REZOLUTE

CLINICAL STUDY PROTOCOL

Study Title:	An Open-Label Multiple-Dose Study of RZ358 in Patients with Congenital Hyperinsulinism
Study Number:	RZ358-606-US
Investigational Product:	RZ358
Indication:	Congenital Hyperinsulinism
Phase of Development:	2
Study Sponsor:	Rezolute, Inc. 201 Redwood Shores Parkway Suite #315 Redwood City CA 94065, USA
IND Number:	119319
EudraCT Number:	2016-004186-83
Protocol Version and Date:	Amendment 5.0 (US), 15 March 2021 Amendment 4.0 (US), 26 May 2020 Amendment 3.0, 12 August 2019 Amendment 2.0: 10 May 2017 Amendment 1.0: 15 December 2016 Original Protocol: 01 November 2016

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

This document contains confidential information of Rezolute, Inc.
Do not copy or distribute without written permission from the Sponsor.
CONFIDENTIAL

Protocol Approval

(b) (4)

15-Mar-21

Signature **Date**

Sponsor Medical Monitor:

(b) (4)

National Coordinating Investigator /Principal Investigator Agreement

I, _____, (NCI/PI's name) have read this protocol and agree it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete it within the time designated.

The information contained in this protocol is provided to me in confidence, for review only by myself, the ethics committee authorized to review and approve the trial at this trial site, and designated trial staff participating in this clinical trial.

I agree to the conditions set out in this protocol and will not implement changes to or deviate from the protocol. I fully accept that any change requires prior approval by the Sponsor and prior review and approval of the Institutional Review Board/Independent Ethics Committee (IRB/IEC) except where necessary to eliminate an immediate hazard to patients, in which case I will notify the Sponsor and the IRB/IEC immediately.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure they are fully informed regarding the IMP and the conduct of the trial.

I will use only the informed consent form approved by the Sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the IRB/IEC responsible for this trial. I will not begin to conduct the study until I am advised in writing of the IRB/IEC's approval.

I agree to carry out all terms of this protocol in accordance with the ICH GCP (Good Clinical Practice) Guidelines, the Declaration of Helsinki and local regulations. I will ensure that the Investigational Medicinal Product is used only as described in the protocol or any subsequent amendment.

I understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorization from the trial sponsor except to the extent necessary to obtain informed consent from potential trial patients.

_____ _____

Investigator's Signature Date

_____

Clinical Trial Site Name

PROTOCOL SYNOPSIS

Title:	An Open-Label Multiple-Dose Study of RZ358 in Patients with Congenital Hyperinsulinism
Study Number:	RZ358-606-US
Development Phase:	Phase 2
Sponsor:	Rezolute, Inc.
IND # / EudraCT #	119319 / 2016-004186-83
Objectives and Endpoints	The objectives of this study are to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and glycemic efficacy of multiple ascending doses of RZ358 over 8 weeks in patients with hyperinsulinemic hypoglycemia due to congenital hyperinsulinism (CHI). **The primary endpoints in this study are as follows:** • Glycemic efficacy of RZ358 as evaluated by the average daily percent time within a glucose target range of 70-180 mg/dL (3.9-10 mmol/L) by continuous glucose monitoring (CGM); • Repeat-dose safety and tolerability of RZ358; • Repeat-dose pharmacokinetics of RZ358. **The secondary endpoints of this study are as follows:** • Average weekly incidence of hypoglycemia (< 70 mg/dL) by self-monitored blood glucose (SMBG) • Average daily duration (min) and percent time with hypoglycemia at thresholds of <70, <60, and <50 mg/dL (3.9, 3.3, and 2.8 mmol/L, respectively) by continuous glucose monitoring (CGM); • Average daily hypoglycemia incidence (event rate) at each of the specified glucose thresholds by CGM; • Average 8h overnight percent time in glucose target range of 70-180 mg/dL (3.9-10 mmol/L) by CGM; • Occurrence of hypoglycemia during a 12h fasting challenge. **Additional exploratory endpoints of this study are as follows:** • Average 8h overnight duration (min) and percent time with hypoglycemia at thresholds of <70, <60, and <50 mg/dL (3.9, 3.3, and 2.8 mmol/L, respectively) by CGM; • Average 8h overnight hypoglycemia incidence (event rate) for each of the specified glucose thresholds by CGM; • Average daily and 8h overnight area over and under the glucose curve (AUC, AOC) to each of the above glucose thresholds by CGM; • Average glucose level between midnight and 8:00 AM (or nearest pre-breakfast time point) by CGM; • Average weekly hypoglycemia incidence (event rate) at each of the specified glucose thresholds by SMBG • Intravenous (IV) or enteral nutritional (glucose/dextrose) supplementation; • Use of standard of care (SOC) or rescue medications for hypoglycemia (dextrose or other); • Incidence of fasting blood glucose values >200, >250, and >300 mg/dL (>11.1, >13.9, and >16.6 mmol/L, respectively);

	• PD biomarkers of RZ358 activity including fasting glucose, insulin, C-peptide, glucagon, free fatty acids (FFAs), and ketones (beta-hydroxybutarate).
Study Design and Description:	This is a Phase 2, multi-center, open-label, multiple ascending dose study to evaluate the safety, tolerability, PK, PD, and glycemic efficacy of RZ358 in patients with hypoglycemia due to CHI. The study will consist of up to 4 dose cohorts, which are to be enrolled independently and conducted sequentially, comprised of 6-8 patients per cohort. Eligible patients will be successively enrolled into the cohort that is open for enrollment at that time, at the lowest dosing cohort that is yet to be filled. A randomization checklist will be provided, requiring Medical Monitor approval prior to patient placement within a cohort. Following informed consent, patients will complete a Screening Period to determine eligibility. After the preliminary screening assessment, patients who are otherwise eligible will undergo scheduled self-monitoring of blood glucose (SMBG) by point of care (POC) glucometer as well as have a CGM sensor placed for completion of a 10-day outpatient CGM evaluation, to assess glycemic eligibility and establish a baseline. (b) (4) To meet glycemic qualification criteria, patients must have glucose values <70 mg/dL (3.9 mmol/L) for ≥4% of the overall monitored CGM time with at least 3 severe hypoglycemia events by CGM threshold of <50 mg/dL (2.8 mmol/L) during the last 7 days of a10-day CGM evaluation period **AND** be experiencing ≥ 3 hypoglycemia events (<70 mg/dL) per week by SMBG and/or according to the Investigator's evaluation. A (b) (4) During the Screening Period and throughout the study, patients will be requested to follow their usual diet (including enteral feeding, as applicable) and activity level, as evaluated and instructed by qualified study personnel. At the conclusion of the CGM and glycemic evaluation, final eligibility will be determined, and eligible patients will check in to the inpatient facility on Day -1, to begin the Treatment Period. On Day -1, patients will be required to start a 12h baseline fasting challenge evaluation, which will conclude prior to Day 1 dosing. Re-screening may be permitted under certain extenuating circumstances (e.g. laboratory outlier suggesting result artifact, insufficient duration of CGM collection), only with pre-approval by the Sponsor. Beginning at Day 1 of the Treatment Period, patients will receive study drug via IV infusion every two weeks over an 8 week total Treatment Period.

In Cohorts 1, 2, and 3 the dose amount will be fixed during the entire 8-week Treatment Period, while in Cohort 4 there will be a scheduled bi-weekly dose-titration for the first 4 weeks, followed by a fixed dose amount thereafter for the remaining 4 weeks. The Sponsor may decide to add a cohort to repeat a dose level or to study an additional dose level, but the dose level for any cohort will not exceed the planned dose level for that cohort, as specified in this protocol.

Table 1 Study Design/Cohort Dosing Regimens

	Dosing (mg/kg)			
Cohort	**Wk 1**	**Wk 3**	**Wk 5**	**Wk 7**
1	3	3	3	3
2	6	6	6	6
3	9	9	9	9
4	3	6	9	9

Day 1 will mark the beginning of the Treatment Period at Week 1, and "Day 1" relative to the nominal dose will also denote the beginning of each subsequent dosing week. At subsequent visits during the Treatment Period, patients must check in to the inpatient facility the day prior to each dose at each dosing visit (Day -1). On Day 1 of each dosing week, PD blood samples will be collected before breakfast for glucose, insulin, C-peptide, glucagon, FFAs, and ketones (beta-hydroxybutarate), and again at 1-hour post-dosing. Patients will remain under inpatient observation for at least 48h following dosing on Week 1 and for 24h following dosing on Weeks 3, 5, and 7, for completion of PK blood sampling and safety assessments.

Samples for PK are to be taken within 1 hour before and at 1 hour (±5 min) after the start of infusion on each dosing day (Day 1), at 24h (±15 min) post-dose on inpatient Day 2 of each dosing week (Weeks 1, 3, 5, and 7), at 48h (±30 min) post-dose on inpatient Day 3 (at Week 1 only), and at each outpatient follow-up visit (see PK Sampling Table). The PK sampling timepoints may be modified as the study progresses, based on interim PK analyses. At the discretion of the Investigator, patients may be asked to remain inpatient for longer than the specified times, as necessary for safety monitoring.

Throughout the Treatment Period and through post-treatment follow-up Day 42 (cumulative study day 85), glucose levels will be assessed and recorded by CGM. (b) (4)

Patients will undergo CGM sensor placement or replacement at the beginning of the Treatment Period and no less often than every 10 days thereafter, or otherwise as needed for replacement (see Schedule of Assessments).

Throughout the Treatment Period and through the End of Treatment Visit on post-treatment follow-up Day 14 (cumulative study day 57), SMBG by POC glucometer must be performed (b) (4)

	(b) (4)  At the conclusion of Week 7 dosing and discharge from the clinic, each patient will complete outpatient post-treatment follow-up visits at Days 14 (End of Treatment [EOT]), 28, and 42 (each ±3 days), and a final End of Study (EOS) follow-up visit on Day 105 (±3 days). This is for purposes of evaluating extended PK and safety over a period of 5 half-lives of the study drug. Blood glucose will continue to be monitored by CGM through post-treatment follow-up Day 42 and by POC SMBG (b) (4) through the post-treatment follow-up visit on Day 14 (EOT). (b) (4) Thereafter, during the remainder of the Follow-up Period, CGM and scheduled POC glucometer SMBG will be stopped but blood glucose monitoring by POC glucometer may be performed at the discretion of the patient and/or Investigator. In addition to ensuring an acceptable safety multiple and proven safe dose for the initial cohort, advancement to subsequent cohorts will be dependent on acceptable interim safety, PK, and pharmacology reviews from ongoing and completed cohorts. The cohorts will be enrolled independently and conducted sequentially. Advancement to subsequent cohorts will not occur until at least 4 patients from the prior cohort have each received at least 4 weeks of study drug (2 bi-weekly doses), without safety concerns. A Dose Escalation Review Committee (see Section 10.6) will assess all available and relevant interim data from each cohort to determine the appropriateness of dose escalation to a new cohort (see Section 5.1.2).
Study Population:	Male and female patients aged ≥12 years and ≤45 years with clinically diagnosed CHI

Inclusion Criteria:	Patients may be included in the study if ALL of the following criteria are met: 1. Provide written informed consent and, as applicable, assent, before any study-specific procedures are performed. 2. At Screening, aged ≥12 years and ≤45 years. 3. An established clinical diagnosis, with or without a genetic diagnosis, of congenital hyperinsulinism. 4. Patient is currently receiving SOC medications (e.g., diazoxide, lanreotide, sirolimus, pasireotide, or octreotide) and/or nutritional supplementation for CHI, with at least 2 months of stable treatment; OR is not on treatment, at the time of Screening. 5. Glucose values <70 mg/dL (3.9 mmol/L) for ≥4% of the overall monitored CGM time with at least 3 severe hypoglycemia events by CGM threshold of <50 mg/dL (2.8 mmol/L) during the last 7 days of a 10-day Screening CGM evaluation period. (b) (4) **AND:** Experiencing ≥ 3 hypoglycemia events (<70 mg/dL) per week by SMBG and/or according to the Investigator's evaluation. 6. Hepatic ultrasound at Screening without clinically significant findings, including clinically significant gallstones as judged by the Investigator (e.g. large size, obstructive, biliary colic, or LFT abnormalities exceeding protocol thresholds), or evidence or peliosis hepatitis. 7. For female patients of childbearing potential, a negative serum or urine pregnancy test within 7 days before dosing: – Females of childbearing potential are defined as fertile following menarche and until becoming postmenopausal or permanently sterile. (Postmenopausal is defined as absence of vaginal bleeding or spotting for at least 1 year. Permanently sterile is defined as having had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.) 8. For female patients of childbearing potential, a willingness to use highly effective* contraceptive measures adequate to prevent a new pregnancy for the duration of the study, including for at least 105 days after receiving the last dose of study drug. For women with reproductive potential who use a hormonal method of contraception, concurrent use of a second (barrier) method is recommended. **Highly effective methods of birth control are defined as those that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly (e.g. implants, injectables, oral contraceptives, some intrauterine devices, bilateral tubal occlusion, true sexual abstinence in line with the preferred and usual lifestyle of the patient, or vasectomized partner).* 9. For sexually active males, a willingness to use contraceptive measures, e.g. a condom, for the duration of the study, including for at least 105 days after receiving the last dose of study drug. In addition, males must agree not to donate sperm over the same study period.

