (male or female) and (ii) diaphragm with spermicide

Germany*: Only highly effective methods of birth control are accepted (i.e., one that results in less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices), or sexual abstinence.*

5. Able and willing to comply with trial procedures
6. Following receipt of oral and written information about the trial, the patient (depending on local institutional review board [IRB]/independent ethics committee [IEC] requirements) must provide assent and one or both parents* or guardian of the patient must provide signed informed consent before any trial-related activity is carried out. ***France, Germany, Israel:*** *The consent must correspond to the patient's presumed will where such a will can be ascertained.*

* If required by local regulations, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

8.2.2. Exclusion Criteria

A patient will be excluded from the trial if he or she meets any of the following criteria:

1. The patient developed any conditions prohibited by the lead-in trial, requires medication prohibited by the lead-in trial, or has other new complications that preclude participation in the investigator's opinion.
2. Has participated in an interventional clinical trial (investigational or marketed product) within 3 months before baseline or 5 half-lives of the drug under investigation (whichever comes first) or plans to participate in another clinical trial. Excluded from this is participation in Trial ZP4207-17103, Trial ZP4207-17109, and/or 18F-Dopa positron emission tomography computed tomography/magnetic resonance imaging investigation (when performed as a part of a clinical trial) for diagnosis of focal CHI.

8.3. Patient Participation Stopping Criteria

8.3.1. Efficacy Reasons

Treatment should be discontinued if there is no longer any evidence of beneficial effect of dasiglucagon due to inadequate or complete lack of response, or in case continuation of treatment is not considered needed any longer due to natural course of the disease, i.e. improvement or full resolution.

The decision should be taken at the discretion of the investigator and involve the parents/LAR in the decision making. The decision should be based on all efficacy and safety assessments performed during participation in the trial. A temporary treatment interruption can be applied in order to inform the decision. If deemed needed, the patient can be admitted to the hospital during the treatment interruption.

8.3.2. Safety Reasons

Treatment should be permanently discontinued in case risk outweighs the benefit, i.e. unacceptable safety issues related to the treatment that are life-threatening, or associated with significant comorbidity.

8.4. Premature Patient Withdrawal

Patients' parent(s)/guardian will be advised that they are free to withdraw their children from participation in this trial at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep patients in the trial. However, patients must be withdrawn from the trial if their parent(s)/guardian withdraw consent to participate.

Investigators must attempt to contact patients' parent(s)/guardian who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Attempts to contact the patient must be documented. At least 3 phone calls and 3 written attempts to contact the patient will be made prior to considering them lost to follow-up. Should an AE be the cause of withdrawal, it must be documented, reported, and followed as described in Section 11.2.

If a patient/parent(s)/guardian withdraws consent, the reason for withdrawal and the date of withdrawal will be recorded on the appropriate page of the electronic case report form (eCRF). Whenever possible and reasonable, the evaluations that were to be conducted at the completion of the trial should be performed at the time of premature withdrawal.

8.5. Treatment Discontinuation

To prevent missing data, patients should to the extent possible be kept in the trial. Therefore, treatment discontinuation is often the preferred option in case of, e.g., substantial non-compliance with trial procedures or initiation of prohibited treatment that interferes with the efficacy and safety evaluation. If it is an investigator decision to discontinue the patient's treatment, the investigator should, whenever possible, discuss the potential discontinuation of the treatment with the medical monitor. If the patient is discontinued from trial treatment by the investigator or by parent(s)/guardian's decision, the reason and date of treatment discontinuation will be recorded on the appropriate page of the eCRF. The patient should be asked to continue in the trial by following the planned visit schedule. At a minimum, the patient will be asked to attend the Follow-up Visits at 4 weeks and 12 weeks (± 7 days) after discontinuation of trial treatment. If the patient is treatment-induced or treatment-boosted ADA-positive at Trial Completion the patient will be offered continued ADA monitoring until the ADA levels return to baseline (defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial) or until 2 years after End of Trial, whichever occurs first. See Section 10.1.3.1 and Section 17.1.

8.6. Patient Replacement Criteria

Patients who withdraw from the trial prematurely will not be replaced.

Enrolled patients who are subsequently withdrawn from the trial may not reenter. The patient number for a withdrawn patient will not be reassigned to another patient.

8.7. Trial Stopping Criteria

In case of 2 or more serious safety concerns of similar nature potentially related to treatment, that are either life-threatening or associated with significant comorbidity and/or permanent disability, the trial will be temporarily paused. If relationship between the concerns and IMP is confirmed or there is reasonable evidence that the concerns are probably or possibly related to the IMP and overall benefit of dasiglucagon is outweighed, the trial will be permanently stopped.

9. TREATMENTS

9.1. Identification of Investigational Product

Dasiglucagon injection 4 mg/mL will be supplied by the sponsor in a 3 mL vial containing 1 mL.

Dasiglucagon will be provided in the form of solution for injection for subcutaneous administration through an infusion pump.

Trial drug products, as applicable, must be transferred from the vial to an Accu-Chek® Spirit Cartridge. The amount of drug product dosed via the pump will vary between patients.

Cartridges and infusion sets should be replaced as indicated in the instructions for use.

9.1.1. Packaging and Labeling

Trial drug products will be packaged and labeled by the sponsor.

Dispensing unit configuration: 6 vials containing dasiglucagon, 4 mg/mL, packaged in an outer carton. The vial and carton will be packaged and labeled in local language indicating the content (open label).

The storage conditions for trial drug products will be described on the trial drug product label. The labels will supply no information about the patients. Each treatment unit (containing 6 vials) will have a unique Dispensing Unit Number for drug allocation, drug accountability, and traceability purposes.

Labelling will be performed according to Annex 13 of the Good Manufacturing Practice guidelines of the European Commission, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, local laws, and regulations.

9.2. Treatments Administered

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

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

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

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

The combined treatment of SOC and dasiglucagon should aim to reduce gastric dextrose infusions and glucose fortified meals as much as possible, maintaining the patient's PG within 70 and 120 mg/dL (3.9-6.7 mmol/L) at all times.

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

Plasma glucose assessments will be performed throughout the trial as instructed by the investigator. For patients using the Dexcom G5 CGM, SMPG assessments will be performed at least 2 times per day for CGM calibration. For PG monitoring, the same hand-held PG meter as in the lead-in trials will be used.

Details on the administration instructions and guidelines for preparation and handling of the trial drug product are in the pharmacy manual/trial materials manual (TMM).

9.3. Trial Supplies

The device and ancillaries listed in the following table will be supplied by the sponsor throughout the trial. Trained trial personnel will train parent(s)/guardian on the use of the infusion pump, the PG meter, and CGM.

Instructions for the use of all these supplies will be provided in a separate manual.

Item	Name	Manufacturer
Pump	Accu-Chek Spirit Combo	Hoffman-La Roche AG, Basel, Switzerland
Cartridge	Accu-Chek Spirit 3.15 mL Cartridge system	Hoffman-La Roche AG, Basel, Switzerland
Infusion sets	Accu-Chek FlexLink Infusion set (Accu-Chek® UltraFlex Infusion set in US) and Accu-Chek Rapid-D Link Infusion set	Hoffman-La Roche AG, Basel, Switzerland
Infusion set inserter	Accu-Chek LinkAssist Insertion device (can be used with FlexLink & UltraFlex)	Hoffman-La Roche AG, Basel, Switzerland
PG monitoring	StatStrip Xpress2	Nova Biomedical, Waltham, MA, USA
CGM	Dexcom G5 Dexcom G6	Dexcom Inc., San Diego, CA, USA

The infusion pump system is Conformité Européene (CE)-marked for the management of diabetes mellitus in persons requiring insulin, as prescribed by a physician. In this trial, the pump system is used outside the CE-marked intended use since the pump system will be delivering dasiglucagon to patients with CHI. The PG meter is used as intended according to the CE mark, except for the use by a lay person in a home care setting. The CGM devices are used as intended according to the CE mark, except for the age group and the disease.

The pump, the SMPG, and the CGM will be labeled for use in an investigational trial. For more information on the devices please refer to Section 19.

9.4. Dispensing and Storage

The trial drug product supplied by the sponsor is to be dispensed exclusively to patients in this clinical trial according to the instructions of this protocol and the pharmacy manual/TMM. The investigator is responsible for dispensing the trial drug product according to the dosage scheme.

Dasiglucagon for injection 4 mg/mL must be stored at 2–8°C in a refrigerator.

The investigator must ensure the availability of proper storage conditions. All trial drug product provided for this trial will be stored in a secure area with restricted access at the trial site.

The temperature should be monitored by recording the actual, minimum, and maximum temperatures using a calibrated thermometer or thermocouple, or by continuous recording using a qualified temperature monitoring system. The temperature should be evaluated and documented at least on working days on a temperature log. This log must be included in the Investigator Site File (ISF) upon trial termination.

The investigator must contact the clinical research associate (CRA) in case of temperature deviations outside the acceptable range.

Please refer to the pharmacy manual/TMM for additional information on handling of the trial drug.

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the trial drug product, including the date, quantity, batch or code number, and identification of patients (patient number) who received the trial drug. The investigator will not supply the trial drug product to any person except subinvestigators, designated trial personnel, and patients in this trial. The trial drug product may not be relabeled or reassigned for use by other patients. If any of the trial drug product is not dispensed, is lost, stolen, spilled, unusable, or is received in a damaged container, this information must be documented and reported to the sponsor and the appropriate regulatory agencies as required.

9.5. Method of Assigning Patients to Treatment Groups

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

9.6. Blinding and Unblinding Treatment Assignment

This is an open-label trial.

9.7. Selection of Doses in the Trial

Both the starting dose and the maximum allowed doses are based on experience with glucagon products in this patient population.[11]

At the time of protocol development, no pediatric PK data were available for dasiglucagon. An approximate estimation of expected drug concentration in a 3 kg patient was made by extrapolation of a previously made PK model for pediatric patients with weights between 25 and 45 kg.[15]

The predicted plasma concentration is expected to give a low PD response in the lowest dose level and be above maximum effect at the highest dose level. The maximum expected plasma concentrations of dasiglucagon is in the range of what is achieved following a rescue dose to adults. The doses of dasiglucagon will be titrated to meet the needs of the individual patient. The titration will stop when no additional PD effects are observed as the infusion rate is increased. The infusion rate of dasiglucagon will be monitored and adjusted to meet the needs of the individual patient throughout the trial period. Since the dasiglucagon dose is titrated individually based on the desired PD response, it does not need to be related to any measure of the patient's size.

9.8. Selection of Timing of Dose for Each Patient

Dosing details are provided in Section 9.2.

9.9. Dose Adjustment Criteria

Dosing details are presented in Section 9.2.

9.10. Treatment Compliance

Compliance data will be collected. Infusion details will be recorded in the patient's eCRF, and drug accountability will be performed as detailed in the pharmacy manual/TMM.

9.11. Permitted and Prohibited Therapies

All concomitant medications used (including over-the-counter medications and herbal supplements) will be recorded in the source document and on the appropriate eCRF.

9.11.1. Permitted Therapies

Concomitant CHI treatments (e.g., somatostatin analogs) that were initiated prior to trial entry are permitted throughout the trial. Somatostatin analogs may also be added throughout the trial at the investigator's discretion if the maximum dose level of dasiglucagon (70 µg/hr) has been reached or if further titration is not possible due to undesirable side effects.

Other CHI-specific treatments to be added during the trial need to be discussed with the medical monitor.

Caution is advised when beta-blockers, indomethacin, anticholinergic drugs, and warfarin are prescribed, due to reports of interaction with marketed glucagon products.

9.11.2. Prohibited Therapies

The following therapies are prohibited during the trial:

- Systemic corticosteroids, e.g., hydrocortisone >20 mg/m2 body surface area (or equivalent)
- Anti-inflammatory biological agents, kinase inhibitors, or other immune-modulating agents
- Exogenous insulin
- Use of paracetamol/acetaminophen is strongly discouraged for the duration of trial when patients are using the Dexcom G5 CGM because it interferes with the accuracy of the device. Parent(s)/guardian should contact the trial site before dosing child with paracetamol/acetaminophen. Both the site staff and the parent(s)/guardian should explore other options of treating fever and mild pain before deciding paracetamol/acetaminophen is needed
  When patients are using the Dexcom G6 CGM the use of paracetamol/acetaminophen is allowed
- Other investigational agents
- Marketed glucagon products throughout the trial unless necessary for rescue therapy to treat severe hypoglycemia, as per local standard of care
- Prescription or non-prescription medications known to cause QT prolongation

Continuation in the trial after the patient received excluded therapies will be at the discretion of the investigator after consultation with the medical monitor.