Exclusion Criteria:	Patients will be excluded from the study if ANY of the following criteria are met: 1. Any out-of-range laboratory value at Screening that has not been reviewed, approved, and documented as not clinically significant by the Investigator, with the exception of liver function tests for total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), which must be within 1.5X the upper limit of normal (ULN) for the reference range. 2. Body mass index (BMI) ≥35 kg/m^2 for patients aged 18 years and above or BMI ≥99% (percentile) per CDC growth charts for patients >12 and < 18 years of age. 3. History of malignancy within 3 years before Screening, other than carcinoma in situ of the cervix or adequately treated non-metastatic squamous or basal cell carcinoma of the skin. 4. History of seropositivity for HIV antibody, hepatitis B, or hepatitis C antibody. 5. Major general surgery within 3 months before Screening or anticipated during the study period. 6. Use of systemic corticosteroids within 30 days before Screening. 7. Known allergy or sensitivity to RZ358 or any component of the drug. 8. Treatment with an investigational drug or device within 30 days or 5 half-lives of the investigational drug before Day 1 of Week 1, whichever is longer. Participation in registries and purely diagnostic studies is allowed. 9. Female patients who are pregnant, planning to become pregnant during the course of the study, have recently delivered (within 3 months before Screening), or are breastfeeding. 10. Male patients who are planning a pregnancy with a female partner during the course of the study or within 105 days after administration of study drug. 11. Any organ condition, concomitant disease (e.g. psychiatric illness, severe alcoholism, or drug abuse, cardiac, hepatic, or kidney disease), or other abnormality that itself, or the treatment of which, could interfere with the conduct of the study (e.g. may affect absorption, distribution, metabolism, or elimination of the study drug) or that, in the opinion of the Investigator and/or Sponsor's Medical Monitor would pose an unacceptable risk to the patient in the study.
Number of Patients:	Approximately 24 and up to 32 patients are planned to be enrolled into this study. Each of the (up to) 4 cohorts will comprise of ~6-8 patients per cohort. Patients who discontinue the study before the Week 5 treatment and evaluation period may be replaced at the discretion of the Sponsor, if discontinuation was not due to a dose-limiting toxicity (DLT).
Countries/Number of Sites:	This study will be conducted at approximately 15 investigative sites in approximately 10 countries.
Investigational Product:	RZ358 (a fully humanized monoclonal antibody [mAb] of IgG sub-type). There will be no placebo or active control in this study. Further details regarding study drug storage, preparation, and administration are provided in the Pharmacy Study Manual.

Duration of Participation:	The anticipated study duration for each patient is approximately 26 weeks. This includes a Screening Period of up to 5 weeks, a Treatment Period of approximately 8 weeks through the post-treatment Day 14 End of Treatment visit, and an additional 13-week Follow-up Period thereafter. At the discretion of the Sponsor and Investigator, patients perceived to benefit from RZ358 on the present trial may be eligible for continued treatment with RZ358 under an expanded access/extension program, which is intended to be available once RZ358 enters Phase 3 development, as applicable and appropriate.,
Criteria for Evaluation: – **Efficacy assessments** – **PK Assessments** – **PD assessments** – **Safety Assessments:**	**Efficacy evaluation:** The glycemic efficacy of RZ358 will be assessed by CGM, SMBG by POC glucometer, a modified 12h fasting challenge, serial fasting blood glucose, and the impact on background use of SOC treatment, at each of the specified evaluation timepoints and at end of treatment compared to baseline. Criteria for evaluation will include: • CGM: Average daily (primary efficacy endpoint) and 8h overnight percent time in glucose target range of 70-180 mg/dL (3.9-10 mmol/L) ; • CGM: Average daily and 8h overnight duration (min) and percent time with hypoglycemia at thresholds of <70, <60, and <50 mg/dL (<3.9, <3.3, and <2.8 mmol/L, respectively) by CGM; • CGM: Average daily and 8h overnight hypoglycemia incidence (event rate) at each of the specified glucose thresholds; • CGM: Average daily and 8h overnight area over and under the glucose curve (AOC, AUC) for each of the specified glucose thresholds; • CGM: Average glucose level between midnight and 08:00 (or nearest pre-breakfast timepoint); • POC glucometer SMBG: Average weekly hypoglycemia incidence (event rate) at each of the specified glucose thresholds; • Occurrence of hypoglycemia during a 12h fasting challenge, by the following parameters; o Time to termination of fast; o Glucose nadir during fast; o Percentage of patients able to complete a fast; o Ketone levels at the conclusion of fast. • IV or enteral nutrition (glucose/dextrose) supplementation; • Patient incidence and rate of SOC or rescue medication use for hypoglycemia (dextrose or other). **PK evaluation:** Concentrations of RZ358 will be obtained throughout the treatment period and through post-treatment follow-up Day 105 after the final dose of study drug. The single and repeat-dose PK of RZ358 will be assessed by population PK modeling which will be used to estimate parameters including, but not limited to: • AUCss: steady state area under the concentration-time curve; • Cmaxss: steady state maximum concentration; • Cavgss: steady state average concentration; • $t_{1/2}$: effective half-life; • CL: total drug clearance;

	• V: volume of distribution of the central compartment.
	PD evaluation: The PD of RZ358 compared to baseline will be assessed by: • Fasting levels of glucose, insulin, c-peptide, glucagon, FFAs, and ketones (beta-hydroxybutarate) at each of the specified collection timepoints; • Incidence of fasting blood glucose values >200, >250, and >300 mg/dL (>11.1, >13.9, and >16.6 mmol/L, respectively) at each of the specified collection timepoints.
	Safety evaluation: Safety assessments will adhere to all recommendations outlined in the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and the protection of human safety, and will include: • Incidence, severity, and relationship of adverse events (AEs) and serious adverse events (SAEs), and AEs leading to study drug discontinuation; • Actual values and changes from baseline, and incidence of clinically significant changes in clinical laboratory, 12-lead electrocardiogram (ECG), and vital sign assessments; • Physical examination findings, including infusion site reactions and tolerability. • The occurrence of anti-drug antibodies (ADAs) to RZ358.
Statistical Methods:	General Statistical Considerations: The sample size for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives. Patients who withdraw from the study may be replaced on a case-by-case basis after discussion and agreement with the Sponsor's Medical Monitor. Detailed methodology for analyses and summary of the data will be documented in a Statistical Analysis Plan (SAP), which will supersede the protocol, where applicable (see Section 7). However, any major modification of the outcome measures and/or its analysis will also be reflected in a protocol amendment. Continuous variables will be summarized by using the following descriptive statistics: mean, standard deviation (SD), number of observations, median, minimum, and maximum. The frequency and percent of observed levels will be reported for categorical measures. In general, all data will be listed, sorted by patient and dose cohort and, when appropriate, by study day and study timepoint. Analytical Methods: The populations used for this analysis will be further defined in the SAP. *Safety Analysis:* The interpretation of the safety and tolerability of RZ358 will be made based on the assessment of safety parameters evaluated throughout the study, including AEs, vital signs, ECGs, physical examinations results, infusion-site observations, (b) (4) results, and clinical laboratory evaluations including glucose values. The reporting of the safety data is descriptive, and will include all patients who received at least one dose of RZ358. Individual patient listings will be reviewed, and summary results with descriptive statistics will be provided, where appropriate. No statistical testing will be performed on safety data. *Pharmacokinetics*: All patients who received RZ358 and for whom the

	primary PK data are considered to be sufficient and interpretable will be included in the PK analyses. Individual and mean plasma concentration data will be plotted over time by dose level and day, and summarized descriptively at the specified timepoints. Descriptive statistics will be presented for PK parameters, including, but not necessarily limited to: C_{max}, T_{max}, $t_{1/2}$, and AUC. The relationships between dose and C_{max} and AUC will be analyzed for dose proportionality. The PK results of this study may be combined with those of other studies for analysis and modeling (e.g., population PK and PK-PD), and reported separately. *Pharmacodynamics and Efficacy:* CGM glucose data will be compiled and output into the specified parameters that will be listed by patient and summarized in aggregate. Actual data and change from baseline will be summarized descriptively for each continuous CGM parameter, as well as for POC glucometer SMBG, fasting glucose, and other biomarkers, at the protocol-specified timepoints and pre-specified evaluation periods. Incidence rates will be normalized to the daily (CGM) or weekly (SMBG) average. Categorical events will be summarized by frequency counts, as applicable. The requirement for rescue and the use of background SOC medication or supplemental nutrition will be listed by patient and summarized, where appropriate. Statistical comparisons may be performed as appropriate, and will be described in the SAP and/or clinical study report. The primary efficacy and PD analysis will be conducted in the per-protocol population, (b) (4)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AOC	Area over the curve
AST	Aspartate aminotransferase
AUC	Area under the curve
BG	Blood glucose
CEOI	Concentration at end of infusion
CGM	Continuous glucose monitoring
CHI	Congenital hyperinsulinism
CHMP	Committee for Medicinal Products for Human use
cm	Centimeters
CPMP	Committee for Proprietary Medicinal Products
dL	Deciliter
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
eCRF	Case report form
FDA	Food and Drug Administration
FFA	Free fatty acids
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HV	Healthy Volunteers
IEC	Independent Ethics Committee
ICH	International Conference on Harmonization
IGF-1R	Insulin-like Growth Factor-1 receptor
IgG2	Immunoglobulin G, subclass 2
INSR	Insulin receptor
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intent-to-treat
IV	Intravenous
Kg	Kilograms
K_{ATP}	Potassium adenosine triphosphate

Abbreviation	Definition
LAR	Long-acting release
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NOAEL	No-observed adverse-effect levels
PD	Pharmacodynamics
PGBH	Post-gastric bypass hypoglycemia
PK	Pharmacokinetics
POC	Point of care
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SMBG	Self-Monitored Blood Glucose
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
WHO	World Health Organization

1 INTRODUCTION

1.1 Overview of Congenital Hyperinsulinism

Insulin, secreted by the β cells of the Islets of Langerhans in the pancreas, is the major hormone for lowering blood glucose levels in the fasting and postprandial states. Abnormal elevations in insulin secretion can lead to profound hypoglycemia with cerebral damage and even death. Thus, under normal conditions, the control of insulin secretion is highly regulated to prevent hypoglycemia. Overproduction of insulin results in hyperinsulinemic hypoglycemia, characteristic of diseases such as CHI and post-gastric bypass hypoglycemia (PGBH).

CHI is the most common cause of recurrent hypoglycemia in neonates and infants. The incidence of CHI is estimated at 1 in 50,000 live births in the general population, but in certain populations with substantial consanguinity incidence may be as high as 1 in 2,500 (Arnoux et al., 2011). Based on information from therapeutic area experts, global prevalence has been calculated to be approximately 1.87 in 10,000.
There are now 11 identified genetic loci underlying CHI. A genetic diagnosis is possible for up to 55% of patients with CHI (Mohamed et al., 2012). For the majority of these mutations, the entire pancreas is affected, resulting in dysregulated, excess secretion of insulin from beta-cells throughout the pancreas (i.e. diffuse disease). However, in the case of paternally inherited mutations of the potassium adenosine triphosphate channel (K_{ATP}) channel, there may be only a focal region of abnormal beta-cells and the remainder of the pancreas is normal (i.e. focal disease). The specific genetic mutation not only affects the pattern and timing of disease expression and the clinical severity, but also guides medical and surgical therapy.

CHI, despite improved recognition and early intervention with currently available therapies, can result in serious neurological and developmental complications, including persistent feeding problems (Banerjee et al., 2016), recurrent seizures, learning disabilities, and focal brain lesions (Avatapalle et al., 2013; Bahi-Buisson et al., 2008; de las Heras et al., 2010; Gataullina et al., 2012; Mazor-Aronovitch et al., 2007).

1.2 Current Treatment Options

Despite improved recognition of CHI, there is no satisfactory treatment or cure for this disease. The two most commonly used long-term medications, diazoxide and octreotide, are not Food and Drug Administration (FDA) approved for this condition, and often are ineffective or have intolerable side effects.