10. TRIAL PROCEDURES

The patient (depending on local IRB/IEC requirements) must provide assent and one or both parent(s)/guardian (according to local law) must provide written informed consent before any trial-related procedures are initiated, including the cessation of prohibited concomitant therapy. ***France, Germany, Israel:*** *The consent must correspond to the patient's presumed will where such a will can be ascertained. Depending on local IRB/IEC requirements, the patient should also provide assent before any trial-related procedures are initiated.*

For the timing of assessments and procedures throughout the trial, refer to the Schedule of Events (Section 17.1). Throughout the trial, trial personnel should make every reasonable effort to follow the timing of assessments and procedures in Section 17.1 for each patient. If a patient misses a trial visit for any reason, the visit should be rescheduled as soon as possible.

At enrollment and throughout the trial, the investigator will ensure:

- Appropriate re-training of patient's parent(s)/guardian in the use of dasiglucagon in the Accu-Chek Spirit Combo pump based on the training material provided
- Parent(s)/guardian are trained appropriately on the use of CGM device
- Parent(s)/guardian are trained appropriately on how to perform SMPG measurements and on how to complete the diary. They will check their child's SMPG as instructed by the investigator. When the patient is using the Dexcom G5 CGM, the SMPG sould be measured at least 2 times per day for calibration of the CGM device.
- Parent(s)/guardian are instructed not to change the dose of trial drug without prior consultation with the investigator
- Parent(s)/guardian are instructed how to recognize and handle signs of hypoglycemia
- Parent(s)/guardian are instructed to call the investigator/site staff in case of questions

10.1. Assessments

Quality of life should be the first assessment performed at each visit according to the Schedule of Events (Section 17.1).

10.1.1. Efficacy

10.1.1.1. Plasma Glucose Monitoring

Plasma glucose assessments will be performed regularly throughout the trial. During the trial, SMPG assessments (using StatStrip Xpress2) will be performed as instructed by the investigator. When a patient is using the Dexcom G5 CGM, SMPG assessments will be performed at least 2 times per day for CGM calibration.

At each visit the investigator will ensure that SMPG data are downloaded from the patient's device. The investigator will check for patient compliance in SMPG measurements. The procedure for download of SMPG data will be described in the pharmacy manual/TMM.

10.1.1.2. Continuous Glucose Monitoring

Both the Dexcom G5 and Dexcom G6 can be used for continuous glucose monitoring during the trial. The Dexcom G5 will be taken off the market by the supplier during 2020 and all patients should be shifted to the Dexcom G6 CGM device.

The CGMs (Dexcom G5 and Dexcom G6), supplied for use throughout the trial, will be used to guide treatment decisions, as well as to evaluate efficacy after trial completion. Continuous glucose monitoring should be used for the entire trial period. Pauses are allowed, but CGM must be used for the 30 days leading up to each site visit (see Section 17.1).

At each visit, the investigator will ensure that CGM data are downloaded from the patient's device. The procedure for download of CGM data will be described in the pharmacy manual/TMM.

The CGM devices should be calibrated and used according to the manufacturer's instructions; the Dexcom G5 should be calibrated 2 times per day, the Dexcom G6 does not require calibration.

The contract research organization (CRO) or delegate will handle the device sourcing, configuration for use in the trial, procedures for data extraction, device service, and return handling.

10.1.1.3. Quality of Life

Quality of life (Appendix B) will be assessed using the PedsQL and additional CHI disease-specific QoL questions (parent-reported versions) according to the Schedule of Events (Section 17.1).

The PedsQL Measurement Model is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL Measurement Model integrates seamlessly both generic core scales and disease-specific modules into one measurement system.

The 23-item PedsQL Generic Core Scales was designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning.

The 4 Multidimensional Scales and 3 Summary Scores are:

Scales	**Summary Scores**
• Physical Functioning (8 items)	• Total Scale Score (23 items)
• Emotional Functioning (5 items)	• Physical Health Summary Score (8 items)
• Social Functioning (5 items)	• Psychosocial Health Summary Score (15 items)
• School Functioning (5 items)	

The CHI disease-specific questions were developed by the patient association Congenital Hyperinsulinism International and taken from the patient-reported registry, the HI Global Registry. The HI Global Registry questions are grouped mostly under general QoL; however, some questions relate specifically to diet and feeding, surgical management, glucose monitoring, and child development. The HI Global Registry is governed by a Global Steering Committee, including key global clinical experts.

10.1.1.4. Other Assessments

Resource Utilization:

- Emergency department visits for hypoglycemia
- Number and length of hospitalizations caused by CHI or CHI-related events
- Number of visits to health care providers (family doctors, specialist, etc.) caused by CHI or CHI-related events
- Number of home visits by paramedics due to hypoglycemia

Diary:

The patient's parent(s)/guardian will be provided with a paper diary at all visits, except at the End of Treatment and Follow-up Visits. The investigator will instruct the patient's parent(s)/guardian on how to complete the diary. The diary should be completed throughout the trial until the end of treatment. The following information should be recorded in the diary:

- Hypoglycemic events for which there was an intervention, regardless whether the event was detected via SMPG or CGM
- Concomitant medications
- AEs
- Hospitalizations, visits to health care providers or emergency room/ accident & emergency department (ER/A&E), and visits by paramedics
- Data regarding suspicion of NME and neurological findings

Diary entries should be reviewed at each visit and the review be documented in the diary. Data from the diary entries should be transcribed to the eCRF on an ongoing basis.

Prescribed continuous gastric carbohydrates:

Total amount of prescribed carbohydrates as part of continuous gastric infusion and infusion duration as listed in this section will be collected on the 7 days prior to the the following visits: Start of the lead-in trial (ZP4207-17103 or ZP4207-17109), Visit 1, Visit 4, Visit 6 and at End of Treatment.

In ZP4207-17103 start of trial is defined as the 7 days prior to the run-in period and in ZP4207-17109 start of trial is defined as the 7 days prior to the randomization visit.

- Total amount (g) of prescribed carbohydrates as part of continuous gastric infusion
- Total duration (h) of prescribed continuous gastric infusion

Total duration (h) of prescribed nightly (8 pm – 8 am) continuous gastric infusion

10.1.2. Pharmacokinetics/Drug Exposure

Blood samples will be collected to measure dasiglucagon levels at steady-state (Schedule of Events; Section 17.1).

Details on sampling/collection, shipment, and analysis will be provided in the laboratory manual.

10.1.3. Safety

Safety assessments will include the evaluation of AEs, clinical laboratory assessments (hematology, biochemistry, and ADAs), vital signs, physical examination, ECGs, echocardiography, and local tolerability.

10.1.3.1. Laboratory Safety Assessments

Trial procedures require a maximum total of approximately 4 mL blood per visit. No more than 1 mL blood per kg body weight should be sampled per visit day. Where this limit is exceeded,[16,17] safety laboratory tests (2 mL per sampling) will be prioritized over immunogenicity (1 mL) and drug exposure (0.4 mL) samples.

All measurements described in this section are recognized standard methods.

Hematology and Biochemistry

Samples for hematology and biochemistry will be collected at the time points specified in the Schedule of Events (Section 17.1).

Hematology:	hemoglobin, hematocrit, red blood cell (RBC) count, RBC indices, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, platelet count (or estimate), and white blood cell count, including differential
Biochemistry:	albumin, total bilirubin, total protein, calcium, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine, sodium, potassium, chloride, estimated glomerular filtration rate (eGFR), urea, insulin, ketones (measured at the local laboratory or with PG meter), free fatty acids, and hemoglobin A1c (HbA1c)

Laboratory specimens will be analyzed at local laboratories.

Immunogenicity

Blood samples will be collected to test for antibodies against dasiglucagon at Visits 1, 3, 4, 6; in intervals of 6 months throughout the Treatment Period, at final drug administration (last dose of trial treatment), and at the Follow-up Visits (Section 17.1); and processed and shipped according to instructions provided in the laboratory manual.

Patients who are treatment-induced or treatment-boosted ADA-positive at trial completion will be offered continued ADA monitoring until the ADA levels return to baseline or until 2 years after End of Trial, whichever occurs first. The patients will be invited to come to the site for ADA blood sampling visits 1 to 3 times a year with a minimum of 4 months between the visits. Baseline is defined as the ADA levels prior to dasiglucagon dosing in the lead-in trial.

Patients who are ADA-positive at the EoT Visit and are continuing treatment with dasiglucagon commercially or through an EAP will not be offered continued ADA monitoring because they are expected to remain ADA-positive while exposed to dasiglucagon.

Samples for ADA measurement will be analyzed in batches during the trial. The ADA samples will be analyzed at a special laboratory.

The clinical ADA assays have been validated in accordance with existing guidelines and recommendations.[18,19]

Samples will be measured in anti-dasiglucagon antibody screening and confirmatory assays. Due to the limited sample volume, in the CHI pediatric patients, the ADA characterization of confirmed positive samples will be conducted according to the following priority:

- Cross-reactivity against endogenous glucagon (cross-reactivity Yes/No)
- Establishment of anti-dasiglucagon binding titer
- Dasiglucagon in-vitro-neutralizing potential of the antibodies
- Glucagon in-vitro-neutralizing potential of the antibodies (only if positive for crossreactivity)
- Neutralizing antibody titers, in case of a positive result in the in-vitro neutralizing antibody assays

The in vitro neutralizing effects of antibodies will be measured using an assay based on glucagon receptor-transfected human embryonic kidney cells. The sensitivity in the 1st generation NAb assay initially used was approximately 51.8 ng/mL. In the recently developed 2nd generation NAb assay, the sensitivity is 89.8 ng/mL. The assays were also validated for recombinant glucagon with similar results. The cell-based neutralizing antibody analyses will be performed by a special laboratory (BioAgilytix, Durham, NC, USA). No further serum sampling will be needed since the ADA samples can be used for neutralizing antibody analysis.

The neutralizing potential in samples from ADA-positive patients will be evaluated on the basis of drug exposure/PD data (steady-state exposure and plasma glucose) if the assessment for NAb activity in confirmed ADA-positive samples is not possible due to the limited sample volume.

The ADA samples will be analyzed in batches during the trial, and patients who develop treatment induced anti-dasiglucagon antibodies (treatment induced or treatment boosted, titer increase above 4 fold) will be offered follow up until the ADA level is back to baseline or until the outcomes related to anti-drug antibodies are no longer detected.

For patients with a body weight <10 kg, it will not be possible to collect back-up ADA samples. However, any residual serum samples may be stored until approval of market authorization by the health authorities.

For patients with a body weight ≥10 kg, a back-up ADA sample and residual serum samples may be stored until approval of market authorization since further characterization of the antibody response may be requested.

Pregnancy Testing

A serum pregnancy test will be performed every 3 months in females of child-bearing potential.

Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all trial personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of patient samples, specific regulations exist regarding the shipment of biologic/etiologic samples. Procedures and regulations for the packaging and

shipping of infectious samples are outlined in the laboratory manual. The investigator is responsible for ensuring that all trial samples that are to be transported to another location are appropriately packed and shipped according to the applicable regulations.

Evaluation of Laboratory Values

The normal ranges of values for the laboratory assessments in this trial will be provided by the responsible laboratory and submitted to the sponsor before the beginning of the trial. They will be regarded as the reference ranges on which decisions will be made.

If a laboratory value is out of the reference range, the investigator must evaluate if the value is clinically significant and record his or her assessment in the appropriate eCRF.

All laboratory values that in the investigator's opinion are clinically relevant during or after termination of the treatment have to be reported as AEs and followed, as described in Section 11.2.

10.1.3.2. Clinical Examinations

Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, and blood oxygen saturation level (SpO_2) will be measured according to the Schedule of Events (Section 17.1).

Twelve-lead Electrocardiogram

A standard 12-lead ECG will be performed while the child is in a sleeping or calm state according to the time points specified in the Schedule of Events (Section 17.1). If it is not practical or possible, then a 2-lead ECG may be used.[20] If arrhythmia is detected on a 2-lead ECG, this should be followed by a 12-lead ECG. All ECG recordings will be identified with the patient number, date, and time of the recording and will be attached to his or her medical record.