Diazoxide is an oral K_{ATP} channel agonist that maintains the beta-cell K_{ATP} channel in the open state. This prevents beta-cell depolarization and thus inhibits insulin secretion. Although it is the preferred and most widely used medical treatment for chronic hyperinsulinemic hypoglycemia, the most common form of CHI results from mutations in the K_{ATP} channel, and so diazoxide is ineffective in this subset of patients. Even in individuals where diazoxide is effective, side effects are frequent and include fluid retention, edema, hypertrichosis, and hirsutism resulting in abnormal facial features in children (Mohamed et al. 2012). Less common side effects include bone marrow suppression, elevation of uric acid, and importantly, pulmonary hypertension, for which the FDA has issued a black box warning (FDA, 2015).

Octreotide or long-acting release (LAR) agents in the same class (lanreotide) are subcutaneous somatostatin analogs, acting to prevent calcium influx and resultant insulin secretion, downstream of the K_{ATP} channel. While somatostatin analogs have

therapeutic potential in diazoxide-unresponsive patients (Buraczewska et al., 2015; Guemes and Hussain, 2015), this class of medications is only modestly effective in some patients, and can lead to tachyphylaxis. Due to the mechanism of action, somatostatin analogs may suppress other hormones including thyroid stimulating hormone and growth hormone, and have the potential to stunt growth when administered to children over long periods of time. Cholestasis and necrotizing enterocolitis are other less common but serious side effects.

In cases of CHI that are unresponsive to medical management with diazoxide or somatostatin analogs, surgical removal of a portion or the entire pancreas is required. In those with focal pancreatic disease, surgical removal of the specific affected area often results in a cure. In those with diffuse pancreatic disease, a near-total pancreatectomy is undertaken, but residual hypoglycemia requiring adjuvant medical management remains in ~50% of patients (Lord and De Leon, 2013).

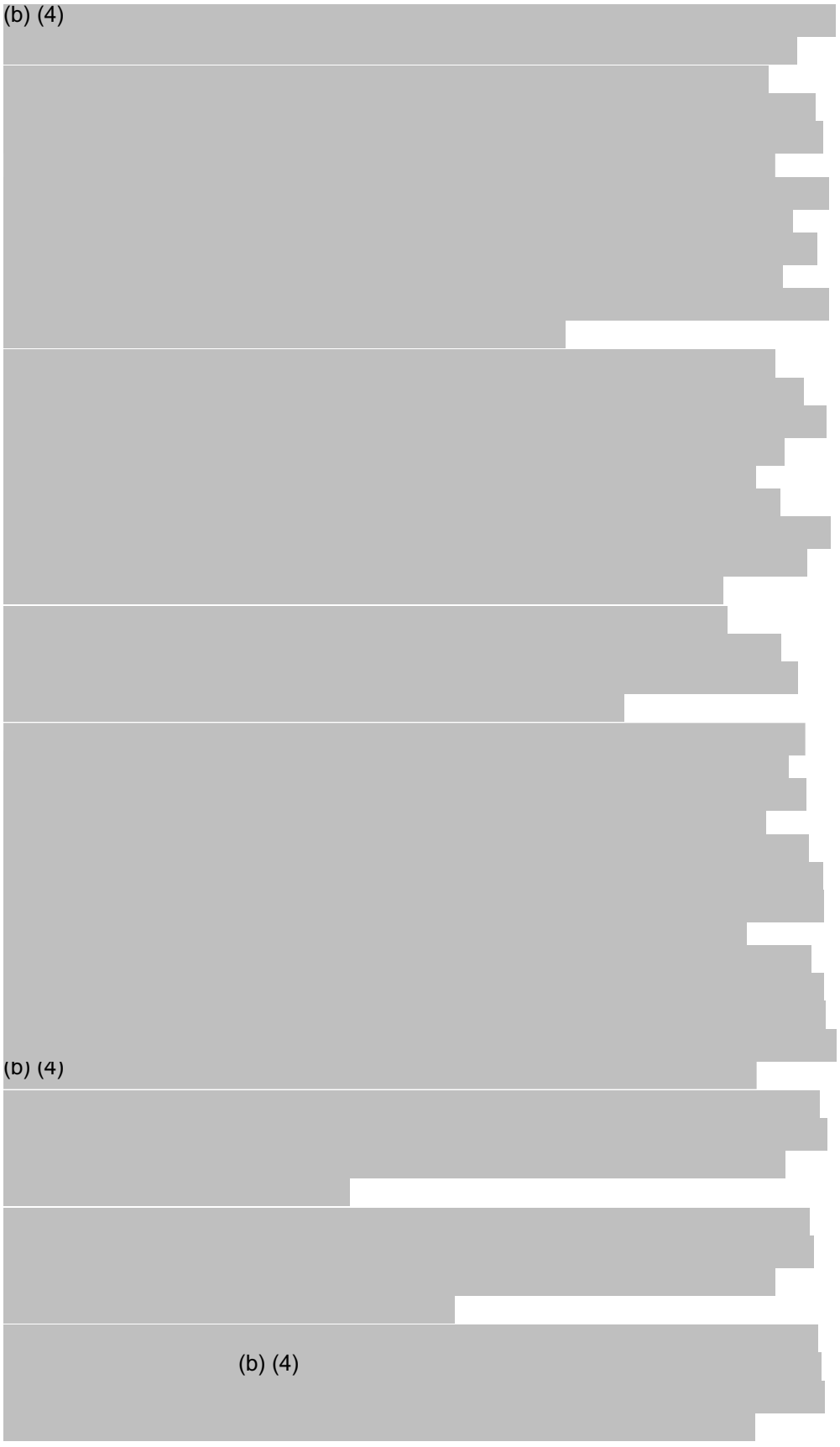
Despite improved recognition of CHI and early intervention with currently available therapies, persistent hypoglycemia exists and can result in serious neurological and developmental complications, including persistent feeding problems (Banerjee et al., 2016), recurrent seizures, learning disabilities, and focal brain lesions (Avatapalle et al., 2013; Gataullina et al., 2013; de las Heras et al., 2010; Bahi-Buisson et al., 2008; Mazor-Aronovitch et al., 2007). Current medical therapies for conditions of hyperinsulinism are directed at reducing or eliminating insulin production and/or secretion from the beta-cell, however, they achieve sub-optimal glycemic control and/or have undesirable side effects. Thus, there is a significant unmet medical need to develop new therapies aimed at preventing chronic recurrent hypoglycemia in CHI.

1.3 Overview of RZ358

Current medical therapies for conditions of hyperinsulinism are directed at reducing or eliminating insulin production and/or secretion from the beta-cell. These current medications, however, achieve sub-optimal glycemic control and/or have undesirable side effects.

Diminution of insulin action at target tissues may represent a novel therapeutic approach for the treatment of conditions associated with hyperinsulinism. RZ358, previously referred to as XOMA-358 or XMetD, is a fully human immunoglobulin G, subclass 2 (IgG2) mAb that binds with high potency and selectivity to an allosteric site on the insulin receptor (INSR), acting as a negative modulator of insulin action on target cells by attenuating both the binding of insulin and its downstream signaling (Corbin et al., 2014; Issafras et al., 2014). This unique mechanism of action confers properties of reversibility and graded activity which are dependent on the extent of insulin elevation. Therefore, RZ358 is ideally suited as a potential therapy for hyperinsulinism, and it is being developed to treat the hypoglycemia associated with diseases such as CHI.

1.4 (b) (4)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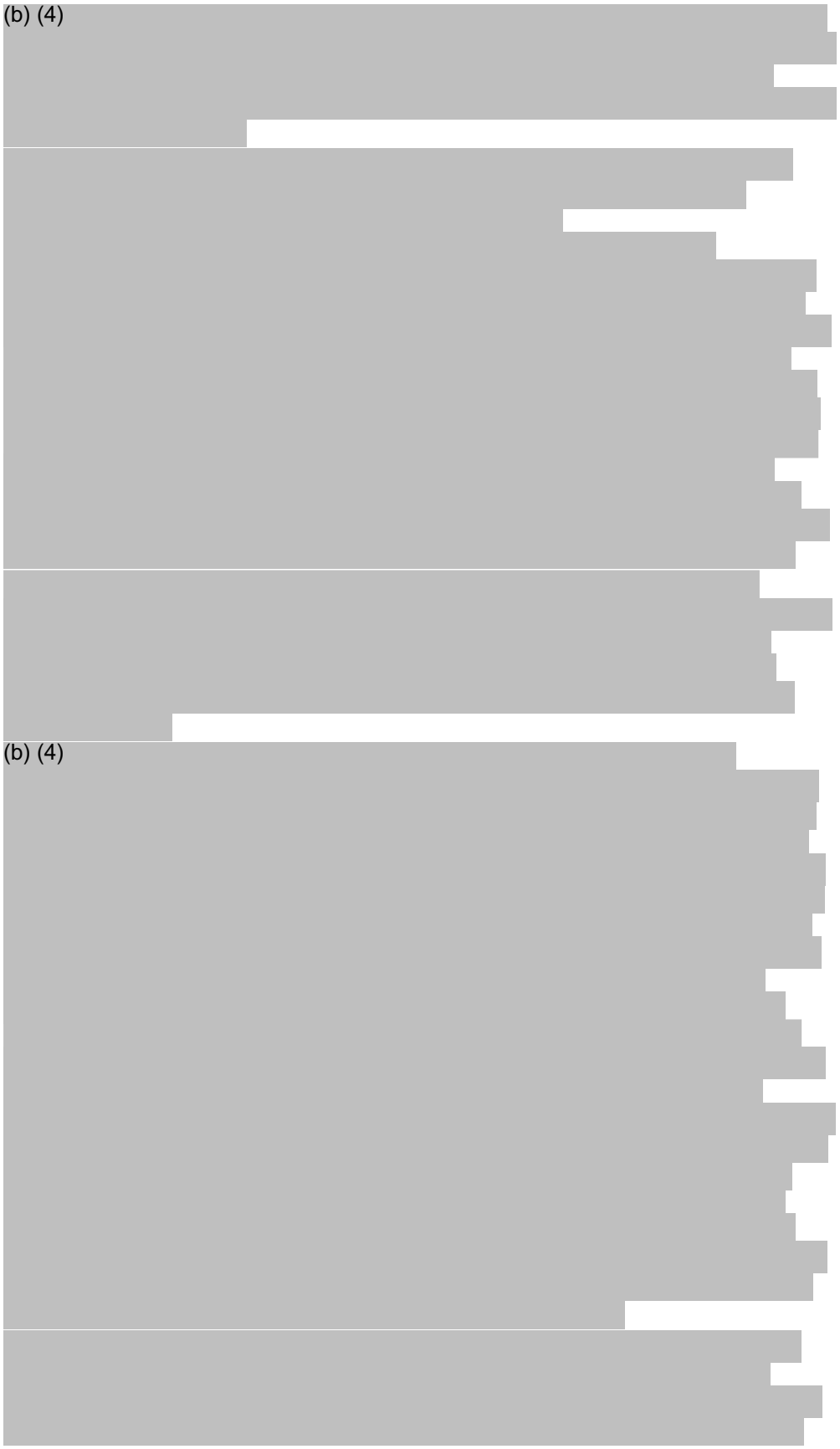

(b) (4)

1.6 Rationale

There is a significant unmet medical need to develop new therapies aimed at preventing chronic recurrent hypoglycemia in CHI. Current medical therapies for conditions of hyperinsulinism are directed at reducing or eliminating insulin production and/or secretion from the beta-cell; these current medications achieve sub-optimal glycemic control and/or have undesirable side effects (Banerjee et al., 2016; Avatapalle et al., 2013; Gataullina et al., 2013; de las Heras et al., 2010; Bahi-Buisson et al., 2008; Mazor-Aronovitch et al., 2007).

Diminution of insulin action at target tissues may represent a novel therapeutic approach for the treatment of conditions associated with hyperinsulinism. RZ358, previously referred to as XOMA-358 or XMetD, is a fully human immunoglobulin G, subclass 2 (IgG2) mAb that binds with high potency and selectivity to an allosteric site on the insulin receptor (INSR), acting as a negative modulator of insulin action on target cells by attenuating both the binding of insulin and its downstream signaling (Corbin et al., 2014; Issafras et al., 2014). This unique mechanism of action confers properties of reversibility and graded activity which are dependent on the extent of insulin elevation. Therefore, RZ358 is ideally suited as a potential therapy for hyperinsulinism, and it is being developed to treat the hypoglycemia associated with diseases such as CHI. The combined non-clinical and clinical programs conducted to date support continued clinical development of RZ358 for CHI, and the present study represents the progression of the clinical development plan into repeat-dose studies in younger patients with CHI, in a cohort-based dose-escalation manner.

1.7 Risk-Benefit Assessment

The available information suggests that the present study has a favorable risk-benefit ratio. Previous studies have shown that single-dose administration of RZ358 up to 9 mg/kg, and repeat-dose administration of up to 3 mg/kg weekly for 4 weeks, was generally safe and well tolerated, with evidence of proof-of-mechanism and concept. No experiments have been performed to determine a specific antidote to RZ358 in the setting of an overdose. General supportive measures should be taken as appropriate.

(b) (4)

As of yet there are no identified risks associated with the use of RZ358 in humans. A summary of non-specific and compound-specific potential risks, based on the presumptive mechanism of action and non-clinical safety data, are described subsequently, along with a summary of mitigation strategies that are implemented into clinical studies of RZ358.

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2 STUDY OBJECTIVES AND ENDPOINTS

The objectives of this study are to evaluate the safety, tolerability, PK, PD, and glycemic efficacy of multiple ascending doses of RZ358 over 8 weeks in patients with hyperinsulinemic hypoglycemia due to CHI.

2.1 Primary Endpoints

- Glycemic efficacy of RZ358 as evaluated by the average daily percent time within a glucose target range of 70-180 mg/dL (3.9-10 mmol/L) by CGM;
- Repeat-dose safety and tolerability of RZ358;
- Repeat-dose PK of RZ358.

2.2 Secondary Endpoints

- Average weekly incidence of hypoglycemia (< 70 mg/dL) by self-monitored blood glucose (SMBG)
- Average daily duration (min) and percent time with hypoglycemia at thresholds of <70, <60, and <50 mg/dL (3.9, 3.3, and 2.8 mmol/L, respectively) by CGM;
- Average daily hypoglycemia incidence (event rate) at each of the specified glucose thresholds by CGM;
- Average 8h overnight percent time in glucose target range of 70-180 mg/dL (3.9-10 mmol/L) by CGM;
- Occurrence of hypoglycemia during a 12h fasting challenge.

2.3 Additional (Exploratory) Endpoints

- Average 8h overnight duration (min) and percent time with hypoglycemia at thresholds of <70, <60, and <50 mg/dL (3.9, 3.3, and 2.8 mmol/L, respectively) by CGM;
- Average 8h overnight hypoglycemia incidence (event rate) at each of the specified glucose thresholds by CGM;
- Average daily and 8h overnight area over and under the glucose curve (AUC, AOC) for each of the specified glucose thresholds by CGM;
- Average glucose level between midnight and 8:00 AM (or nearest pre-breakfast time point) by CGM;
- Average weekly hypoglycemia incidence (event rate) at each of the specified glucose thresholds by SMBG;
- IV or enteral nutritional (glucose/dextrose) supplementation;
- Use of SOC or rescue medications for hypoglycemia (dextrose or other);
- Incidence of fasting blood glucose values >200, >250, and >300 mg/dL (>11.1, >13.9, and >16.6 mmol/L, respectively);
- PD Markers of RZ358 activity including fasting levels of glucose, insulin, c-peptide, glucagon, FFAs, and ketones (beta-hydroxybutarate).

3 STUDY DESIGN AND DESCRIPTION

3.1 Overview

This is a Phase 2, multi-center, open-label, multiple ascending dose study to evaluate the safety, tolerability, PK, PD, and glycemic efficacy of RZ358 in patients with hypoglycemia due to CHI. The study will consist of up to 4 dose cohorts, which are to be enrolled independently and conducted sequentially, comprised of 6-8 patients per cohort. Eligible patients will be successively enrolled into the cohort that is open for enrollment at that time, at the lowest dosing cohort that is yet to be filled.

Advancement to subsequent cohorts will not occur until at least 4 patients from the prior cohort have each received at least 4 weeks of study drug (2 bi-weekly doses), without safety concerns. A Dose Escalation Review Committee will assess all available and relevant interim data from each cohort to determine the appropriateness of dose escalation to a new cohort (see Section 5.1.2).

In Cohorts 1, 2, and 3 the dose amount will be fixed during the entire 8-week Treatment Period, while in Cohort 4 there will be a scheduled bi-weekly dose-titration for the first 4 weeks, followed by a fixed dose amount thereafter for the remaining 4 weeks. The Sponsor may decide to add a cohort to repeat a dose level or to study an additional dose level, but the dose level for any cohort will not exceed the planned dose level for that cohort, as specified in this protocol.

Table 2: Study Design/Cohort Dosing Regimens

	Dosing (mg/kg)			
Cohort	**Wk 1**	**Wk 3**	**Wk 5**	**Wk 7**
1	3	3	3	3
2	6	6	6	6
3	9	9	9	9
4	3	6	9	9

Following informed consent, patients will complete a Screening Period to determine eligibility. After the preliminary screening assessment, patients who are otherwise eligible will undergo scheduled self-monitoring of blood glucose (SMBG) by point of care (POC) glucometer as well as have a CGM sensor placed according to the instruction manual, for completion of a 10-day outpatient CGM evaluation to assess glycemic eligibility and establish a baseline.(b) (4) patients will use an SMBG for their POC throughout the trial. Patients taking existing and stable doses of SOC medications or nutritional supplementation for CHI at the time of screening should continue the same regimen and doses throughout this period. (b) (4) o meet glycemic qualification criteria, patients must have glucose values <70 mg/dL (3.9 mmol/L) for ≥4% of the overall monitored CGM time with at least 3 severe hypoglycemia events by CGM threshold of <50mg/dL (2.8 mmol/L) during the last 7 days of a 10-day CGM evaluation period **AND** be experiencing ≥ 3 hypoglycemia events (<70 mg/dL) per week by SMBG and/or

according to the Investigator's evaluation. (b) (4)

During the Screening Period and throughout the study, patients will be requested to follow their usual diet (including enteral feeding, as applicable) and activity level, as evaluated and instructed by qualified study personnel.

At the conclusion of the CGM and glycemic eligibility evaluation, final eligibility will be determined, and fully eligible patients will check in to the inpatient facility on Day -1, to begin the Treatment Period. On Day -1, patients will begin a 12h baseline fasting challenge evaluation, which will conclude prior to Day 1 dosing. Re-screening may be permitted under certain extenuating circumstances (e.g. laboratory outlier suggesting result artifact, insufficient duration of CGM collection), only with pre-approval by the Sponsor.

Beginning at Day 1 of the Treatment Period, patients will receive study drug via IV infusion every 2 weeks over an 8 week total Treatment Period. Thus, patients who complete the entire Treatment Period will receive 4 doses of study drug over a total of 8 weeks (Figure 1). Patients will remain under inpatient observation for at least 48h following dosing on Week 1 and for at least 24h following dosing on Weeks 3, 5, and 7, for completion of PK blood sampling and safety assessments. Throughout the Treatment Period and through post-treatment follow-up Day 42 after the patient's final dose in the study (cumulative study Day 85), glucose levels will be assessed and recorded by CGM. (b) (4)

patients will continue to use an SMBG as their POC throughout the trial.

Throughout the Treatment period and through the End of Treatment visit (EOT) on post-treatment follow-up Day 14 (cumulative study Day 57), SMBG by POC glucometer must be performed a(b) (4)

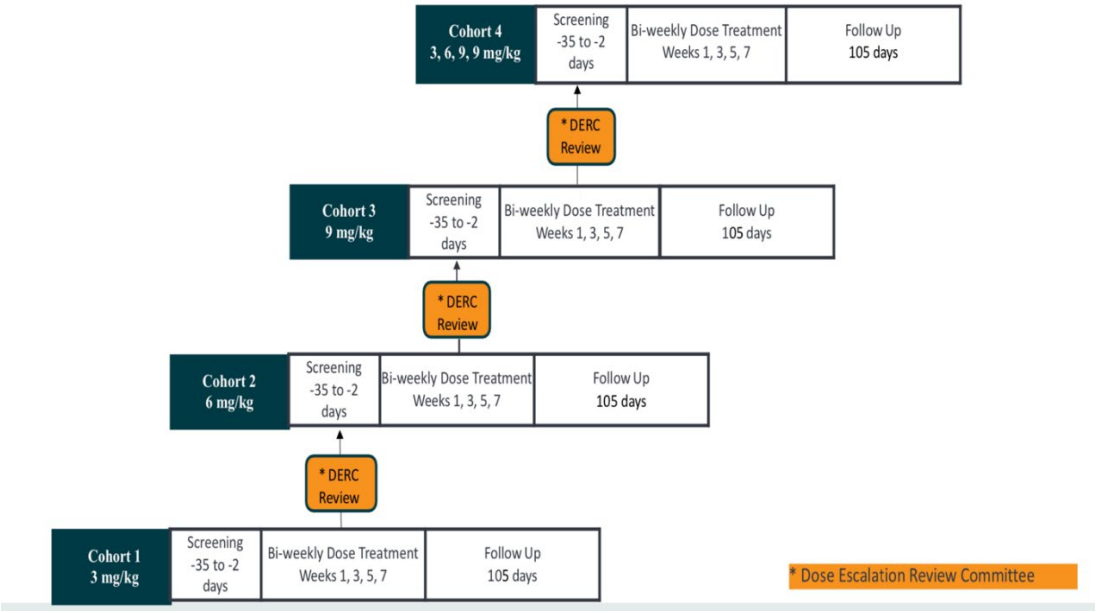
Otherwise, changes in the dose or regimen of background SOC therapies should not occur, except in the event that hypo- or hyperglycemic rescue criteria are met (see Section 5.3.1), or changes are deemed medically necessary by the Investigator.

(b) (4)

At the conclusion of Week 7 dosing and discharge from the clinic, each patient will complete outpatient follow-up visits at Days 14 (EOT), 28, and 42 (each ±3 days), and a final End of Study (EOS) follow-up visit on Day 105 (±3 days), for purposes of evaluating extended PK and safety over a period of 5 half-lives of the study drug.

A detailed description of study procedures and assessments are provided in **Section 6** and are outlined in **Appendix 1** (Schedule of Assessments).

Figure 1: Study Design



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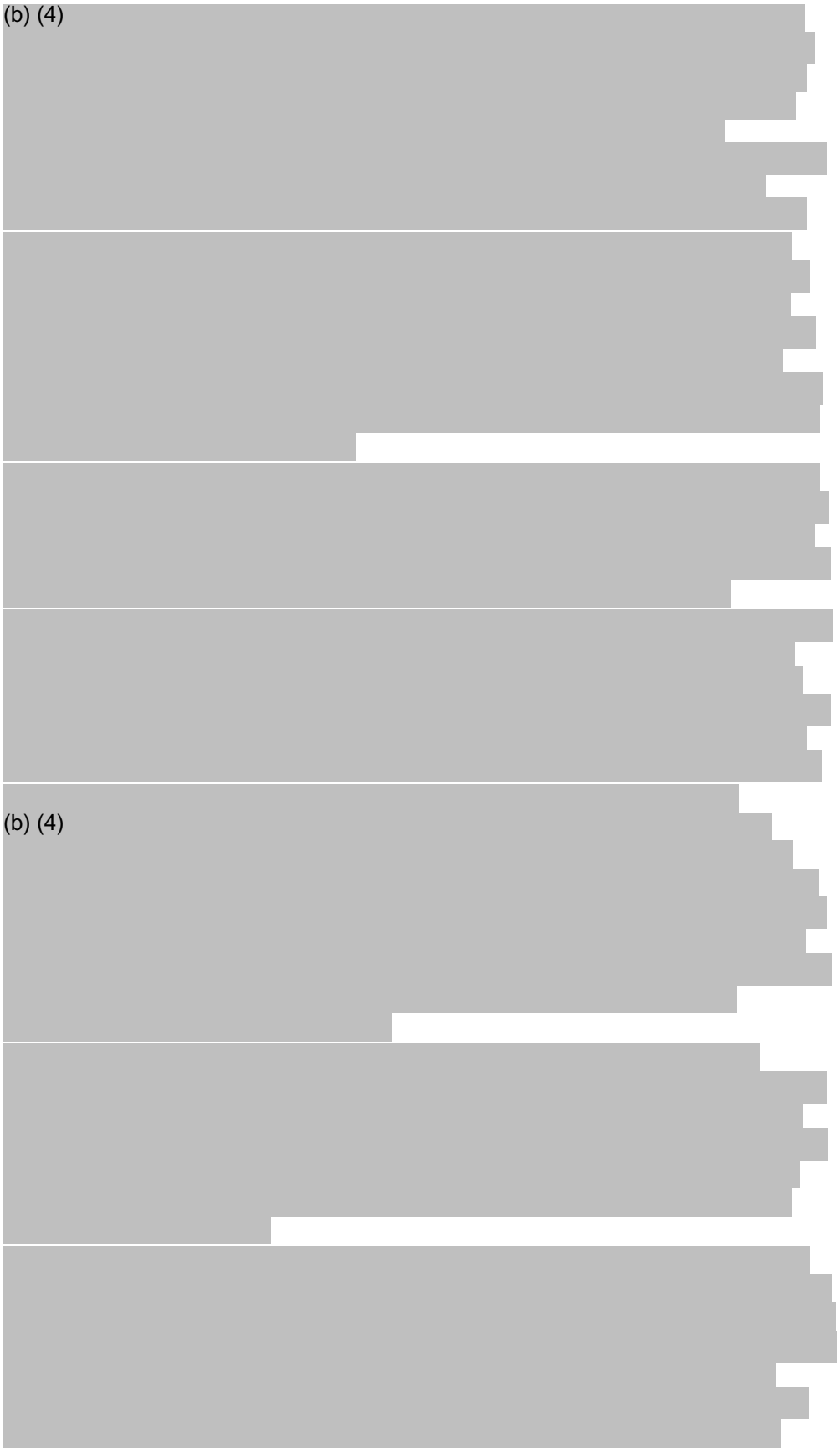

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3.3 End of Study Definitions and Study Duration

End of Treatment (EOT) is defined as the time at which a patient has received all 4 doses of study drug over the course of the 8-week Treatment Period AND completed the associated key EOT assessments at Day 14 (EOT).