The ECG parameters (heart rate, PQ, QRS, QT, and QTcF) and any abnormality will be recorded and described in the eCRF, including the investigator's assessment of clinical significance (Abnormal, Clinically Significant; or Abnormal, Not Clinically Significant). At subsequent visits, any clinically significant deterioration of a pre-existing condition, as well as any new clinically significant findings, will be recorded as AEs.

Echocardiogram

An echocardiogram will be performed according to the time points specified in the Schedule of Events (Section 17.1).

Physical Examination and Neurological Examination

A complete physical examination of body systems (excluding breast and genitourinary, nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait, all as applicable for the patient's age) will be performed according to the Schedule of Events (Section 17.1).

Local Tolerability

Local tolerability data will be collected separately from AEs. Within the eCRF, data will be collected on the nature of any reaction (erythema, pain, swelling, etc.), the severity (mild, moderate, severe), and any action take (e.g., no action, interruption of infusion). The likely cause of the reaction will also be collected (e.g., insertion site, drug, adhesive dressing).

Other skin findings will be collected along with other AEs. If clinical suspicion of NME is made, data describing the lesion(s) will be collected as an AE of special interest (AESI, see Section 11.1.8), together with a photograph or series of photographs of the lesion(s) uploaded to a central repository.

10.1.3.3. Reporting of Hypoglycemia Events

Hypoglycemic episodes (below 70 mg/dL / 3.9 mmol/L) that require intervention are to be reported via the dedicated hypoglycemia eCRF form. Hypoglycemic episodes that fulfill the definition of an SAE should furthermore be recorded as an SAE. The following information should be collected:

- Date, start time, source (SMPG/CGM)
- Selected symptoms (e.g., unconsciousness, seizures)
- Intervention:
  - type and amount of food, route of administration (oral vs. NG tube/gastrostomy)
  - use of marketed glucagon as rescue therapy
  - contact with trial doctor or emergency services, paramedic visit, ER/A&E admission, hospitalization

10.1.3.4. Technical Complaints

Reporting of Technical Complaints

Technical complaints should be reported to the sponsor on any of the following products, if technical issues occur between their first and last use:

- Dasiglucagon 4 mg/mL-vial containing 1 mL
- Accu-Chek Spirit pump
- Accu-Chek Spirit 3.15 mL Cartridge system, Accu-Chek Flex-link Infusion set (Accu-Chek UltraFlex Infusion set in the US), and Accu-Chek Rapid-D Link infusion set
- Accu-Chek Link-Assist Insertion device
- SMPG meter, StatStrip Xpress2
- Dexcom G5/G6 system

The investigator must report whether the technical complaint is associated with any AEs or SAEs. Any AE/SAE associated with a technical complaint must be reported in accordance with Section 11.2; the relationship between the technical complaint and the AE/SAE must be assessed by the investigator.

Technical complaints must be reported on a dedicated technical complaint form.

The investigator must complete the technical complaint form in the eCRF according to the following timelines, starting from the time the trial site becomes aware of the technical complaint:

- Technical complaint assessed as related to an SAE **within 24 hours**
- Technical complaint which could have led to serious medical occurrence if either suitable action had not been taken, if intervention had not been made, or if circumstances had been less fortunate **within 24 hours**

- All other technical complaints within **5 calendar days**

Use the paper technical complaint form when reporting a technical complaint for an item that is not yet allocated to a patient. The form should be sent by email to the safety CRO, refer to Appendix A for contact details.

Collection, Storage, and Shipment of Technical Complaint Item(s)

The investigator must collect and store the item(s) and notify the CRA (including photo documentation) **within 5 calendar days** of obtaining the item at trial site. Upon request, the CRA must coordinate the shipment as per instruction from the sponsor.

10.1.3.5. Adverse Events

The definitions and management of and special considerations for AEs are provided in Section 11 and Appendix D.

11. ADVERSE EVENTS AND PREGNANCIES

Timely, accurate, and complete reporting and analysis of safety information from clinical trials are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical trial patient administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not related to the product or medical device.

AEs include:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory AE: a clinical abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, e.g., change of dose or more frequent follow-up due to the abnormality

The following should **not** be considered as AEs:

- Pre-existing conditions, including those found as a result of baseline procedures (pre-existing conditions should be reported as medical history or concomitant illness)
- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the patient has signed the informed consent

11.1.2. Severity

When assessing the severity of an AE, the following definitions are used:

Mild: No or transient symptoms, no interference with the patient's daily activities

Moderate: Marked symptoms, moderate interference with the patient's daily activities

Severe: Considerable interference with the patient's daily activities, which the patient find unacceptable. A severe reaction does not necessarily deem the AE as serious (SAE) and an SAE is not always severe in nature.

11.1.3. Causality

When assessing the cause of an AE, the following definitions are used:

Probable: Good reason and sufficient documentation to assume a causal relationship

Possible: A causal relationship is conceivable and cannot be dismissed

Unlikely: The event is most likely related to etiology other than the product

Not related: No relationship to product

Causality will take into consideration whether the cause of the AE was related to the trial drug. For SAEs it will additionally be reported if the event is at least possibly related to any concomitant drug/therapy, study procedure or other (including any device).

11.1.4. Outcome

When assessing the outcome of an AE, the following definitions are used:

Recovered/resolved: The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the patient signed the ICF

Recovering/resolving: The condition is improving and the patient is expected to recover from the event. This term is only applicable as final outcome of an event if the patient has completed the trial or has died from another AE

Recovered/resolved with sequelae: The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE

Not recovered/not resolved: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known

Fatal: This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved," "recovering/resolving," "recovered/resolved with sequelae," or "not recovered/not resolved." An AE with fatal outcome must be reported as an SAE

Unknown: This term is only applicable if the patient is lost to follow-up.

11.1.5. Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose results in any of the following:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is otherwise medically important, that may not result in death, be life threatening or require hospitalization may be considered an SAE when (based on appropriate medical judgement) it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE. Examples could be emergency room or home treatment of allergic bronchospasm or convulsion

11.1.6. Other Important Events

The following events must always be reported in the electronic data capture (EDC) system on a dedicated form, regardless of whether it is related to an AE:

- suspicion of transmission of infectious agents via the trial product
- overdose of the trial product
- medication error involving the trial product
- inadvertent or accidental exposure to the trial product

11.1.7. Non-serious Adverse Events

A non-serious AE is any AE that does not fulfill the definition of an SAE.

11.1.8. Adverse Events of Special Interest

For this trial, the following events are to be regarded as AEs of special interest (AESI events or AESI), with data collected under a specific eCRF form:

- Suspicion of NME
- Risk of liver injury defined as ALT or AST >3 x ULN AND total bilirubin >2 x ULN, where no alternative etiology exists (Hy's law)
- Loss of consciousness, partial and generalized seizures
- Clinically significant changes in blood pressure or heart rate

11.1.9. Suspected Unexpected Serious Adverse Reactions

An AE is considered a suspected unexpected serious adverse reaction (SUSAR) if the nature or severity is not consistent with the applicable product Reference Safety Information (RSI). For dasiglucagon, the expectedness of an AE will be determined by whether or not it is listed in the RSI section of the IB.

11.1.10. Adverse Events Associated with Devices

Adverse events associated with devices must be reported to the ethics committee and competent authority according to local requirements. Such events include the following:

11.1.10.1. Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational device.

11.1.10.2. Serious Adverse Device Effect

A serious ADE (SADE) is an ADE that has resulted in any of the consequence characteristics of an SAE, meaning that the SAE is related to one of the investigational devices.

11.1.10.3. Unanticipated Serious Adverse Device Effect

An unanticipated SADE (USADE) is an SADE which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

11.1.10.4. Device Deficiency

A device deficiency is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. It also includes malfunctions, use errors, and inadequate labelling. In this clinical trial, these are covered by the term technical complaint (see reporting requirements in Section 10.1.3.4). Reporting of technical complaints is synonymous with device deficiency. The device deficiencies will be monitored and managed by the sponsor throughout the trial.

11.2. Collection, Recording, and Reporting of Adverse Events

All AEs, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until the patient's Trial Completion. In addition, patients will be observed for any signs or symptoms. They or their parent(s)/guardian, depending on the patient's age, will be asked about their condition by open questioning, such as "How have you been feeling since you were last asked?" at each contact with the trial site (visit or telephone). Patients or their parent(s)/guardian, depending on the patient's age, will also be encouraged to spontaneously report AEs occurring at any other time during the trial. At site visits and during monthly telephone contacts, the investigator should ask the patient and their caregiver(s) about any possible signs and symptoms of seizures as described in Appendix D.

All AEs, regardless of seriousness, severity, or presumed relationship to trial drug, must be recorded and evaluated by the investigator. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. If no diagnosis can be made, the investigator should record each sign and symptom as individual AEs. Investigators must record their opinion concerning the relationship of the AE to the trial drug. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

Each AE must be reported on the AE eCRF within 5 calendar days of the investigator becoming aware of the event.

All AE information should at a minimum include the following:

- Date and time of onset
- Date and time of investigator's first information about the AE
- Seriousness
- Severity
- Causal relationship with trial product
- Measures taken due to AE
- Interruption or discontinuation of treatment with trial product
- Date and time of resolution and final outcome

Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

All SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of trial drug, must be reported within 24 hours after obtaining knowledge about the event by completing the SAE form in the EDC system. A separate SAE form should be completed for each SAE.

All SAEs will be reported in EDC, and for each reported event a system-generated email will be sent to the safety CRO ([redacted]), the medical monitor, sponsor medical director, and trial manager.

Specific information about AESIs will be collected via SAE form (if qualifying for serious adverse events [SAEs]) as well as via dedicated AESI eCRF page(s). Reporting requirements for serious and non-serious AEs as described above also apply for serious and non-serious AESIs.

Other important events (Section 11.1.6) will be reported via a dedicated eCRF page. Reporting timelines will be within 24 hours if related to an SAE and 5 calendar days for all other events.

It is the responsibility of [redacted] to report all SUSARs that occur in this trial to competent authorities, the IRB, or IEC in accordance with the local requirements in force and the ICH guideline for GCP..

All SAEs, SADEs, and USADEs must be reported to the ethics committee and competent authority according to local requirements.

11.2.1. Serious Adverse Event Reporting Process in Germany

The Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) is to be informed about events as defined per Medical Device Directive 93/42/EEC, and the Ordinance on Medical Device Vigilance Section 3, Sub-section 6.

The Principal Investigator must report all SAEs and events with SADE potential to the Sponsor within 24 hours via the eCRF. Device- and/or procedure-related SAEs and events with SADE potential occurring in Germany will be reported individually by the Sponsor to the BfArM immediately by using the SAE Form available on the BfArM website. Device- or procedure-related SAEs and events with SADE potential occurring in all other countries in this trial will be reported by the Sponsor to the BfArM immediately using the European Medical Device Vigilance System (MEDDEV) 2.7/3 SAE Reporting Form. Serious adverse events deemed unrelated to the device and the procedure, occurring both in Germany and in all other

countries, will be reported by the Sponsor to BfArM quarterly by using the MEDDEV 2.7/3 SAE Reporting Form next to the procedure laid out in the protocol.

11.2.2. Contact Information

Pharmacovigilance for this trial is outsourced to [redacted]; refer to Appendix A for contact details.

11.3. Follow-up of Adverse Events

The investigator must record follow-up information on the eCRF for non-serious AEs and on the SAE form for SAEs. Follow-up questions to investigators regarding SAEs are queried directly by [redacted] to the investigator.

Follow-up information must be reported according to the following:

- **SAEs:** All SAEs must be followed until the outcome of the events is "recovered/resolved," "recovered/resolved with sequelae," or "fatal," and until all queries have been resolved. Cases of chronic conditions, cancer, or AEs that are ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved." Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the investigator to recover.

The SAE follow-up information should only include new (e.g., corrections or additions) information and must be reported **within 24 hours** of the investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- **Non-serious AEs:** Non-serious AEs must be followed until the outcome of the event is "recovered/resolved," or "recovered/resolved with sequelae" or until the patient has completed the trial, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer, or AEs that are ongoing at time of death (where death is due to another AE) may be closed with the outcome of "recovering/resolving" or "not recovered/not resolved." Cases can be closed with the outcome of "recovering/resolving" when a patient has completed the trial.