A patient is considered to have completed the study if he/she has completed all phases of the study including the last (EOS) visit and the last scheduled procedure shown in the Schedule of Assessments (Appendix 1). The anticipated study duration for each patient is approximately 26 weeks. This includes a Screening Period of approximately 5 weeks, a Treatment Period of approximately 8 weeks, and an additional 13-week Follow-up Period.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Assessments for the last patient in the trial globally (Appendix 1).

4 SELECTION AND WITHDRAWAL OF STUDY POPULATION

4.1 Study Population

The study population will consist of male and female patients aged ≥12 years and ≤45 years with clinically diagnosed CHI.

4.2 Number of Sites Planned

This study will be conducted at approximately 15 investigative sites in approximately 10 countries.

4.3 Inclusion Criteria

Patients who meet ALL of the following criteria are eligible to participate in the study.

1. Provide written informed consent and, as applicable, assent, before any study-specific procedures are performed.
2. At Screening, aged ≥12 years and ≤45 years.
3. An established clinical diagnosis, with or without a genetic diagnosis, of congenital hyperinsulinism.
4. Patient is currently receiving SOC medications (e.g., diazoxide, lanreotide, sirolimus, pasireotide, or octreotide) and/or nutritional supplementation for CHI, with at least 2 months of stable treatment; OR is not on treatment at the time of Screening.
5. Glucose values <70 mg/dL (3.9 mmol/L) for ≥4% of the overall monitored CGM time with at least 3 severe hypoglycemia events by CGM threshold of <50 mg/dL (2.8 mmol/L) during the last 7 days of a 10-day Screening CGM evaluation period.

   (b) (4)

   AND:

   Experiencing ≥ 3 hypoglycemia events (<70 mg/dL) per week by SMBG and/or according to the Investigator's evaluation.
6. Hepatic ultrasound at Screening without clinically significant findings, including clinically significant gallstones as judged by the Investigator (e.g. large size, obstructive, biliary colic or LFT abnormalities exceeding protocol thresholds), or evidence or peliosis hepatitis.

7. For female patients of childbearing potential, a negative serum or urine pregnancy test within 7 days before dosing;
   - Females of childbearing potential are defined as fertile following menarche and until becoming postmenopausal or permanently sterile. (Postmenopausal is defined as absence of vaginal bleeding or spotting for at least 1 year. Permanently sterile is defined as having had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.)

8. For female patients of childbearing potential, a willingness to use highly effective* contraceptive measures adequate to prevent a new pregnancy for the duration of the study, including for at least 105 days after receiving the last dose of study drug. For women with reproductive potential who use a hormonal method of contraception, concurrent use of a second (barrier) method is recommended.

   **Highly effective methods of birth control are defined as those that alone or in combination result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly (e.g. implants, injectables, oral contraceptives, some intrauterine devices, bilateral tubal occlusion, true sexual abstinence in line with the preferred and usual lifestyle of the patient, or vasectomized partner).*

9. For sexually active males, a willingness to use contraceptive measures, e.g. a condom, for the duration of the study, including for at least 105 days after receiving the last dose of study drug.

4.4 Exclusion Criteria

Patients will be excluded from the study if ANY of the following criteria are met:

1. Any out-of-range laboratory value at Screening that has not been reviewed, approved, and documented as not clinically significant by the Investigator, with the exception of liver function tests for total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), which must be within 1.5X the upper limit of normal (ULN) for the reference range.
2. Body mass index (BMI) ≥35 kg/m^2 for patients aged 18 years and above, or BMI ≥99% (percentile) per CDC growth charts for patient >12 and <18 years of age.
3. History of malignancy within 3 years before Screening, other than carcinoma in situ of the cervix or adequately treated non-metastatic squamous or basal cell carcinoma of the skin.
4. History of seropositivity for HIV antibody, hepatitis B, or hepatitis C antibody.
5. Major general surgery within 3 months before Screening or anticipated during the study period.

6. Use of systemic corticosteroids within 30 days before Screening.
7. Known allergy or sensitivity to RZ358 or any component of the drug.
8. Treatment with an investigational drug or device within 30 days or 5 half-lives of the investigational drug before Day 1 of Week 1: whichever is longer. Participation in registries and purely diagnostic studies is allowed.
9. Female patients who are pregnant, planning to become pregnant during the course of the study, have recently delivered (within 3 months before Screening), or are breastfeeding.
10. Male patients who are planning a pregnancy with a female partner during the course of the study or within 105 days after administration of study drug.
11. Any organ condition, concomitant disease (e.g. psychiatric illness, severe alcoholism, or drug abuse, cardiac, hepatic, or kidney disease), or other abnormality that itself, or the treatment of which, could interfere with the conduct of the study (e.g. may affect absorption, distribution, metabolism, or elimination of the study drug) or that, in the opinion of the Investigator and/or Sponsor's Medical Monitor would pose an unacceptable risk to the patient in the study.

4.5 Patient Withdrawal and Replacement

4.5.1 Patient Withdrawal Criteria

An individual patient may be withdrawn from the study at any time, for any of the following reasons:

- Withdrawal of written informed consent (a patient has the right to withdraw from the study at their own request, at any time, without giving a reason [although whenever possible, the reason should be obtained], and without prejudice to their continued care);
- Required treatment with any concomitant medication known or suspected to interfere with the study drug or study evaluations or be prohibited/contraindicated. However, patients should not be automatically discontinued from the study if this occurs, unless it poses a significant risk to the patient in the opinion of the Investigator: otherwise, such instances should first be discussed between the Investigator and Sponsor Medical Monitor;
- Adverse events, where the Investigator or Medical Monitor feels that discontinuation from the study is in the best interest of the patient;
- Patient becomes pregnant or begins breast-feeding;
- Lack of compliance with the study protocol;
- Lost to follow-up;
- Study termination by the Sponsor;
- Any other condition which, in the opinion of the Investigator or Sponsor, no longer permits safe participation in the study. The investigator can stop a patient's participation in the study at any time if continuation could lead to disadvantages for the patient which cannot be justified by the Investigator;

- The patient meets one of the pre-specified stopping criteria outlined in Section 5.1.2.3.

4.5.2 Patients lost to follow-up

A patient will be considered lost to follow-up if he or she fails to return for their scheduled visits and is unable to be contacted by the site staff. The following actions must be taken if this occurs:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible.
- The site will counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- If multiple attempts to regain contact with the site are unsuccessful (e.g. multiple phone calls at different dates/times, followed-by a certified letter to the patient's last known mailing address), the patient may then be considered to have withdrawn from the study with a primary reason of discontinuation as 'Lost to Follow-up'. These contact attempts should be documented in the patient's study file.

4.6 Patient Randomization and Identification

This is an open-label study, but the study will utilize a randomization and trial supply management (RTSM) application built within the EDC platform to unify randomization, trial supply and EDC. Each patient will be provided a unique 6-digit patient ID number. The first three digits will represent the site number and the last three digits will represent the patient number at the site. The patient ID number will remain the same for both Screening and randomization.

4.7 Withdrawal Procedures

Once enrolled, every effort should be made by the Investigator to keep patients in the study for the duration, unless patient consent has been withdrawn or the Investigator or Sponsor deems it in the best interest of the patient to withdraw from the study. Interruption of the study drug does not automatically and/or immediately require discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol, until such time that the final disposition is determined. Once it becomes apparent that the patient will not be able to resume study drug in a reasonable timeframe (final disposition), then the patient should be withdrawn from the study, and undergo Early Termination (ET) procedures within 2 weeks of the last dose received, as outlined in Section 6.1.6 and the Schedule of Assessments. After ET, patients should also complete the Follow-up Period, if possible. Patients who terminate the study early (at any point during the study) will not be considered Study Completers, even if they complete ET procedures and the post-ET Follow-up Period. In the event an enrolled patient is withdrawn from the study, the Study Monitor and Sponsor should be informed immediately. Patients should be treated with SOC after ET, as appropriate. In the event of a withdrawal due to an AE, the event will be followed until resolution, or until it is deemed stable, in the Investigator's opinion, or until a determination of a cause unrelated to the study drug or study procedure is made.

The Investigator should attempt to obtain information on patients in the case of withdrawal or discontinuation. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation.

4.8 Replacement of Patients

Patients who discontinue the study before the Week 5 treatment and evaluation period may be replaced at the discretion of the Sponsor, if the reason for discontinuation was not a dose-limiting toxicity (DLT). The allocation of a replacement patient will be managed by the Medical Monitor to help ensure that each cohort meets the thresholds for sample size.

5 STUDY DRUG

5.1 Dosing Regimen

Beginning at Day 1 of the Treatment Period, patients will receive study drug via IV infusion every two weeks over an 8 week total Treatment Period. Thus, patients who complete the entire Treatment Period will receive a total of 4 doses. Study drug will be administered as a 30-minute IV infusion in the clinic, ideally in the morning at approximately the same time on each dosing day, after the collection of fasting blood samples followed by a standardized breakfast.

The planned RZ358 dose levels and regimen are described in Table 2. The Sponsor may decide to add a cohort to repeat a dose level or to study an additional dose level, but the dose level for any cohort will not exceed the planned dose level for that cohort, as specified in this protocol. Cohorts will be enrolled independently and conducted sequentially. Advancement to subsequent cohorts will not occur until at least 4 patients from the prior cohort have each received at least 4 weeks of treatment with 2 bi-weekly doses of study drug, without safety concerns.

In Cohorts 1, 2, and 3 the dose amount will be fixed during the entire 8-week Treatment Period, while in Cohort 4 there will be a scheduled bi-weekly dose-titration for the first 4 weeks, followed by a fixed dose amount thereafter for the remaining 4 weeks.

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5.1.2 Cohort Dose Escalation and Stopping Rules

5.1.2.1 Dose Escalation Procedures

In addition to ensuring an acceptable safety multiple for the Cohort 1 starting dose, advancement to subsequent cohorts will be dependent on acceptable interim safety, PK, and pharmacology reviews from ongoing and completed cohorts. Advancement to subsequent cohorts will not occur until at least 4 patients from the prior cohort have each received at least 4 weeks of treatment with 2 bi-weekly doses of study drug without safety concerns. A Dose Escalation Review Committee will be established to assess all available and relevant interim data from each cohort to determine the safety and appropriateness of dose escalation to a new cohort. In the study, dose escalation will follow pre-specified criteria. If 2 or more patients within the same dosing cohort experience DLTs, dose escalation to the planned dose will be stopped, or an intermediate dose may be tested. If dose escalation is stopped due to DLTs, the maximum tolerated dose (MTD) will be defined by the dose in the previous cohort, unless an intermediate dose is subsequently tested by the same algorithm. Toxicity will be evaluated as described in Section 5.1.2.2. Dose escalation may also be halted based on a review of drug PK (e.g., if exposures do not increase between successive dose cohorts).

More conservative dose escalation or evaluation of intermediate doses are permissible following discussions between the Sponsor and Investigator(s) if needed for patient safety or for a better understanding of the toxicity, exposure, or other properties of the study drug.

Patients withdrawn from treatment before completing Week 5 dosing, for reasons other than a DLT, may be replaced within the cohort, at the discretion of the Sponsor.