If a potential hypersensitivity reaction is observed, additional blood samples may be required to further characterize the potential hypersensitivity reaction. If an anaphylactic shock is suspected, samples may be taken for the measurement of tryptase. In this case, a blood sample should be taken 3-4 hours after the event and again approximately 1-2 weeks later to determine tryptase baseline levels. In addition, assessments for elevated histamine levels may be considered.

The investigator must ensure that the worst-case severity and seriousness of an event is kept throughout the trial, i.e., if the severity of an AE changes over time then it should be reported as 1 AE with the most severity. A worsening of an unresolved AE must be reported as follow-up with re-assessment of severity and/or seriousness of the event.

If an AE is resolved and re-appears later then it should be reported as a new AE.

Queries or follow-up requests must be responded within 14 calendar days from the date of receipt of the request, unless otherwise specified in the follow-up request.

11.4. Pregnancy

Parent(s)/guardian of female patients who are of childbearing potential must be instructed to notify the investigator immediately if their child becomes pregnant or if they suspect she is pregnant during the trial. All initial reports of pregnancy in female patients must be reported by trial site personnel using the appropriate pregnancy form in EDC within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs and must be reported using the SAE form. If a patient becomes pregnant during the trial, treatment must be discontinued.

The investigator must follow the pregnancy until its outcome is known and the newborn infant is 1 month of age. The investigator must report information about the pregnancy, pregnancy outcome, and health of the newborn infant(s), as well as AEs in connection with the pregnancy, and AEs in the fetus and newborn infant.

11.5. Precautions

Normal precautions taken for a clinical trial, including the provision of emergency equipment, will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct patients and parent(s)/guardian. During a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to patients for any AEs, including clinically significant laboratory values related to the trial. The investigator should inform the patient's parent(s)/guardian when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

For further information on safety precautions for dasiglucagon, refer to the current version of the IB.

11.6. Safety Committee

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

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

11.7. Independent Data Monitoring Committee

An independent data monitoring committee (DMC) will be established for this trial and will work according to written procedures, e.g., the DMC charter.

12. STATISTICS

12.1. Sample Size Determination

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

12.2. Analysis Populations

Three analysis populations have been defined for this trial:

- The Safety Set: defined as all patients administered any trial drug. This population will be used to provide descriptive summaries of safety data.
- The Full Analysis Set (FAS): defined as all patients in the Safety Set who complete at least 1 day of trial drug. This population will be used to analyze efficacy data.
- The Pharmacokinetic Analysis Set (PK): defined as all patients in the Safety Set who have at least one measurement with quantifiable plasma concentration of dasiglucagon. This population will be used to provide descriptive summaries of PK data.

Inclusion in the analysis populations will be determined prior to database lock.

12.3. Statistical Analyses

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) that describes the details of the analyses to be conducted will be written prior to database lock.

Unless otherwise indicated, all testing of statistical significance will be 2 sided with a significance level of $\alpha = 0.05$.

For analyses involving trial site, if the number of patients per site is small, sites may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

Continuous endpoints will be summarized with number (n), mean, standard deviation (SD), median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively; the exception to this is the time of PG within pre-specified ranges, which will not have a baseline value. For categorical endpoints, descriptive summaries will include counts and percentages.

All data will be presented in the data listings.

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

12.3.1. Trial Patients and Demographics

12.3.1.1. Disposition and Withdrawals

The numbers of patients randomized, completing, and withdrawing, along with reasons for withdrawal, will be tabulated overall. The number of patients in each analysis population will be reported.

12.3.1.2. Protocol Deviations

Protocol deviations will be provided in a listing and summarized if appropriate.

12.3.1.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, ethnicity, weight, and length/height) at baseline will be summarized using descriptive statistics. No formal statistical analyses will be performed.

Prior and concomitant medications and procedures will be summarized by the number and percentage of patients taking each medication, classified using World Health Organization Drug Dictionary Anatomical Therapeutic Chemical classes, and preferred term (PT).

12.3.2. Duration of Exposure and Compliance

Trial drug administration (i.e., amount administered) will be summarized in terms of each patient's mean, mode, and final dose, and in terms of duration of exposure. Descriptive statistics for these quantities, including the mean, median, SD, minimum, maximum, and quartiles, will be provided.

12.3.3. Efficacy Analyses

All efficacy endpoints will be analyzed using average weekly results over the 3-month period between visits.

Due to the impact of pancreatectomy on efficacy endpoints, primary analysis for all endpoints will not handle any endpoint assessment after any pancreatectomy (endpoints set to missing after pancreatectomy). A sensitivity analysis will be run on key secondary efficacy endpoint without censoring data after any pancreatectomy.

12.3.3.1. Key Secondary Analysis

The first key secondary endpoint, total amount of carbohydrates administered to treat hypoglycemia, will be analyzed by using a mixed-model for repeated measures using restricted maximum likelihood (REML). The model will include time period, region as fixed effects, baseline as covariate and patient as random effect. Baseline is defined as the total amount of carbohydrates administered to treat hypoglycemia during the last 2 weeks of the lead-in trial. Time period is defined as up to Month 1, Month 1 to Month 3 and then 3-month period of time for the first year and 6-month period of time for subsequent years. This endpoint will also be described by region and on a sub-group of patients with gastrostomy or NG-tube at entry in extension trial.

Time to event data (including time to remove of NG tube/gastrostomy and time to pancreatic surgery) will be analyzed using Kaplan-Meier methods. Those analysis will be performed on subgroup of patient from FAS with an NG tube or gastrostomy at the time of entry into the

extension study/without any pancreatic surgery at the time of entry into the extension study respectively. Time to pancreatic surgery will also be analyzed by region.

The secondary endpoint of CGM percent time <70 mg/dL (3.3 mmol/L), where percent time is calculated as (number of minutes in hypoglycemia / total number of minutes patient is wearing CGM) * 100%, will be analyzed by using a mixed-model for repeated measures using REML. The model will include time period, region as fixed effect, baseline as covariate and patient as random effect. Baseline is defined as the CGM percent time <70 mg/dL during the last 2 weeks of the lead-in trial.

The endpoints of Rate of CGM-detected hypoglycemic episodes (<70 mg/dL [3.9 mmol/L]) and Rate of clinically significant CGM-detected hypoglycemic episodes (<54 mg/dL [3.0 mmol/L] for 15 minutes or more) will be analyzed using generalized linear mixed-model (GLMM) regression approach assuming a negative binomial distribution, with time period and region as fixed effects and patients as a random effect. Baseline hypoglycemic rate is defined as the rate in the last 2 weeks of the lead-in trial.

12.3.3.2. Secondary and Other Efficacy Analysis

The endpoint of reduction in concomitant medication usage from start of lead-in trial, namely diaxozide and somatostatin analogs, will be summarized on subgroup of patients with diazoxide / somatostain dose at start of lead-in trial respectively.

Number of gastric carbohydrate administrations (NG tube or gastrostomy) to treat hypoglycemia will also be described by region.
For all other efficacy endpoints, continuous and categorical endpoints will be presented using summary statistics or frequencies, respectively. If warranted, continuous measures will be analyzed using a paired t-test or mixed model with region as a fixed effect and baseline value as a covariate; categorical measures will be analyzed using a Chi-square goodness-of-fit test or binomial test for proportions, as data permit, to determine whether there is a difference from the previous time point.

An interim analysis will be performed as appropriate to support the application for approval of dasiglucagon.

Quality of Life

Quality of life will be assessed by the PedsQL and a CHI disease-specific questionnaire (Appendix B).

For each item of the PedsQL instrument (parent), a 5-point response scale is used (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always). Items are reverse-scored and linearly transformed to a 0-100 scale (0 → 100, 1 → 75, 2 → 50, 3 → 25, 4 → 0) so that higher scores indicate better health-related QoL (less negative impact). Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the scale score is not computed. Change from baseline for PedsQL for each of the scales (physical functioning, emotional functioning, social functioning, and school functioning) and summary scores (total scale score, physical health summary score, and psychosocial health summary score) will be summarized.

Answers to each question on the CHI disease-specific questionnaire will be summarized using frequencies at each relevant visit.

Resource Utilization

The number and percentage of patients with admissions/emergency department visits for glycemia, hospitalizations caused by CHI, visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and need for home visits by parameters will be summarized. Additionally, number and length (in days) of hospitalizations caused by CHI, number of visits to health care providers (family doctor, specialists, etc.) caused by CHI or CHI-related events, and number of home visits by paramedics will be summarized.

12.3.4. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population (as defined in Section 12.2). Safety assessments will include the evaluation of AEs; clinical laboratory assessments (hematology, biochemistry, and ADAs); vital signs, physical examinations; ECGs, and local tolerability issues. No formal inferential analyses will be conducted for safety variables, unless otherwise noted.

12.3.4.1. Primary Endpoint: Adverse Events

The primary endpoint of number of AEs will be analyzed using the incidence of AEs occurring up to Month 1, Month 1 to Month 3 and in each 3-month period for the first year; subsequent years will have longer periods assigned for analysis.

Adverse events will be coded using the latest version of MedDRA.

A treatment-emergent AE is defined as an AE with an onset at the time of or following the start of treatment with the trial drug until the patient has completed the trial and no longer than 12 weeks after treatment discontinuation, whichever occurs first.

The number and percentage of patients with AEs will be displayed by system organ class and PT. The incidence of AEs will also be presented by severity and relationship to the trial drug. Serious AEs and AEs resulting in discontinuation of trial drug will be summarized separately in a similar manner. Patient listings of AEs, SAEs, and AEs causing discontinuation of trial drug will be produced.

12.3.4.2. Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual (absolute) values and changes from baseline values will be presented for clinical laboratory values by time point.

The number of patients with clinical laboratory values categorized as below, within, or above normal ranges will be tabulated showing change from baseline (shift tables) for each clinical laboratory analyte.

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

12.3.4.3. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and SpO2.

The number of patients with vital signs values categorized as Abnormal, Clinically Significant or Abnormal, Not Clinically Significant will be tabulated showing change from baseline (shift tables) for each parameter.

12.3.4.4. Twelve-lead Electrocardiograms

The number and percentage of patients with normal and abnormal ECG findings will be summarized for each time point. Abnormal results will be grouped as Abnormal, Clinically Significant; or Abnormal, Not Clinically Significant.

12.3.4.5. Physical Examination Findings

The number and percentage of patients with normal and abnormal findings in the complete physical examination will be displayed.

12.3.4.6. Local Tolerability

The number and percentage of patients with local tolerability findings, collected separately from AEs, will be summarized.

12.3.5. Interim Analysis

An interim analysis may be performed as appropriate to support a possible New Drug Application.

13. TRIAL CONDUCT

The accuracy and reliability of data is ensured, among others, by the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and associated personnel before the trial, periodic monitoring visits, and meticulous data management.

13.1. Sponsor and Investigator Responsibilities

13.1.1. Sponsor Responsibilities

The sponsor is obligated to conduct the trial in accordance with strict ethical principles (Section 15). The sponsor reserves the right to terminate participation of a trial site at any time (Section 13.7), and/or to discontinue the trial (Section 13.6 for US trials and Section 13.6.2 for trials conducted outside of the US).

The sponsor agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the trial according to the trial protocol.

13.1.2. Investigator Responsibilities

By signing the Investigator's Agreement (Section 17.2), the investigator indicates that he/she has carefully read the protocol, fully understands the requirements, and agrees to conduct the trial in accordance with the procedures and requirements described in this protocol.

The investigator also agrees to conduct this trial in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including the November 2016 ICH Guidance for Industry E6(R2) GCP, and in agreement with the 2013 version of the Declaration of Helsinki. While delegation of certain aspects of the trial to subinvestigators and trial coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the trial

and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated trial-related responsibilities (e.g., subinvestigators and trial coordinators) and their specific trial-related duties.

Investigators should ensure that all persons who have been delegated trial-related responsibilities are adequately qualified and trained in the protocol, trial drug handling, and their specific duties within the context of the trial. Investigators are responsible for providing the sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the trial may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all trial documentation by authorized individuals.

13.2. Site Initiation

Trial personnel may not screen or enroll patients into the trial until after receiving notification from the sponsor or its designee that the trial can be initiated at the trial site. The trial site will not be authorized for trial initiation until:

1. The trial site has received the appropriate IRB/IEC approval for the protocol and the appropriate ICF.
2. All regulatory documents have been submitted to and approved by the sponsor or its designee.
3. The trial site has a Clinical Trial Agreement in place.
4. Trial site personnel, including the investigator, have participated in a trial initiation meeting.

The regulatory documents must be received from the investigator before the sponsor will authorize shipment of trial drug to the trial site, Regulatory Green Light. Copies of the investigator's regulatory documents must be retained at the trial site in a secure location in the ISF. Additional documents, including a copy of the protocol and applicable amendment(s), the dasiglucagon IB, eCRF completion guidelines, copies of regulatory references, copies of IRB/IEC correspondence, and trial drug accountability records should also be retained in the ISF. It is the investigator's responsibility to ensure that copies of all required regulatory documents are organized, current, and available for inspection.

13.3. Screen Failures

Only patients completing trials ZP4207-17103 or ZP4207-17109 are eligible for inclusion, upon confirmation of a positive benefit-risk balance for continued dasiglucagon treatment and meeting the inclusion/exclusion criteria. There is no Screening Period for entry into this trial.

13.4. Trial Documents

All documentation and material provided by the sponsor for this trial are to be retained in a secure location and treated as confidential material.

13.4.1. Investigator's Regulatory Documents

The regulatory documents will be maintained by the investigator in the ISF.

13.4.2. Case Report Forms

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories for all patients who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The sponsor or its designee will provide the necessary training on the use of the specific eCRF system used during the trial to ensure that the trial information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual patient visits should be completed as soon as possible after the visit. All requested information must be entered in the EDC system according to the completion guidelines provided by the sponsor or its designee.

The eCRF must be signed by the investigator or a subinvestigator when all data are entered and cleaned. These signatures serve to attest that the information contained in the eCRF is accurate and true.

13.4.3. Source Documents

Information recorded in the eCRF should be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

Clinical laboratory data required by the protocol will be entered into the eCRF at the site.

The investigator should permit trial-related monitoring, IEC review, regulatory inspections, and sponsor audit by providing direct access to source data and documents.

13.5. Data Quality Control

The sponsor and its designees will perform quality control checks on this clinical trial.

13.5.1. Monitoring Procedures

The sponsor and/or its designee will conduct site visits to monitor the trial and ensure (i) the safety and rights of the patients are respected, (ii) compliance with the protocol, GCP, and applicable regulations and guidelines and (iii) that accurate, valid, and complete data are collected. The assigned CRA(s) will visit the investigator and trial site at periodic intervals and maintain periodic communication; this is described in detail in the Monitoring Plan. The investigator agrees to allow the CRA(s) and other authorized sponsor personnel access to ISF and source data (original documents, data, and records). The CRA(s) will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the investigator and staff. While on site, the CRA(s) will review:

- regulatory documents
- entries in the EDC system compared with the source documents
- consents
- adherence to the inclusion/exclusion criteria

- AE records
- storage and accountability of trial drug and trial materials
- adherence to the protocol and ICH-GCP

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs are described in the Trial Reference Manual. As representatives of the sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement (Section 17.2), the investigator agrees to meet with the CRA(s) during trial site visits; to ensure that trial staff is available to the CRA(s) as needed; to provide the CRA(s) access to all trial documentation, to the clinical supplies dispensing and storage area; and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the sponsor or designee auditors or inspectors from regulatory agencies to review records, and to assist the inspectors in their duties, if requested.

13.5.2. Data Management

The sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and Premier standard operating procedures. A comprehensive data management plan will be developed, including a data management overview, description of database contents, annotated eCRF, pre-entry review list, self-evident correction conventions, query contacts, and consistency checks.

Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries are described in the trial manual.

A partial database lock is planned for interim analyses prior to NDA submission. Additional partial database locks may be performed for analyses to support the NDA process.

13.5.3. Quality Assurance/Audit

This trial will be subject to audit by the sponsor/its designee or national/international regulatory authorities. Audits may be performed to check compliance with GCP guidelines, and can include:

- Site audits
- Trial master file (TMF) audits
- Database audits
- Document audits (e.g., protocol and/or the clinical trial report [CTR])

The sponsor or its designee may conduct additional audits on a selection of trial sites, requiring access to patient notes, trial documentation, and facilities or laboratories used for the trial.

The trial site, facilities, all data (including source data), and documentation will be made available for audit by quality assurance auditors and for IRB/IEC or regulatory authorities according to GCP guidelines. The investigator agrees to cooperate with the auditor during the visit and will be available to supply the auditor with eCRFs or other files necessary to conduct that audit. Any findings will be strictly confidential.

If a regulatory authority informs the investigator that it intends to conduct an inspection, the investigator shall notify the sponsor immediately.

13.6. Trial Termination

The trial may be terminated at the sponsor's discretion at any time and for any reason.

13.6.1. Regular Trial Termination

The end of this trial is defined as the date of the last visit of the last patient completing the Trial Period as described in Section 7.2. Monitoring of treatment-induced or treatment-boosted ADA-positive patients after Trial Completion will continue until the ADA levels return to baseline or until 2 years after End of Trial, whichever occurs first. Within 90 days of the end of the clinical trial, the sponsor or its designee and/or the site will notify the IRBs and IECs and regulatory authorities on the regular termination of the trial, as required according to national laws and regulations.

13.6.2. Premature Trial Termination

The trial may be terminated prematurely for any reason and at any time by the sponsor, the IRBs/IECs, regulatory authorities, respective steering committees, or the coordinating investigator. A decision to terminate the trial prematurely is binding to all investigators at all trial sites.

Within 15 days of premature termination of a clinical trial, the sponsor or its designee and/or the site will notify the IRBs/IECs and regulatory authorities on the premature termination as required according to national laws and regulations. The sponsor or its designee must clearly explain the reasons for premature termination.

If the trial is terminated prematurely, all investigators must inform their patients and take care of their appropriate follow-up and further treatment to ensure protection of their interests. Trial sites may be asked to have all patients currently participating in the trial complete all of the assessments for an Early Termination Visit.

13.7. Trial Site Closure

At the end of the trial, trial sites with no treatment-induced or treatment-boosted ADA-positive patients will be closed. Sites with treatment-induced or treatment-boosted ADA-positive patients will remain open until the ADA level of their last ADA-positive patient has returned to baseline or until 2 years after End of Trial, whichever occurs first.

The sponsor may terminate participation of a trial site at any time. Examples of conditions that may require premature termination of a trial site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines
- Inadequate patient enrollment

13.7.1. Record Retention

After trial completion at sites in the US, the investigator shall retain and preserve 1 copy of all data generated in the course of the trial, specifically including, but not limited to, those defined by GCP as essential until:

- At least 2 years after the last marketing authorization for the trial drug has been approved or the sponsor has discontinued its research with the trial drug, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the trial drug

However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor.

At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

After trial completion at sites in Europe, the sponsor will receive a copy of their data in electronic format (e.g., CD) and retain them for at least 25 years.

One copy will remain with the investigator. The investigator shall arrange for the retention of the patient identification codes, patient files, and other source data until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. These documents need to be retained for a longer period of time if required by applicable regulatory authorities or by agreement with the sponsor.

The investigator shall keep copies of these trial records (and all trial-related documents, including source data) for the maximum period of time permitted by the hospital, institution, or private practice.

13.7.2. Sample Retention

Samples will only be used for purposes related to this trial.

All blood samples will be destroyed upon completion of the CTR, except for residual ADA samples, which will be stored until approval of market authorization because further characterization of the antibody response may be requested by the health authorities. Identifiable samples can be destroyed at any time at the request of the patient.

13.8. Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of the sponsor. The protocol amendment must be signed by the investigator and approved by the IRB/IEC before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the trial.

13.9. Use of Information and Publication

All information concerning dasiglucagon, the sponsor's operations, patent applications, formulae, manufacturing processes, basic scientific data, and formulation information supplied by the sponsor or its designee to the investigator and not previously published, is considered confidential and remains the sole property of the sponsor. Case report forms also remain the property of the sponsor. The investigator agrees to use this information for purposes of trial

execution through finalization and will not use it for other purposes without the written consent of the sponsor.

The information developed in this trial will be used by the sponsor in connection with the continued development of dasiglucagon and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this trial is the property of the sponsor. Publication or other public presentation of dasiglucagon data resulting from this trial requires prior review and written approval of the sponsor. Abstracts, manuscripts, and presentation materials should be provided to the sponsor for review and approval at least 30 days prior to the relevant submission deadline. Data from individual trial sites must not be published separately.

It is agreed that the results of the trial will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until the sponsor has reviewed and commented on such a presentation or manuscript for publication.

14. FINAL CLINICAL TRIAL REPORT

The sponsor will retain ownership of the data.

The final CTR will be reported on the Trial Period and will be prepared and reviewed in cooperation with the signatory investigator. The coordinating investigator will be appointed by the sponsor to review and sign the CTR on behalf of all participating investigators. This report will include a summary of the trial results based on a statistical evaluation and clinical assessment of the protocol-defined endpoints. The results from the neutralizing antibody assay may be included or reported separately pending availability of the results. The results of the ADA follow-up samples will be reported separately after completion of the ADA Follow-up Period.

The final CTR may be submitted to the regulatory authorities.

15. ETHICAL AND LEGAL CONSIDERATIONS

15.1. Declaration of Helsinki and Good Clinical Practice

This trial will be conducted in compliance with the November 2016 ICH Guidance for Industry E6(R2) GCP (including archiving of essential trial documents), the 2013 version of the Declaration of Helsinki, and the applicable regulations of the country(ies) in which the trial is conducted.

See Appendix C for regulations and guidelines.

15.2. Patient Information and Informed Consent

According to the Declaration of Helsinki and ICH GCP, patients' parent(s)/guardian must provide their written informed consent (and the child must provide assent, depending on local IRB/IEC requirements) prior to enrollment in a clinical trial and before any protocol-specified procedures are performed. Patients' parent(s)/guardian (and the patient, depending on local IRB/IEC requirements) must declare their consent by personally signing and dating the ICF.

France, Germany, Israel: *The consent must correspond to the patient's presumed will where such a will can be ascertained.*

The written ICF will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Each patient's parent(s)/guardian (and patient, depending on local IRB/IEC requirements) should be made aware by the investigator of the nature of the trial (objectives, methods, and potential hazards and benefits) and the procedures involved using the information on the ICF.

France, Germany, Israel: *Additionally, the patient will be informed about the nature, significance, risks, and implications of the trial with age-appropriate information, and his or her assent will be obtained in accordance with local regulations, as applicable*.

Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB/IEC. Patients, their relatives, or, if necessary, legal representatives must be given ample opportunity to inquire about details of the trial.

Patient information and the ICF must be in a language fully comprehensible to the prospective patient's parent(s)/guardian (and patient, depending on local IRB/IEC requirements). The written information must be provided to the patient's parent(s)/guardian (and the patient, depending on local IRB/IEC requirements) to give him or her sufficient time to understand the information and to prepare questions before being asked for his or her consent (and assent). The investigator must confirm that the text was understood by the patient's parent(s)/guardian (and patient where applicable). The patient's parent(s)/guardian (and patient, where applicable) will then sign and date the IRB/IEC-approved consent (and assent) form indicating that he or she has given his or her consent for his or her child to participate in the trial. The signature confirms that the consent is based on information that has been understood. The form will also be signed by the investigator obtaining the consent and annotated with the trial patient number. Each signed ICF and assent must be kept on file by the investigator for possible inspection by regulatory authorities, the sponsor, and/or the sponsor's designee. Collection of informed consent has to be documented on the eCRF.

Furthermore, the patient's parent(s)/guardian will be informed that if he or she wishes to withdraw his or her child (see Section 8.4) at any time during the trial, this will not have any negative consequences. Patients may be withdrawn by the investigator if any change related to safety or ethics precludes further participation in the trial. Patients' parent(s)/guardian (and patient, where applicable) will be asked to agree to a final assessment in the event of an early termination of the trial.

If information becomes available that may be relevant to the patient's willingness to continue participating in the trial, the Investigator must inform the patients' parent(s)/guardian in a timely manner, and a revised written informed consent must be obtained.

Patients' parent(s)/guardian (and patient where applicable) will be informed that data from their child's case may be stored in a computer without inclusion of his or her name and that such data will not be revealed to any unauthorized third party. Data will be reviewed by the monitor, an independent auditor, and possibly by representatives of regulatory authorities and/or IRBs/IECs. The terms of the local data protection legislation will be applied as appropriate.