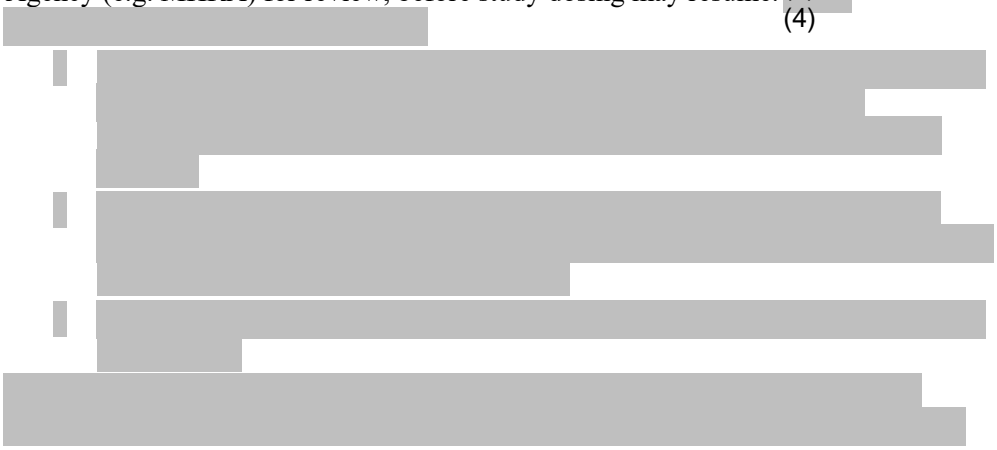
5.1.2.2 Cohort Dose Advancement Criteria

Upon review of pooled cohort data by the Dose Escalation Review Committee, dose escalation to the next highest cohort may proceed upon review, confirmation, and documentation of acceptable interim safety, PK, and pharmacology findings from all available interim data. (b) (4)

5.1.2.3 Additional Study Stopping Criteria

In addition to the pooled cohort criteria that prospectively define the events that will result in halting escalation to the next cohort, under certain additional circumstances

further study dosing in the representative patient(s), as well as enrollment and dosing of new patients, will be halted until the Dose Escalation Review Committee deems it safe to proceed, based on a comprehensive review of all relevant case and interim study data. Additionally, a safety report will be submitted to the applicable Regulatory Agency (e.g. MHRA) for review, before study dosing may resume. (b) (4)



5.1.2.4 Individual Patient Dose Stopping Criteria

- Study drug infusion/administration will be stopped for an individual patient if an infusion reaction is suspected, (b) (4)

5.2 Study Drug Materials and Management

5.2.1 Identity and Description

RZ358 is a sterile, aqueous, colorless to slightly yellow solution for infusion and will be provided as single use vials of 1.27 mL filled with RZ358 drug product of 80 g/L (80 mg/mL) in a pH 5.8 formulation buffer. There is approximately 270 ul of overfill in each vial, allowing for a minimum of 1.0 mL to be extracted. For details on the formulation composition, formulation dose strength, packaging, and container fill, please see the Investigator's Brochure.

5.2.2 Procedure for Preparation and Administration

The study drug will be administered as an IV infusion over 30 minutes. Further details regarding the preparation and administration procedures for RZ358 will be provided in the study Pharmacy Manual.

5.2.3 Packaging, Labeling and Storage

(b) (4)

Packaging and labelling of study drug will comply with Good Manufacturing Practice (GMP) Annex 13, Good Clinical Practice (GCP) rules, and country-specific regulatory requirements; this information will be available in the local language.

5.2.4 Drug Management

Drug management will be the responsibility of the Investigator and can be delegated to the pharmacist or other qualified personnel of the medical institution. The Investigator, the pharmacist of the medical institution, or another designated person must complete, in real time, all the documents concerning treatment management. Treatment management will be verified on a regular basis by the Study Monitor.

The study drug can only be administered by health care professionals who are qualified by training and experience in the safe use and handling of investigational drugs. The study drug should not be used if the solution is cloudy or opaque.

For additional information about the study drug, refer to the Investigator's Brochure and Pharmacy Manual.

5.2.5 Drug Accountability

The Investigator is responsible for maintaining accurate study drug accountability records throughout the study.

The Investigator or their assigned designee is responsible for maintaining up-to-date inventory and accountability logs. Each dispensing of study drug will be documented in the medical records and/or inventory/accountability logs and reported to the Sponsor through the RTSM. The study site pharmacy should dispense drug kits sequentially, starting with the lowest kit number.

Local destruction of all unused or partially used study drug is permissible if the study site has an SOP to govern this procedure. Alternatively, the Investigator is responsible for returning all unused or partially used study drug to the Sponsor and must verify that they have been returned and that no remaining supplies are in the Investigator's possession.

5.2.6 Compliance

The administration of the study drug should be recorded in the Source Data and transferred to the appropriate sections of the eCRF.

Study drug will be administered at the study site by qualified personnel under the supervision of the Investigator or their designee during inpatient periods. Study drug will only be administered to eligible patients, according to the procedures stipulated in

this Protocol. It is strictly prohibited to use the supplied medication for any purpose other than those described in this Protocol.

5.3 Prohibited Study Medications

Restrictions on pre-study use of medications are described in the exclusion criteria (Section 4.4), and these restrictions will continue throughout the study. Initiation or escalation of therapies or interventions for the underlying disease under study is limited to circumstances meeting protocol-specified rescue criteria, (b) (4)

5.3.1 Rescue Therapies and Guidelines

Rescue therapy guidelines are provided to standardize the use of rescue therapy across the study, and to optimize the safety of study patients. Blood glucose monitoring will be performed throughout the duration of the study. CGM values or trends may be used to guide the conduct of a POC glucometer blood glucose measurement but should not be exclusively used to make rescue or treatment decisions, without confirmation from a POC glucometer measurement.

5.3.2 (b) (4)

(b) (4)

5.3.4 Treatment of Overdose

In case of an overdose of study drug, treatment should be suspended, and the patient should receive appropriate medical treatment according to the clinical condition. See Section 6.3.15.3 for a description of the requirements for overdose reporting.

5.3.5 Treatment at the End of the Study

After the completion of the study, the Investigator is responsible for ensuring that consideration has been given to the patient's post-study care. At the conclusion of the study, patients should be treated with SOC, as appropriate.

6 STUDY CONDUCT AND ASSESSMENTS

6.1 Study Schedule

A signed and dated IRB/IEC-approved informed consent must be obtained before any study-specific assessments are performed. Assessments that are part of routine care are not considered study-specific and may be used at Screening to determine eligibility. All patients will be screened for eligibility before enrollment. Only eligible patients will be enrolled into the study. The schedule of assessments to be performed during the study is provided in Appendix 1.

6.1.1 Screening

All screening procedures must be performed within 35 days of Day 1. Study procedures to be performed during the Screening Period can be found in the Schedule of Assessments (Appendix 1). Inclusion and exclusion criteria and other study assessments required in the screening period, including CGM, SMBG by POC glucometer, and Central laboratory results, will be used to determine eligibility. An RTSM system will be utilized for this study. All enrolled patients will be entered in the clinical database (EDC).

6.1.2 8 Week Treatment

The Treatment Period for this study is 8 weeks. Patients will receive bi-weekly dosing for Weeks 1, 3, 5 and 7. Therefore, patients who complete the study will receive a total of 4 doses of study drug (at the specified dose corresponding to the cohort to which the patient is assigned). Throughout the Treatment Period, safety will be monitored, and blood samples will be collected for the PK of RZ358. CGM, SMBG by POC glucometer, fasting challenges, and fasting blood samples will be performed to assess the PD and glycemic efficacy of the study drug. Study procedures to be performed during the Treatment Period can be found in the Schedule of Assessments (Appendix 1).

6.1.3 Follow-up Period and End of Study

After the patient's last dose of study drug and post-treatment Day 14 End of Treatment visit, thereafter the follow-up period will be for an additional 13 weeks. Each patient will return for 4 outpatient post-treatment follow-up visits, scheduled at Days 14 (EOT), 28, 42, and Day 105 (EOS), all ±3 days.

During this period, safety will continue to be monitored, and blood samples will continue to be collected for the PK of RZ358. In addition to the scheduled follow-up visits, patients may be asked, at the Investigator's discretion, to undergo additional safety procedures, additional PK and PD sample collection, or both. Various PD markers, including glucose, ketones (beta-hydroxybutyrate), insulin, glucagon, FFAs, and c-peptide, will be assessed.

Under extenuating circumstances, home-health follow-up visits and/or virtual care may be conducted in lieu of on-site follow-up visits.

A patient is considered to have completed the study if he/she has completed all phases of the study including the last (EOS) visit and the last scheduled procedure shown in the Schedule of Assessments.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Assessments for the last patient in the trial globally.

6.1.4 Missed Visits

Study treatment may be withheld/interrupted due to safety reasons, resulting in a "missed" visit. Adjustments to the dosing schedule for RZ358 should be discussed with the study Medical Monitor. If a visit is missed and not rescheduled, it will be captured accordingly in the clinical database.

6.1.5 Unscheduled Visits

Unscheduled visits/assessments may be required at the discretion of the Investigator. These data will be captured accordingly in the clinical database.

6.1.6 Early Termination Visit

Interruption of the study drug does not automatically and/or immediately require discontinuation from the study, and remaining study procedures should be completed as indicated by the Protocol, until such time that the final disposition is determined. If it becomes apparent that the patient will not be able to resume study drug in a reasonable timeframe (final disposition), then the patient should be withdrawn from the study, and undergo Early Termination (ET) procedures within 2 weeks of the last dose received, as outlined in Appendix 1, Schedule of Assessments.

6.2 Additional Study Procedures and Restrictions

6.2.1 Management of Background Standard of Care Therapy

Eligibility criteria for this study permit the inclusion of patients currently receiving SOC medications (e.g., diazoxide, lanreotide, sirolimus, pasireotide, or octreotide) and/or nutritional supplementation for CHI, with at least 2 months of stable treatment, or are not on treatment at the time of Screening.

Those patients taking existing and stable doses of SOC medications or nutritional supplementation (including enteral feeding, as applicable) for CHI at the time of Screening should continue the same regimen and doses during the Screening Period and throughout the remainder of the study until the post-treatment follow-up Day 42.

(b) (4)

Throughout the study, patients will also be requested to follow their usual diet (including enteral feeding, as applicable) and activity level, as evaluated and instructed by qualified study personnel.

(b) (4)

Otherwise, changes in the dose or regimen of background SOC therapies should not occur, except in the event that hypo- or hyperglycemic rescue criteria are met, or changes are deemed medically necessary by the Investigator. (b) (4)

6.2.2 Use of Rescue Therapy

Rescue therapy guidelines are provided to standardize the use of rescue therapy across the study, and to optimize the safety of study patients. A(b) (4)

6.3 Study Assessments and Criteria for Evaluation

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study.

6.3.1 Assessment of Efficacy

6.3.1.1 CGM

A CGM system will be used to evaluate glycemic eligibility and efficacy endpoints for glycemic control. Throughout the study, the CGM device will continuously monitor glucose levels. (b) (4)

Several parameters to measure glycemic control by CGM will be evaluated over the 2-week End of Treatment period after the final dose, compared to baseline. Criteria for evaluation will include:

- The average daily (primary efficacy endpoint) and 8h overnight percent time in glucose target range of 70-180 mg/dL (3.9-10 mmol/L);
- The average daily and 8h overnight duration (mins) and percent time with hypoglycemia will be measured, using thresholds of <70, <60, and <50 mg/dL (<3.9, <3.3, and <2.8 mmol/L, respectively);
- The average daily and 8h overnight hypoglycemia incidence (event rate) at each of the specified glucose thresholds will be recorded;
- The average daily and 8h overnight glucose AOC and AUC at each of the specified glucose thresholds;
- The average glucose level by CGM between midnight and 08:00 (or nearest pre-breakfast timepoint).

6.3.1.2 SMBG by POC Glucometer

Throughout the study glucose will be robustly monitored and evaluated via CGM and POC glucometer. As a supplement to CGM, self-monitoring of blood glucose by POC glucometer will be used as an additional tool to evaluate glycemic eligibility and

efficacy endpoints for glycemic control. POC glucometer readings will be collected (b) (4) from Screening through the Follow-up/EOT Visit on Day 14 after the patient's final dose in the study (cumulative study Day 57). (b) (4) glucometer manufacturer and model should be recorded in the study records. Several parameters to measure glycemic control by SMBG will be evaluated over the 2-week End of Treatment period after the final dose, compared to baseline. Criteria for evaluation, during treatment will include:

- The average weekly incidence (event rate) of hypoglycemia at the glucose thresholds of <70, < 60, and < 50 mg/dL (or < 3.9, < 3.3, and < 2.8 mmol/L, respectively)

6.3.1.3 Fasting Challenge

Patients will undergo a 12h fasting challenge on Day -1 both at baseline (Week 1) and Week 7 of treatment. (b) (4) fast should be ended when any of the following criteria have been met:

- Predetermined fasting time of 12 hours has been reached; **or**
- Blood glucose is <60 mg/dL (3.3 mmol/L); **or**
- Patient has symptoms consistent with hypoglycemia.