15.3. Approval by Institutional Review Board and Independent Ethics Committee

For Investigational New Drug studies, the minimum standards of conduct and requirements for informed consent are defined in the FDA regulations.

A valid IRB/IEC must review and approve this protocol before trial initiation. Written notification of approval is to be provided by the investigator to the sponsor's monitor and project manager before shipment of investigational drug supplies, and will include the date of the committee's approval and the chairperson's signature. This written approval must consist of a completed sponsor form, IRB/IEC Approval Form, or written documentation from the IRB/IEC containing the same information.

Until written approval by the IRB/IEC has been received by the investigator, no patient may undergo any procedure not part of routine care for the patient's condition.

Protocol amendments must also be reviewed and approved by the IRB/IEC. Written approval from the IRB/IEC, or a designee, must be received by the sponsor before implementation. This written approval will consist of a completed IRB Approval Form or written documentation from the IRB/IEC containing the same information.

15.4. Finance and Insurance

Details on finance and insurance will be provided in a separate agreement between the investigator and the sponsor.

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17. ATTACHMENTS

17.1. Schedule of Events

Table 1 Schedule of Events

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

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

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

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

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

17.2. Investigator's Agreement

PROTOCOL NUMBER:	ZP4207-17106
PROTOCOL TITLE:	An Extension Trial Evaluating the Long-term Safety and Efficacy of Dasiglucagon for the Treatment of Children with Congenital Hyperinsulinism
FINAL PROTOCOL:	Version 17.0 (Germany), 09-Apr-2024

The undersigned acknowledges possession of and has read the product information (e.g., IB) on the trial drug and has discussed these data with the trial monitor. Having considered fully all the available information, the undersigned considers that it is ethically justifiable to give the trial drug to selected patients in his/her care, according to the trial protocol.

- He or she agrees to use the trial material, including trial drug, only as specified in the protocol. He or she understands that changes cannot be made to the protocol without prior written approval of the sponsor.
- He or she understands that any deviation from the protocol may lead to early termination of the trial.
- He or she agrees to report to the sponsor within time any clinical AE or abnormal laboratory value that is serious, whether or not considered related to the administration of trial drug.
- He or she agrees to comply with the sponsor and regulatory requirements for the monitoring and auditing of this trial.

In addition, he/she agrees that the trial will be carried out in accordance with the revised Declaration of Helsinki (2013) and the local laws and regulations relevant to the use of new therapeutic agents.

I, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the trial.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Investigator's name and address (stamp)

18. APPENDICES

A. Contact Information
B. List of Quality of Life Questionnaires
C. Regulations and Good Clinical Practice Guidelines
D. Seizure Checklist

A. Contact Information

Safety CRO:

Name: [redacted]
Address: [redacted]
[redacted]
Email: [redacted]
Telephone: [redacted]

B. List of Quality of Life Questionnaires

- Infants 1-12 Months: "PedsQL™ Pediatric Quality of Life Inventory Infant Scales – Version 1 - Parent Report for Infants (ages 1-12 months)"
- Infants 13-24 Months: "PedsQL™ Pediatric Quality of Life Inventory Infant Scales – Version 1 - Parent Report for Infants (ages 13-24 months)"
- Parent Report for Teens 13-18 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Teens (ages 13-18 yrs)"
- Parent Report for Children 8-12 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Children (ages 8-12 yrs)"
- Parent Report for Children 5-7 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Young Children (ages 5-7 yrs)"
- Parent Report for Toddlers 2-4 Years: "PedsQL™ Pediatric Quality of Life Inventory – Version 4 - Parent Report for Toddlers (ages 2-4 yrs)"
- CHI Disease-Specific Questionnaire Developed by the Patient Association, Congenital Hyperinsulinism International, and Taken from the Patient-Reported Registry, the HI Global Registry

C. Regulations and Good Clinical Practice Guidelines

1.Regulations

Refer to the following United States Code of Federal Regulations (CFR):

- FDA Regulations 21 CFR, Parts 50.20 – 50.27
  Subpart B – Informed Consent of Human Subjects
- FDA Regulations 21 CFR, Parts 56.107 – 56.115
  Part 56 – Institutional Review Boards
  Subpart B – Organization and Personnel
  Subpart C – IRB Functions and Operations
  Subpart D – Records and Reports
- FDA Regulations 21 CFR, Parts 312.50 – 312.70
  Subpart D – Responsibilities of Sponsors and Investigators

Refer to the following European Directives [and applicable regulations/guidances]:

- European Directive 2001/20/EC and related guidance documents
- European Directive 2005/28/EC and related guidance documents

2.Good Clinical Practice Guidelines

ICH GCP guidelines can be found at the following URL:
https://www.ich.org/page/efficacy-guidelines

D. Seizure Checklist

At site visits and during monthly telephone contacts, the investigator should ask the patient and their caregiver(s), about any possible signs and symptoms of seizures. The below listed symptoms should be reviewed during the interview:

- Staring episodes
- Temporary confusion
- Not responding to noise or words for brief periods
- Appearing confused or in a daze
- Nodding the head rhythmically, when associated with loss of awareness or even loss of consciousness
- Periods of rapid eye blinking, jerky eye movements, or forced eye deviation.
- Jerking movements of the arms and legs (myoclonus or clonic movements)
- Stiffening of the body (entire body or one arm/leg)
- Loss of consciousness or awareness, fainting
- Falling suddenly for no apparent reason, especially when associated with loss of consciousness
- Breathing problems (abnormal breathing pattern or interruption of breathing)
- Loss of bowel or bladder control
- Auditory/visual aura (episodic hallucinations or distortions of perception
- Myoclonus
- Automatism
- Biting of tongue

An episode of partial or generalized seizure should be reported as an AESI, as described in Section 11.1.8.
Any single signs or symptoms observed by the patient/caregiver(s) and evaluated by the investigator to not be a seizure should be reported as an AE(s).

19. ADDENDUM

19.1. Administrative Information

The Coordinating Investigator for Germany is:

[redacted]

A list of all participating investigational sites, including name, address, and professional position of the Principal Investigator for each site is maintained in the trial master file.

19.2. Device Information

This clinical trial is being conducted solely to investigate the safety and efficacy of dasiglucagon usage in children with CHI. More information can be found in Section 5.3.

This clinical trial is not being conducted to verify claims and new intended performance of the medical devices. No risks and device effects will be formally assessed, but only collected and, if appropriate, reported to the applicable bodies. The planned devices are only being used for the administration of dasiglucagon and to measure glucose levels since no other approved devices are available as an alternative for this rare disease. The protocol will be submitted to competent authorities and ethics committees for approval. If additional requirements are imposed by these bodies, those recommendations will be followed.

19.2.1. Planned Devices

19.2.1.1. Pump System Accu-Chek Spirit Combo

The planned drug delivery pump Accu-Chek Spirit Combo System with its components as described in Section 9.3 will be used to administer the investigational drug dasiglucagon. The Accu-Chek Spirit Combo Pump is a portable, battery-operated pump indicated for subcutaneous or intraperitoneal continuous delivery of insulin for the management of diabetes mellitus in persons requiring insulin as prescribed by a physician. It is a CE-marketed Class IIb product under the EC directive 92/42/EEC and is also in conformity with the EU directive 1999/5/EC on radio and telecommunications terminal equipment. The manufacturer is Roche Diabetes Care GmbH, Sandhofer Str. 116, 68305 Mannheim – Germany.

The pump system consists of the following components:

- Programmable Accu-Chek Spirit Combo pump with a display screen
- Adapter that connects the cartridge to the infusion set
- Batteries and battery key
- Sterile disposables:
  - Accu-Chek Spirit 3.15-mL cartridge with luer-lock connection
  - Infusion sets:
    - Accu-Chek FlexLink Infusion set
    - Accu-Chek Ultraflex

- Accu-Chek LinkAssist insertion tool
- Accu-Chek Rapid-D Link Infusion set cannula
- Accu-Chek Rapid-D Transfer Set

The single-use disposable infusion sets and sterile cartridges are packed in sealed pouches and are sterilized with ethylene oxide. Pictures of the pump and system components are provided in the ZP4207-17106 Trial Materials Manual for further information. Additional available accessories for the Accu-Chek Spirit Combo System are an alcantara pouch in black and a neoprene pouch in white with a belly belt.

The trial sites will be supplied with the pumps and their components and will be asked to document receipt of this equipment. Each pump will be identified by a serial number that will be used for accountability and traceability; the device will be labelled "for investigational use only." The trial sites must store the devices in a secure area with restricted access and at the storage conditions indicated in the user manual (+5°C – 45°C). When a patient is enrolled into the trial, the patient will continue to use the pump device already allocated to the patient in the lead-in trial (17109 or 17103); disposables are not accounted for. Upon completion of the trial the patient can keep the pump.

The Roche pump is CE marked and marketed in Germany, and it can administer very low doses. The pump is designed to deliver 0.05 to 25.0 units of U-100 insulin per hour in basal rates, which corresponds to 2 to 1000 µg dasiglucagon per hour. This dosing accuracy allows reliable dosing of dasiglucagon between 10 and 70 µg per hour in the clinical trial. Further, this pump has been used in pediatric diabetes treatment in the EU since 2010. However, the Accu-Chek Spirit Combo pump system will not be used within its approved indication. The pump will be used for the administration of the investigational glucagon analog dasiglucagon for the indication of CHI. Additional compatibility testing and assessments were performed to ensure that the Accu-Chek Spirit Combo pump system and its components are not adversely affected by using dasiglucagon instead of insulin. Also, testing was performed to ensure that dasiglucagon is stable and effective when administered via this pump system. The general management of the device, as well as the duration of contact of the pump material and infusion sets with human tissue, will be based on the approved intended use of the device. The complete infusion set will be changed every 2 days (48 hours) for the Accu-Chek Rapid-D link infusion set, and every 3 days (72 hours) as a maximum for the Accu-Chek FlexLink infusion set. Only the application and dosage of dasiglucagon via the Accu-Chek pump system requires an off-label change in practice compared to the procedure described in the general instruction for use for Accu-Chek Spirit Combo pump system. The pump is programmed to reflect doses of insulin in units (U), whilst dasiglucagon requires weight-based dose administration (µg). The site staff and the patient's parent(s)/guardian(s) will be instructed on the procedures for filling the content of the trial drug vials into the cartridge to be used in the infusion pump and how to convert dasiglucagon (µg) into units (U) as shown on the pump display. For this purpose an extensive, trial-specific instruction for use was developed to accommodate the training of site staff and the patient's parent(s)/guardian(s).

19.2.1.2. Self-Monitoring Plasma Glucose StatStrip Xpress2

To assess plasma glucose levels and events of hypoglycemia, SMPG measurements will be taken. The plasma glucose level will be assessed at least 2 times daily to calibrate the CGM and

more frequently as instructed by the investigator and in case of suspected hypoglycemia throughout the trial.

The hand-held StatStrip Xpress2 meter GLU/KET from Nova Biomedical is to be used to measure glucose and ketone levels in the design of the trial. The ketone measurement will only be performed by trial staff when the patient is in the clinic.

The SMPG meter manufactured by Nova Biomedical is a small (size of 98.0 × 64.0 × 22.9 mm and a weight of 78.5 g) battery-powered meter. Blood sample strips are inserted and glucose (in mg/dl or mmol/L) and ketone values (in mmol/l) will be displayed on the screen. Function and data selection are done by choosing 1 of 3 buttons. Up to 400 measurements can be stored in the device memory.

The test strip is designed with an electrode that measures glucose levels. Glucose in the blood sample mixes with reagent on the test strip, which produces an electric current. The amount of current that is produced depends on the amount of glucose in the blood. The electrical current is detected by the monitor and displayed as the glucose value. The test strip is designed such that when a drop of blood touches the end of the strip, the blood is drawn into the reaction space via capillary action. Test strips are available in cartons of 100 strips: 50 strips/vial. Additionally a QC control glucose/ketone solution is provided to test device functionality.

The manufacturer Nova Biomedical Corporation, 200 Prospect Street, Waltham, MA 02454-9141 – USA (European Authorized Representative Nova Biomedical U.K.; Innovation House Aston Lane South, Runcorn, Cheshire WA7 3FY, UK) have self-declared conformity with the EU Directive 98/79/EC In Vitro Diagnostic Medical Device Directive. This SMPG device is marketed as an In Vitro Diagnostic Device. The SMPG device is intended for in-vitro diagnostic use by health care professionals and for point-of-care usage in the quantitative measurement of glucose in fresh capillary, venous, arterial, and neonate whole blood; it can also be used for quantitative determination of beta-hydroxybutyrate-ketone in fresh capillary and venous blood samples. It is not intended for diagnosing or screening for diabetes.

The SMPG device is reusable with single-use test strips. The SMPG device is not sterile; however, the strips themselves are in sterile packaging. Once the vial containing the strips is opened, the single strips may be used for 180 days or until the expiration date printed on the label has been reached, whichever comes first. The patient's blood will be drawn via single-use lancing devices and a drop is applied to the strip. The strip is then inserted into the device and the glucose level is displayed.

The rationale for selecting this device for the clinical trial is that this blood glucose meter is the only one approved for use in neonates in an intensive care unit setting, based on its accuracy and extensive testing for possible concomitant medication interference. No blood glucose meter for use by lay person in the home care setting is approved for the age group <1 year. To ensure consistency of data between the hospitalized and home-care periods in the trial, it was deemed preferable to continue with the same blood glucose meter, rather than change to ones approved for use by lay persons in home-care settings, but that were not approved for this specific age group.

The trial sites will be supplied with the StatStrip Glucose Xpress2 meter and the StatStrip Glucose and ketone test strips by the sponsor, and are asked to document the receipt of the material. Each SMPG is identified by a serial number that will be used for accountability and

traceability and the device is labelled as “for investigational use only.” The trial sites are asked to store the devices in a secure area with restricted access at the storage conditions indicated in the user manual (+1°C – 30°C); the QC Control GLU/KET solution must be stored between +15 – 30°C. When a patient is enrolled into the trial, the patient will continue to use the SMPG device already allocated to the patient in the lead-in trial (17109 or 17103); disposable accessories are not accounted for. Upon completion of the trial, the SMPG device has to be returned to the site. The site will ship all returned SMPG devices back to the sponsor upon completion of the trial.

The same SMPG StatStrip Glucose Xpress2 meter will be used for each enrolled patient during the hospital stay and at home. The home assessments will be performed by the parent(s)/guardian(s); however, the use of the device by a lay-person is outside the intended purpose. The risk resulting from this deviation from the intended purpose will be minimized by offering extensive training of the parent(s)/guardian(s) by the site staff, before independent measurements are performed.

Upon return to the site, the SMPG data will be uploaded to a tablet provided to the site personnel. The trial tablet is loaded with the applicable software for sending the SMPG data to the Vitalograph Web Portal.

19.2.1.3. Dexcom G5 and G6 Continuous Glucose Monitoring System

In this trial, the Dexcom Continuous Glucose Monitoring systems G5 and G6 from Dexcom will be used. The Dexcom G5 and G6 are indicated for detecting trends and tracking patterns in patients (aged 2 and older) with diabetes. The systems are intended for use by patients at home and in healthcare facilities. They are designed to replace fingerstick blood glucose testing for diabetes treatment decisions. Both systems aid in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments, which may minimize their excursions. Interpretation of CGM results should be based on the trends and patterns noted in several sequential readings over time.

The G5 system components include the following:

- **Sensor (Disposable)** – comprises a sensor applicator, an adhesive pad, transmitter mount, and the sensor probe. The sensor can be worn for up to 7 days. The sensor is a sterile device inserted by the user into the abdominal subcutaneous tissue using the applicator for that purpose. The applicator is attached to the surface of the skin with a standard medical grade adhesive pad. The applicator is a 26-gauge introducer needle that contains the sensor probe. The needle is not exposed, or even visible, to the user during the insertion process. After deployment of the introducer needle, the needle is retracted back into the applicator. The sensor probe remains beneath the surface of the skin and uses the enzyme glucose oxidase to convert the glucose in the interstitial fluid around the sensor into an electrical current proportional to the ambient glucose concentration. The applicator is detached and discarded by the user, exposing a transmitter mount ready for placement of the transmitted current and signal.
- **Transmitter** – The G5 transmitter transmits data with Bluetooth wireless technology. After sensor insertion and removal of the applicator, the user manually places the transmitter into the transmitter mount on the adhesive pad already attached to the skin. The transmitter contains all the electrical circuitry necessary for the operation of the electrochemical sensor and to transmit the sensor signal to the receiver via Bluetooth wireless technology. The transmitter collects the small electrical current from the sensor

and transmits the sensor signal wirelessly to the receiver at regular 5-minute intervals. The transmitter is reusable and can be used for repeated 7-day sessions by a single user over the lifetime of the battery encased in the device.

- **Receiver** – The G5 receiver is a small hand-held device that receives the Bluetooth wireless technology signals from the transmitter. The receiver contains a rechargeable battery. In typical use, the receiver may last for up to 3 days before requiring recharging. The user must maintain the receiver within 6 meters or less of the transmitter, which is attached to the sensor on the body. The receiver also contains calibration and signal processing algorithms required to convert the sensor electrical signal to glucose values. Calibrations are performed twice daily by the patient's parent(s) /guardian(s) using measurements from a standard blood glucose meter device and manually entered into the receiver. In this trial the StatStrip Xpress2 meter GLU/KET from Nova Biomedical will be used to calibrate the CGM.

Other accessories include the following:

- Receiver USB charging / download cable
- Alternating current (AC) power adapter - MT21255
- User's guide
- Site training checklist
- Receiver shield pack containing receiver shield, square seals, triangle seal, and acoustic spacer

The manufacturer is Dexcom, Inc. located at 6340 Sequence Drive – San Diego, CA 92121 United States of America. The European Authorized Representative is MediTech Strategic Consultants B.V., Maastrichterlaan 127-129, 6291 EN Vaals, the Netherlands. The following device classifications and rules were applied to demonstrate compliance with the Medical Device Directives:

- Sensor: Class IIb: Rule 8 according to Annex IX of the MDD 93/42/EEC & 2007/47/EC
- Transmitter: Class IIa, Rule 10 according to Annex IX of the MDD 93/42/EEC and 2007/47/EC
- Receiver: Class IIb, Rule 10 according to Annex IX of the MDD 93/42/EEC and 2007/47/EC
- Dexcom G5 Mobile System: Class IIb, Rule 8 according to Annex IX of the MDD 93/42/EEC and 2007/47/EC

The associate notified body is the British Standards Institution. The device has been marketed since October 2012.

The system components (applicator, transmitter housing, insertion needle and sensor) are sterilized via electron beam radiation using the (VD)max[21] method. Transmitters and receivers are not sterile products.

The G6 system components include the following:

- **Sensor (Disposable)** – comprises a sensor applicator, the sensor, an adhesive pad, and the transmitter holder. The sensor can be worn for up to 10 days. The sensor is a sterile device inserted by the user into the subcutaneous tissue of the abdomen or buttocks using

the applicator for that purpose. The applicator is attached to the surface of the skin with a standard medical grade adhesive pad. The applicator is an introducer needle that contains the sensor probe. The needle is not exposed, or even visible, to the user during the insertion process. After deployment of the introducer needle, the needle is retracted back into the applicator. The sensor probe remains beneath the surface of the skin and uses the enzyme glucose oxidase to convert the glucose in the interstitial fluid around the sensor into an electrical current proportional to the ambient glucose concentration. The applicator is detached and discarded by the user, exposing a transmitter mount ready for placement of the transmitted current and signal.

- **Transmitter** – The G6 transmitter transmits data with Bluetooth wireless technology. After sensor insertion and removal of the applicator, the user manually places the transmitter into the transmitter holder on the adhesive pad already attached to the skin. The transmitter contains all the electrical circuitry necessary for the operation of the electrochemical sensor and to transmit the sensor signal to the receiver via Bluetooth wireless technology. The transmitter collects the small electrical current from the sensor and transmits the sensor signal wirelessly to the receiver at regular 5-minute intervals. The transmitter is reusable and can be used for repeated 10-day sessions by a single user for up to three months.
- **Receiver** – The G6 receiver is a small hand-held device that receives theBluetooth wireless technology signals from the transmitter. The receiver contains a rechargeable battery. In typical use, the receiver may last approximately 2 days before requiring recharging. The user must maintain the receiver within 6 meters or less of the transmitter, which is attached to the sensor on the body. The receiver also contains calibration and signal processing algorithms required to convert the sensor electrical signal to glucose values.

Other accessories include the following:

- Receiver USB charging / download cable
- Alternating current (AC) power adapter
- User's guides
- Training checklist

The manufacturer is Dexcom, Inc. located at 6340 Sequence Drive – San Diego, CA 92121 United States of America. The European Authorized Representative is MDSS GmbH, Schiffgraben 41, 30175 Hannover, Germany. The following device classifications and rules were applied to demonstrate compliance with the Medical Device Directives:

- Dexcom G6 System: Class IIb, Rule 8 according to Annex IX of the MDD 93/42/EEC and 2007/47/EC

The associate notified body is the British Standards Institution.

The system components (applicator, transmitter housing, insertion needle and sensor are sterilized via electron beam radiation using the (VD)max[21] method. Transmitters and receivers are not sterile products.

The trial sites will be supplied with the Dexcom CGM systems by the sponsor and are asked to document the receipt of the material. Each CGM is identified by a serial number which will be used for accountability and traceability and the device is labelled as "for investigational use

only." The trial sites are asked to store the devices in a secure area with restricted access at the storage conditions indicated in the user manual:

- Sensors (+2°C – 25°C)
- Transmitter and receiver (0°C – 45°C)

After the patient is enrolled into the trial, a CGM device is allocated exclusively to this patient; disposable materials are not accounted for. Upon completion of the trial, the CGM must be returned to the site. The site will ship all returned CGMs back to the sponsor upon completion of this trial. Depending on the time of enrollment into the trial the patient may start the trial with the Dexcom G5 CGM and switch to the Dexcom G6 CGM at a later point. If all required approvals for the Dexcom G6 CGM are in place at the time the patient are enrolled, the patient can use the Dexcom G6 CGM from the start and throughout the trial.

CHI is characterized by frequent, often severe episodes of hypoglycemia due to over-secretion of insulin regardless of blood glucose. Therefore, CHI closely mimics the exogenous insulin overdose occurring in insulin-dependent diabetes management. The CGM device is being used in this clinical trial to confirm potential treatment effects on a continuous basis.

The rationale for selecting the Dexcom G5 and G6 CGM devices for this clinical trial is that the patients/parents/guardians are already used to using the similar Dexcom G4 CGM device in the lead-in trials (17109 and 17103) and will be used to the main functionalities of the device. As the Dexcom G5 CGM will be taken off the market by Dexcom in 2020, the Dexcom G6 CGM will replace the G5 CGM in the trial.

For the purpose of this trial the devices will be used outside the intended purpose in regard to the age of the patients (5 weeks and older instead of 2 years and older) and in regard to the indication (CHI instead of Diabetes). No mechanical or design changes have been made to the devices. The CGM devices are used as intended according to the CE mark, except for the age group and the disease. The essential requirements testing performed for CE marking is assessed applicable for proposed use. Additionally, literature shows that CGMs have been successfully used in infants and neonates.[22] The risk resulting from this deviation from the intended purpose, in terms of age, will be minimized by offering extensive training to parent(s)/guardian(s) by the site staff, before the device and its components are used independently.

The results of the CGM will be used by the investigator and parents/guardians to monitor the patients' blood glucose levels and by the sponsor for endpoint evaluation.

At every patient's onsite visit, the site staff will transfer data of the CGM device via the CENDUIT Data Agent, after the device has been initially registered within the CENDUIT IRT system. Full instructions on data transfer are available in the CENDUIT user manual.

19.2.1.4. Other Medical Devices

The following medical devices will be used within their intended purpose during this trial:

- BD Lancet – BD Microtainer® CAL – contact-activated lancet
- Disinfecting wipes (alcohol pads)
- Disinfecting wipes – Diabete ezy

The provided devices are disposable; they will be provided to the patient but not accounted for.