(b) (4)

Several parameters from the fasting challenge will be evaluated at Week 7 of Treatment, compared to baseline. Criteria for evaluation of the 12h fasting challenge will include:

- Occurrence of hypoglycemia during a 12h fasting challenge:
  - Time to termination of fast;
  - Glucose nadir during fast;
  - Percentage of patients able to complete a fast;
  - Ketone levels at the conclusion of fast.

6.3.1.4 Other Efficacy

Data collected regularly from patient diaries, dietary reviews/counseling, fasting glucose blood draws, concomitant medications and other assessments (see Schedule Appendix 1) will be utilized to assess efficacy outcomes including, but not limited to:

- IV or enteral nutrition (glucose/dextrose) supplementation;
- Patient incidence and rate of SOC or rescue medication use for hypoglycemia (dextrose or other);

6.3.2 Assessment of Pharmacokinetics

The single and repeat dose PK of RZ358 will be assessed throughout this study.

Blood samples will be collected for RZ358 at time points per the SOAs in Appendix 1 and Appendix 2. For the first 48 hours after each dose, all samples should be collected from the contralateral arm from infusion. Allowable deviations from the nominal time points are described in the SOAs. In all cases, the actual time of blood collection should be accurately recorded. The Sponsor will supply complete written instructions for collection, handling, processing, storage, and shipping of samples before study initiation.

The single and repeat-dose PK of RZ358 will be assessed by population PK modeling which will be used to estimate parameters including, but not limited to:

- AUC_{ss}: steady state area under the concentration-time curve
- C_{maxss}: steady state maximum concentration
- $Cavg_{ss}$: steady state average concentration
- $t_{1/2}$: effective half-life
- CL: total drug clearance
- V: volume of distribution of the central compartment

6.3.3 Assessment of Pharmacodynamics

Blood samples will be drawn throughout the Treatment and Follow-up Periods of the study to evaluate the PD effects of the study drug, as specified in Appendix 1. Samples should be drawn as close to the scheduled time as possible, and in all cases the actual time of blood collection should be accurately recorded. The PD of RZ358 compared to baseline will be assessed by:

- Average levels of glucose, insulin, c-peptide, glucagon, FFAs, and ketones (beta-hydroxybutarate), at each of the specified collection timepoints;
- Incidence of fasting blood glucose values >200, >250, and >300 mg/dL (>11.1, >13.9, and >16.6 mmol/L, respectively).

6.3.4 Assessment of Demographics, Safety, and Other Procedures

Safety assessments will adhere to all recommendations outlined in the International Conference on Harmonization (ICH), GCP and the protection of human safety. The interpretation of the safety and tolerability of RZ358 will be made based on the collection and assessment of safety parameters evaluated throughout the study, including vital signs, ECGs, physical examinations results, local (site) and systemic infusion observations, (b) (4) , clinical laboratory evaluations including glucose values, and AEs/SAEs.

6.3.5 Medical History

Medical history will be recorded at Screening and will include full CHI history, clinically significant diseases, surgeries, cancer history, reproductive status or cardiovascular events. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

6.3.6 Vital Signs (Including Height and Weight)

Vital signs will be measured and recorded at the time points designated on the Schedule of Assessments (see Appendix 1). The following measurements must be performed: systolic/diastolic blood pressure, pulse, and oral temperature. Vital signs will be measured after the patient has been in the supine position for at least 5 minutes. All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF. When vital signs, ECGs, and/or blood sample collection occur at the same time, vital signs should be performed before ECGs and/or blood sample collection.

Vital signs may be measured at unscheduled timepoints, if deemed necessary by the Investigator.

Body height will be measured in centimeters (cm) and body weight in kilograms (kg).

6.3.7 Physical Examination

The investigator or qualified designee will perform a complete physical examination (genitourinary examination not required) and targeted abbreviated physical examinations as specified in the SOA (see Appendix 1). All pre-dose abnormal findings will be reported on the medical history eCRF. Any adverse change from the baseline physical examination will be documented on the AE eCRF.

A full physical examination will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

An abbreviated physical examination is inclusive of neurological, cardiac, gastrointestinal, and pulmonary assessments.

6.3.8 Electrocardiograms

During the study, 12-lead ECGs will be performed at the time points designated on the Schedule of Assessments.

The patient must be in a supine position in a rested and calm state for at least 5 minutes before the ECG is conducted. If the patient is unable to be in the supine position, they should be in the most recumbent position possible. All ECGs should be performed in a standardized method, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, corrected QT, RR, and PR intervals, as well as an overall interpretation.

The Principal Investigator (PI) or designated site physician will review and sign all ECGs. Results must be summarized in writing and classified as normal; abnormal; abnormal, clinically significant; or abnormal, not clinically significant. Once signed, the original ECG tracing will be retained with the patient's source documents. At the request of the Sponsor, a copy of the original ECG will be made available. Unscheduled ECGs may be performed if there is a change from baseline or as deemed necessary by the Investigator.

6.3.9 Laboratory Evaluation

Laboratory assessments will be performed by a central laboratory (see Laboratory Manual). Central laboratory results should be reviewed by the Investigator as it is received. Any abnormalities must be evaluated in clinical context and the Investigator should determine if it is clinically significant. Patient management is dependent upon close review of the laboratory data.

The tests listed in Table 4 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points designated on the Schedule of Assessments. Tests that are not done must be reported as such on the eCRFs.

(b) (4)

(b) (4)

(b) (4)

6.3.11 Infusion Reactions

6.3.11.1 Assessment of Local Infusion Site Reactions

A local infusion site reaction is any local reaction occurring at the site of injection following study drug administration. A local infusion site reaction, including, but not limited to, erythema, induration, and pain, should be reported as an AE. If needed, local infusion site reactions should be treated, and any treatments should be reported on the eCRF and will be monitored closely. Detailed information regarding local infusion site reactions that occur during the study will be collected regardless of whether the events are serious or non-serious. (b) (4)

(b) (4)

6.3.11.2 Management Guidelines for Systemic Infusion-Related Reactions

Signs of a possible anaphylactic, anaphylactoid or hypersensitivity reaction include but are not limited to, the following:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash;
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension;
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).

Investigators and health care professionals should be trained to recognize and manage the signs and symptoms of a potential anaphylactic, anaphylactoid, or hypersensitivity

reaction and also be trained to accurately and appropriately report these events. If a patient experiences a suspected mild and/or non-serious hypersensitivity reaction, the case should be discussed with the Medical Monitor prior to continued dosing. Patients who experience a moderate to severe infusion-related anaphylactic, anaphylactoid or hypersensitivity reaction should have their infusion stopped immediately and should be treated according to the SOC for management for these reactions. In the case of any serious or severe infusion-related reaction, the study drug should be permanently discontinued. In these cases, the actual time and amount of study drug should be noted in the source and eCRF. Detailed information regarding anaphylactic, anaphylactoid, or hypersensitivity reactions that occur during the study will be collected, regardless of whether the events are serious or non-serious.

In the event of an infusion-related reaction, unscheduled ADA and PK serum samples should be collected at the following three timepoints, in addition to the pre-specified collection schedule: as close to investigator-determined onset of the event as feasible, at investigator-determined resolution of the event, and 30 days after the resolution of the event.

6.3.12 Meals

The patient will be requested to follow his/her usual standard diet. At Screening, a dietician or other qualified medical professional will discuss with the patient/parent the usual diet consumed by the patient and will record the percent fat, protein, and carbohydrate the patient typically consumes per day, along with the patient's usual food choices and frequency and timing of the usual eating pattern.

During the inpatient portions of the study, meals and snacks will be provided by the inpatient facility per the patient's usual standard diet.

Meals will be served at the same time of day while patients are in the inpatient research facility.

An afternoon and evening snack will be served. The evening snack must be consumed at a time that ensures at least 8 hours of fasting can occur before the following morning's breakfast (for patients for whom fasting is feasible). Additional snacks may be served, if needed, at the Investigator's discretion.

Patients will be asked to try to consume their meals in their entirety, as often as possible. The date and time, content, and percent of the total not consumed of each meal and snack will be recorded.

For outpatient days, the patient will be requested to follow the patient's usual standard diet.

6.3.13 Patient Diary

Patients will use an electronic device to record and capture daily glucose events, (b) (4) device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. The Sponsor will have view access only. System backups for data stored by

the Sponsor and records retention for the study data will be consistent with the Sponsor's or designee's standard procedures.

6.3.14 Adverse Events

6.3.14.1 Safety definitions

6.3.14.1.1 Adverse Event

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical study patient, which is either new in onset or pre-existing but worsened in severity or frequency, whether or not it has a causal relationship to the study investigational (medicinal) products or procedures. This includes events with onset from the time of providing written informed consent for participation in the study until the end of study visit, as defined in the protocol. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

(b) (4)

A clinical laboratory AE is any clinically significant laboratory abnormality that suggests a disease and/or organ toxicity and is of a severity, which requires active management, (i.e., change of dose, discontinuation of study product, more frequent follow-up or diagnostic investigation). (b) (4)

A treatment-emergent AE (TEAE) is defined as any clinically significant event that is not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

6.3.14.1.2 Adverse Drug Reaction

AEs judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse drug reactions.

6.3.14.1.3 Unexpected Adverse Reaction

An unexpected adverse event is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

6.3.14.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction

Any untoward medical occurrence (AE) that at any dose meets any of the following criteria:

1. Results in death;
2. Is life-threatening;

(Note: The term "life-threatening" refers to an event in which the patient is at immediate risk of death at the time of the event, not an event that might have caused death if it was more severe.)

3. Requires inpatient hospitalization or prolongation of existing hospitalization;
   (Note: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for administrative, study-related, or social purposes, for elective treatment of a pre-existing condition that did not worsen from baseline, or hospitalization scheduled in advance of study participation is not considered to be an AE/SAE, under this criterion.)
4. Results in persistent or significant disability/incapacity;
   (Note: The term(s) disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions [e.g., following the event or clinical investigation the patient has significant, persistent or permanent change, impairment, damage or disruption in his/her body function or structure, physical activity and/or quality of life]. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g. sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption);
5. Is a congenital anomaly/birth defect in a neonate/infant born to a biologic parent exposed to study drug;
6. Is an important medical event, based on the Investigator's medical judgement.
   (Note: Other events that may not result in death, are not life threatening, or do not require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.3.14.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or Summary of Product Characteristics for an approved product).

6.3.14.2 Procedures for Collecting and Recording Adverse Events

6.3.14.2.1 General

Collection of all AEs (serious AEs and non-serious AEs) will commence from the time the patient signs the informed consent to participate in the study, and continue through the End-of-Study follow-up visit, as specified in the study Schedule of Assessments (Appendix 1). The occurrence of AEs must be sought by non-directive questioning of the patient or the patient's Legally Authorized Representative (LAR) at each visit during the study (e.g., "How are you feeling?", "How has the patient been feeling?") or may be spontaneously reported by the patient (or LAR) during or between visits or through physical examination findings, laboratory test findings, or other assessments. All identified AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded and described in the patient's source records and eCRF Events that occur after the conclusion of the study should also be reported and recorded in the source documentation if there is a reasonable likelihood

that the event is related to study drug, and such events meeting serious criteria should also follow SAE reporting guidelines.

The following attributes must be evaluated and recorded for each event, and guidelines for doing so are provided:

1. Description (i.e. event term);

(b) (4)

2. Dates of onset and resolution, including timing of onset relative to 1st dose of study drug;
3. Severity (as described in Section 6.3.15.2.2);
4. Assessment of causality / relatedness to study drug (as described in Section 6.3.15.2.2);
5. Seriousness (as described in Section 6.3.15.2.2);
6. Action taken (b) (4)
7. Outcome/status of the event. (Note: All AEs and SAEs should be followed up until resolution or permanent outcome of the event [i.e. deemed stable], or until the Investigator and Sponsor conclude that further follow-up is not necessary.

(b) (4)

6.3.14.2.2 Adverse Event Severity Grading

The severity of AE will be assessed by the Investigator and graded according to the NCI Clinical Trial Classification for Adverse Events (CTCAE). Event terms not listed in the NCI-CTCAE will be evaluated using the following grading scale (see Table 6).

Table 6: Grading Scale (Terms Not Listed in NCI-CTCAE)

Term	Definition
Grade 1, Mild	Signs or symptoms easily tolerated and generally not causing interference with normal activities; of little concern to the patient and of little or no clinical significance; is not expected to have any effect on the patient's health or well-being; may or may not require medical intervention
Grade 2, Moderate	Causes interference with some usual activities; experience is of some concern to the patient's health or well-being; may require medical intervention
Grade 3, Severe	Causes interference with most regular activities; experience is of definite concern to the patient and/or poses substantial risk to the patient's health or well-being; likely to require medical intervention
Grade 4, Life-threatening	The patient was at immediate risk of death from the experience, as it occurred
Grade 5, Death	The event resulted in death (but death is not an AE)

6.3.14.2.3 Relationship of AEs

The causal relationship of AEs to the study drug must be assessed by the Investigator, or by a medically qualified designee, in accordance with the following criteria detailed in Table 7.