19.2.2. Risk Evaluation for Off-label Use of Devices

19.2.2.1. Anticipated Clinical Benefit of Planned Devices

The main aim of this clinical trial is to assess the safety and efficacy of the investigational drug dasiglucagon. To achieve this, the Accu-Chek Spirit Combo Pump system, the Self-Monitoring Plasma Glucose StatStrip Xpress2,Dexcom G5 and Dexcom G6 devices are utilized in this trial outside their intended use. There is no direct clinical benefit anticipated by using the Accu-Chek Spirit Combo Pump except the administration of dasiglucagon and therefore, only an indirect benefit can be anticipated, resulting from the drug administration as referenced in Section 5.3.5. The clinical benefit of the SMPG and the CGMs is to help to assess if patients undergo hyper/hypoglycemic events requiring adjustments to gastric and oral feeds or dose. In addition the CGM data will help to confirm treatment effects independent from parents'/guardians' ability to suspect hypoglycemia.

19.2.2.2. Risks Associated with the Planned Devices and their Control

A risk analysis according to EN ISO 14971:2012 was performed specifically for risks related to the off-label use of the planned devices, to identify and mitigate potential risks due to the off-label use of the devices. The analysis rated risks based on their probability of occurrence and the severity of their consequence. Unacceptable risk levels were defined and risks, meeting this definition were mitigated as far as possible to get to an acceptable level. Results of the risk analysis were entered into a risk management report. The identified risks were evaluated and risk mitigation measures were and will be implemented throughout this trial. The main task to mitigate the risks is to educate site staff, parents and guardians on the proper use of the devices to minimize the risks associated with the off-label use.

The following residual risks were identified, which will be specifically addressed in the planned training of the users and thereby risks will be mitigated:

Accu-Chek® Spirit Combo Pump System and Self-Monitoring Plasma Glucose (SMPG) meter (Nova Biomedical / Xpress2 GLU/KET)

Training will cover the following aspects:

- Recognition of hypo- and hyperglycemia in the patient
- Response to hypo- and hyperglycemia
- Usage of the devices according to the instructions for use in the trial
- Communication between patients/parents/guardians and the medical professionals of the trial team.

Dexcom G5 and G6 Continuous Glucose Monitoring (CGM) device

The training will cover the following aspects:

- Avoid to cover the sensor by the diaper in babies
- Avoid that the transmitter is grabbed by baby by covering it with bandage or clothes
- Avoid that the transmitter is misplaced under diaper area or child pollutes around diaper area

Additionally, the assessment identified other risks caused by potential Accu-Chek® Spirit Combo pump system/drug interaction e.g. unintentional misappropriation of drug delivery or hazards caused by direct drug/device interactions. These potential risks were assessed by additional

compatibility and in-use stability testing and no unacceptable risk was noticed. Flow-rate assessments were performed and a conversion table for the use of dasiglucagon in the Accu-Chek® Spirit Combo pump system was developed and tested in a Human Factor trial. This conversion table was included with further instructions in a trial specific "Instruction for Use" for the combination of dasiglucagon with the pump system. By this measure the risk of misappropriation of drug delivery was reduced to an acceptable level.

19.2.2.3. Possible Interactions with Concomitant Medical Treatment

The use of the planned devices is not expected to interfere with other concomitant medical treatments, except those treatments referenced in Section 9.11.2.

19.2.2.4. Risk/Benefit Assessment

At the present time there are no known CE marked devices intended for the delivery of dasiglucagon for the treatment of CHI. Additionally, there are no known devices intended to monitor glycemic control in children with CHI. Since there are no devices currently approved to treat this condition, off-label use of the Accu-Chek Combo Insulin pump system, Dexcom G5 and G6 CGM and Nova Biomedical / Xpress2 GLU/KET for the purpose of delivering dasiglucagon and monitoring glucose levels potentially presents a beneficial alternative to the standard clinical practices of current treatment options, continuous gastric infusion and pancreatectomy for controlling CHI.

The most relevant risks resulting from the off-label use in terms of their potential to cause harm in relationship to their probability are the following:

- Lay persons using devices which are not used according to their intended use, e.g., perform and interpret blood glucose measurements
- Lay person applying devices which require invasive procedures at home for very young children in skin areas which might be contaminated due to the expectable uncleanliness of babies and the fact that they might carry diapers.

To evaluate the risks and the benefits of the clinical trial, the duration of the trial and the effect of the foreseeable risks during the trial period are compared to the current standard of care treatment for CHI. This comparison is done without taking the possible positive results of the trial into account. A positive trial outcome would most likely result in a change in the treatment of CHI towards a continuous delivery of dasiglucagon with devices that are proven to be save in use by children.

In general, the current standard of care (SOC) treatment for patients with CHI bears higher risks than risks associated with the clinical trial participation. The current risks associated with the SOC treatment result from:

- Continuous application of glucose rich liquids via intravenous infusion (infection, skin injury, thrombi, contamination, dosage and content errors, risk of volume overload)
- Frequent tube feedings or gastric infusions
- For patients on diazoxide treatment, the more common side effects comprise hypertrichosis, fluid retention, and gastrointestinal symptoms
- For patients on somatostatin analog (octreotide or lanreotide [long acting]) possible side effects include necrotizing enterocolitis, gallstones, and hepatitis

- Pancreatectomy (and its related exo/endocrine complications, particularly the development of insulin-dependent diabetes)
- Local wound infection

Irrespective if the patient participates in the planned clinical trial or is treated by SOC, parent(s)/guardians need to be able to detect and respond to hypoglycemic events, therefore the risk of not noticing such a situation is not increased by participating in the trial. The blood glucose measurements are performed by SMPGs and/or CGM, where the general functionality of the device can be considered as being equivalent to the proposed Nova Biomedical SMPG and the Dexcom G5 and G6 CGM. It can be concluded, that there will be no additional risks for the clinical trial participants by using the Nova Biomedical SMPG and the Dexcom G5/G6 CGM devices compared to patients who do not take part in the clinical trial, provided the users are adequately trained.

The primary objective of this clinical trial is to evaluate the long-term safety of dasiglucagon administered as SC infusion in children with CHI. The clinical trial aims to determine practicable procedures for treating CHI with dasiglucagon, that can eliminate, minimize or postpone the need for continuous application of glucose via intravenous infusions, frequent tube feedings or continuous gastric infusions and finally, pancreatectomy in the treatment of children with CHI. This will significantly reduce the risks for the patient's health. The nature of the residual risks introduced by the off-label use of the devices selected for the clinical trial is similar to the risks which already exist in the treatment of these patients and their severity is only minor. The most relevant risks result from the usage of the CGM. It is also worth noting, that the patients/parent(s)/guardian(s) enrolled in the proposed clinical trial will have already participated in ZP4207-17103 or ZP4207-17109, in which the same or similar treatment regimens and devices have been prescribed, there was a positive benefit-risk assessment of the treatment for the individual patient in the lead-in trial, and the benefit-risk ratio will be re-assessed at the clinic visits every 3 months, to ensure the patient has a benefit of participation. However, the duration of the trial will be shorter than the duration of the disease or of its long-term side-effects (either of the disease or the treatment). Specifically, enabling convenient and reliable long-term treatment via a pump device in a home setting, which holds the potential to delay and ultimately avoid pancreatectomy and its related exo/endocrine complications, particularly the development of insulin-dependent diabetes. Thus, the potential benefit of a positive trial outcome is estimated higher than the risks introduced, especially when taking into account the risks which are present by the current standard of care treatment of CHI.

19.3. Device-related Safety Section

19.3.1. Anticipated Adverse Device Effects

The following anticipated ADEs may be associated with the use of these medical devices, together with those associated with the application of dasiglucagon. All AEs and ADEs will be assessed if they meet the requirements for competent authority reporting.

The following device-related possible complications/AEs are anticipated:

19.3.2. Pump System Accu-Chek Spirit Combo

- Ketoacidosis, hypo- or hyperglycemic events resulting from incorrect pump usage, a damaged pump, or infusion set blockage[23,24]
- At infusion site:
  - Local infection
  - Irritation
  - Local pain
  - Redness
  - Swelling
  - Lumps
  - Heat
- Strangulation if tubing becomes wrapped around the neck

19.3.3. Self-monitored Plasma Glucose StatStrip Xpress2

Since the StatStrip Xpress 2 Blood Glucose Monitoring System is intended for use outside the body, only the following limited ADEs are expected:

- Hypo- or hyperglycemic events due to incorrect usage or damaged meter or strips
- Indirectly related to SMPG: Local infections caused by the single-use lancing devices to obtain blood

19.3.4. Continuous Glucose Monitoring Dexcom G5 and G6

The following events are possible ADEs of inserting a sensor or wearing the adhesive patch:

- Local infection
- Inflammation
- Pain or discomfort
- Bleeding at the glucose sensor inserting site
- Bruising
- Itching
- Scarring or skin discoloration
- Hematoma
- Tape irritation

- Sensor or needle fracture during insertion, wear of removal

The following risks are inherent to the device, but not anticipated for the trial since the device will be used in a blinded manner and no treatment decisions will be based on the CGM results. However, there are potential risks due to missed alerts, false alerts, false-negative hypoglycemia, hyperglycemic readings, false-positive hypoglycemia, and hyperglycemia readings by the device. There are additional possible risks if the system inaccurately calculates the rate of change of glucose.[25]

19.4. Protocol Clarifications

19.4.1. Informed Consent

A patient is considered enrolled in the trial as soon as the patients' parent(s)/guardian(s) (according to local law) have signed the EC-approved ICF.

19.4.2. Vulnerable Population

As discussed in Section 7.3 children between the ages of 7 days and 13 years with CHI who have completed one of the lead-in trials, ZP4207-17103 or ZP4207-17109, will be enrolled in this clinical trial. The informed consent process is referenced in Section 8.2.1, Inclusion Criteria, Section 10, Trial Procedures, and Section 15.2, Patient Information and Informed Consent. No vulnerable patients other than children are planned to be enrolled in this trial and no enrollment under an emergency situation is allowed.

19.4.3. Addition to Statistical Section

- **Drop-out rate:** N/A. Patients will continue in the trial as long as they are considered to have a positive benefit-risk assessement and therefore the trial length for each patient will vary, hence no drop-out rate defined.
- **Pass/fail criteria:** No pass/fail criteria were defined since no trial endpoints are device-related
- **Criteria for termination of trial on statistical grounds:** N/A. Please refer to Section 12.3.5 Interim Analysis.
- **Procedures for reporting deviation from statistical plan:** Since no medical device data will be evaluated statistically, no reporting of deviations from statistical plan are anticipated in regard to the devices.
- **Enrollment rate per investigational site:** Anticipated enrollment for the German clinical trial sites is 0-5 patients per German site. For analysis involving trial site, if the number of patients per site is small, sites may be pooled for analysis, or omitted from statistical models. The final determination will be made prior to database lock.

19.4.4. Protocol Deviations

A protocol deviation is defined as an event where the investigator or site personnel did not conduct the trial according to the protocol. Investigators are not allowed to deviate from the protocol unless it is necessary to protect the life or physical well-being of a patient in an emergency situation. Those emergency situations or other unforeseen circumstances that are beyond the investigator's control, e.g., the patient did not attend scheduled visits or blood samples were lost by the laboratory, are still considered deviations. Deviations will be reported

to the sponsor, regardless of whether or not they are medically justifiable or done to protect the patient in an emergency. All deviations will be reported in a timely manner on a protocol deviation form.

In addition, the investigator is required to adhere to the ethics committee procedures for reporting protocol deviations. International regulatory body regulations require that investigators maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the trial protocol. The site will receive a list of all site-specific deviations upon completion of the trial.

Deviations include, but are not limited to the following list:

- Failure to obtain informed consent prior to conducting trial-specific activities
- Incorrect version of patient information and/or ICF used
- Patient did not attend a visit or the visit was outside the required time frame
- Assessments as detailed in the Schedule of Events (Table 1) were not conducted or were performed incorrectly
- Adverse events and deficiency with SADE potential not reported by investigators within the required timeframe as specified in the protocol
- Source data were permanently lost

As addressed in Section 13.5.1 of the protocol, the CRA will review the site compliance with regard to deviations at each monitoring visit. The monitor will discuss any deviations directly with the investigator and will summarize the findings in a follow-up letter to the site.

If a trial site deviates from the protocol, those deviations will be analyzed and re-training on the particular topic(s) will be initiated as appropriate, e.g., training on the informed consent process, training on visit window adherence, and planned assessments, etc. Such trainings will be documented on the training logs for the applicable roles. If despite all training efforts an investigational site continues to deviate from the trial protocol, a site can be discontinued from the trial as agreed upon by the Principal Investigator according to his or her signature on the Investigator's Agreement in Section 17.2.