Table 7: Causal Relationship of AE to Study Drug

Term	Definition
Related	There is a temporal relationship between administration of the study drug and the event, and: • The event is known to occur with the study drug or represents a known reaction to drugs in the same class, or is predicted by known pharmacological properties of the drug;

	• The event cannot be reasonably explained by the patient's clinical state or other factors (e.g. medical history, concurrent medications, or concomitant medications); • The event resolves with interruption of study drug (de-challenge) and recurs with resumption of study drug (re-challenge), as applicable.
Not Related	There is not a reasonable possibility that the administration of the study drug caused the event, there is no reasonable temporal relationship between the study drug and event onset, and/or the event can be explained by the patient's clinical state or other factors, i.e. an alternate etiology has been established (eg, disease under the study, concurrent diseases and concomitant medications).

6.3.14.3 Overdose

An overdose is defined as any dose administered to or taken by a study patient, either accidentally or intentionally, that exceeds the highest intended per dose amount or frequency for the assigned cohort, based on the protocol. Investigators should decide whether a dose is to be considered an overdose, in consultation with the Sponsor. Any occurrence of an overdose should be reported to the Sponsor (or designee) within 24 hours of becoming aware, regardless of whether the event represents an AE. The event should also be recorded in the patient's source file and the eCRF. Unless the overdose also meets AE definitions, it should not be reported as an AE.

6.3.14.4 Pregnancy

Pregnant patients will not be allowed to participate in this study. If a patient becomes pregnant while on study, the patient will be discontinued and will complete end of study procedures for safety. The Sponsor must be notified if any patient becomes pregnant either while receiving study drug or within 105 days after having received the last study drug dose. This includes any pregnancies in the partner of a male study patient, or if a patient's sperm is used to impregnate a female during the study. The Investigator must inform the Sponsor as soon as possible and no later than 24 hours after knowing of the pregnancy, by completing the Pregnancy eCRF page. If the site has a temporary interruption in its internet or computer access, the back-up Pregnancy paper form will be completed and e-mailed to the sponsor within 24 hours of awareness. When the eCRF becomes available, the Pregnancy must be entered by the site within 24 hours. Pregnancy should not be recorded on the AE eCRF.
Upon knowledge of a pregnancy, the pregnant female will be asked to sign a release of information form to allow the Investigator to collect information about the pregnancy, delivery, and final outcome, including health of the baby, as required for regulatory reporting purposes. All reported pregnancies (even if a patient withdraws from the study) must be followed up by the Investigator to final outcome, using the pregnancy and pregnancy follow-up forms. Follow-up and outcome, including any premature termination, must be reported to the Sponsor (or designee) in a timely manner. An evaluation after the birth of the child may also be conducted.
Pregnancy itself should not be recorded as an AE, although any complications ensuing from a pregnancy must be recorded as AE(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a SAE.

6.3.15 Procedures for Reporting Serious Adverse Events

All new SAEs, regardless of causal relationship, should be reported to the Sponsor (or designee) in writing within 24 hours of the site's knowledge of the event. A copy of the initial SAE report must be received within 1 business day.

The SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: patient identification, reporting source, event term and a short description of the event, criterion for seriousness, and initial causality assessment. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor (or designee) may contact the investigational site to solicit additional information or to follow-up on the event. The SAE Report Form should be completed by an Investigator following the specific completion instructions.

If there is any doubt whether the information constitutes an SAE, the information will be treated as an SAE for the purposes of this protocol.

All relevant documentation pertaining to the SAE (additional laboratory tests, consultation reports, discharge summaries, post-mortem reports, etc.) will be provided by an Investigator to the Sponsor (or designee) in a timely manner. Investigators must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor (or designee) may have on the AE.

The Sponsor will be responsible for notifying the FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information, and no later than 15 days for all other suspected unexpected serious adverse reactions (SUSARs). The Sponsor must notify FDA and all participating Investigators in an Investigational New Drug Application safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting.

The Sponsor will be responsible for reporting all SUSARs and any other applicable SAEs to regulatory authorities, including the FDA, European Medicines Agency (according to Directive 2001/20/EC), and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations. Any SUSARs will be reported to the IRB/Independent Ethics Committee (IEC) per their institutional policy by an Investigator or Sponsor (or designee) according to country requirements. Investigators should keep copies of each report, documentation of IRB/IEC notification, and acknowledgement of receipt in the site's study file.

7 STATISTICAL METHODS

7.1 General Considerations

This is a Phase 2 Proof of Concept study and is not powered for statistical significance. Detailed methodology for analyses and summary of the data will be documented in the study Statistical Analysis Plan (SAP), which will supersede the protocol, where applicable. However, any major modification of the outcome measures and/or its analysis will also be reflected in a protocol amendment.

Continuous variables will be summarized by using the following descriptive statistics: mean, standard deviation (SD), coefficient of variation (CV), number of observations (N), median, minimum, and maximum. The frequency and percent of observed levels will be reported for categorical measures. In general, all data will be listed, sorted by patient and, when appropriate, by study day and study time point within patient.

Confidence intervals or p-values, without correction for multiplicity, may be produced for hypothesis generating purposes.

Subgroup analyses may also be performed to further explore the study data. These analyses may include t-tests, Wilcoxon rank-sum tests, and Pearson correlation/Spearman correlation for continuous measures; for categorical variables, chi-square and Fisher's exact tests may also be performed, as appropriate. Populations used for sub-analysis will be defined in the SAP.

7.2 Disposition of Patients

The disposition of patients will be described with summaries of the number of patients treated and discontinued from the study, including the primary reason for premature discontinuation by cohort.

7.3 Protocol Deviations

See Section 9.3.4.

7.4 Analysis Populations

For the purposes of this study, the following populations will be identified:

Safety population: all patients enrolled in the study who receive at least one dose of study drug.

Per Protocol Population: All patients who receive at least 4 weeks of study drug (2 bi-weekly doses), with no major protocol violations.

PK population: all patients who receive study drug and have a sufficient number and quality (biologically plausible) of results.

7.5 Demographics, Baseline Characteristics and Concomitant Medications

Summaries of patient disposition, demographics, and baseline characteristics will be provided by cohort.

7.6 Treatment Compliance

Frequency and distribution of the number of received doses will be presented. Treatment duration for all patients will be described.

7.7 Efficacy and Pharmacodynamic Analyses

The primary efficacy and PD analysis will be conducted in the per-protocol population, which will include all patients who received at least 4 weeks of study drug (2 bi-weekly doses), without significant protocol deviations. CGM data will be compiled and output into parameters for analysis. Actual data and change from

baseline will be summarized descriptively for the primary endpoint and each secondary or exploratory continuous CGM parameter, as well as for SMBG by POC glucometer, fasting glucose, and other PD markers, at the protocol-specified timepoints and pre-specified evaluation periods. Corresponding mean (SD) and/or Box-plots will be produced for CGM parameters, to illustrate the descriptive statistics, as appropriate. Figures and graphs will be created to display mean and individual PD results, as appropriate. Incidence rates will be normalized to the daily (CGM) or weekly (SMBG) average. Categorical events will be summarized by frequency counts, as applicable. The requirement for rescue medications and the use of background SOC medication or supplemental nutrition will be listed by patient and summarized, where appropriate. Statistical comparisons may be performed as appropriate, and will be described in the SAP and/or clinical study report.

7.8 Safety Analyses

Safety analyses will involve an examination of AEs, vital signs, ECGs, physical examinations results, infusion-site observations, (b) (4) and clinical laboratory evaluations including glucose values. Individual patient listings will be reviewed, and summary results with descriptive statistics will be provided, where appropriate. No statistical testing will be performed on safety data.

A by-patient TEAE data listing, including verbatim term, preferred term and SOC, treatment, severity, and relationship to cohort, will be provided.

The number of patients experiencing AEs and number of AEs will be summarized by cohort using frequency counts.

Safety data, including laboratory evaluations and vital signs assessments, will be summarized by cohort and time point of collection.

The occurrence of immunogenicity will be assessed and if confirmed, titer values will be reported by cohort and time point collection. No formal statistical evaluation will be performed. Any patient in which ADAs are detected will be followed for further assessment.

Descriptive statistics (arithmetic mean, standard deviation [SD], sample size [N], median, minimum, and maximum) will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

A mean change-from-baseline table will be provided for vital signs, ECGs and clinical laboratory results, per cohort.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results, as appropriate.

A normal-abnormal shift table will be presented for ECGs, as appropriate.

Changes from baseline in physical examinations and (b) (4) will be described in the text of the final report.

AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available to the Sponsor or designee.

Concomitant medications will be listed by treatment and coded using the most current World Health Organization (WHO) drug dictionary available to the Sponsor or designee.

Medical history will be listed by patient.

Infusion site reaction will be assessed.

No formal inferential statistics will be applied to safety assessments.

Additional analyses will be performed as appropriate.

7.9 Pharmacokinetic Analysis

The individual and mean RZ358 serum concentrations will be summarized by treatment cohort and planned sample times in tables and figures. Serum concentrations for samples collected within 30 min after the dosing infusion will be reported as the observed concentration at the end of infusion (CEOI). Concentrations will be summarized using descriptive statistics. The study design and planned PK sample collection are not suitable for the calculation of PK parameters by noncompartmental methods. Specifically, the number of PK samples within dosing intervals is insufficient to support noncompartmental estimation of AUC; and due to the long half-life of RZ358, steady state is not expected to be achieved by the end of the 8-week Treatment Period. Therefore, the observed serum RZ358 concentration-time data will be used to develop a population PK (popPK) model to describe the PK of RZ358 in patients with CHI. PopPK modeling will also investigate the effects of selected covariates on RZ358 PK such as age, body weight, gender and race, as data permit.

The popPK model will be used to estimate PK parameters for each treatment cohort, including but not limited to the following:

- AUC_{ss}: steady state area under the concentration-time curve;
- $Cmax_{ss}$: steady state maximum concentration;
- $Cavg_{ss}$: steady state average concentration;
- $t_{1/2}$: effective half-life;
- CL: total drug clearance;
- V: volume of distribution of the central compartment.

Descriptive statistics will be presented for PK parameters, including but not limited to C_{max}, T_{max}, $t_{1/2}$, and AUC. The relationships between dose and C_{max} and AUC will be analyzed for dose proportionality. The PK results of this study may be combined with those of other studies for analysis and modeling (e.g., population PK and PK-PD), and reported separately Detailed methods for the PK modeling will be provided in a separate PK modeling analysis plan.

7.10 Interim Analyses

This is an open label study. Safety, PD, and PK data will be examined on an ongoing basis to ensure safety of the study patients.

7.11 Determination of Sample Size

The sample size chosen for this study was selected without statistical considerations. It has been determined adequate to meet the study objectives. Patients who withdraw from the study may be replaced on a case-by-case basis after discussion and agreement with the Medical Monitor.

8 DATA MANAGEMENT

8.1 Data Collection

The trained investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture tools as needed), and will upload the CGM data into a 21 CFR Part 11 Web Based Data Capture System. All data collection information must be traceable to these source documents.

Direct recording of the data in the eCRF is not allowed for this study

Responsible Monitor will review eCRFs entered by investigational staff for completeness and accuracy. Checks for data discrepancies in the eCRFs will be performed and the resulting queries will be notified to the investigational site. Designated investigator site staff are required to respond to queries and make any necessary changes to the data.

A validated, electronic database will be employed from the EDC system. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data handling plan/ data management plan with a description of the personnel responsible for data entry.

8.2 Data Correction

Automatic and manual queries will be defined according to the data validation plan. These queries will be generated by the Data Management Department and sent through the electronic data capture (EDC) system for clarification. Corrections will be entered directly into the system. This procedure will be repeated until all queries are resolved. All query forms will be linked to the eCRF in the EDC system.

8.3 Data Handling

The final data will be transferred to the SAS-system for analyses in accordance with the SAP. The MedDRA dictionary will be used for coding of AEs and concomitant diseases. Concomitant medication will be coded using the World Health Organization Drug Dictionary **A**(natomical) **T**(herapeutical) **C**(hemical) code.

8.4 Data Quality Assurance

The Sponsor and/or their designee (i.e. Monitor engaged by CRO company) will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRFs for this study must be consistent with the patient's source documentation (i.e. medical records).

8.5 Handling of Missing, Unused, and Spurious Data

All available efficacy and safety data collected for the study will be included in data listings and/or summary tables. The handling of missing data will be described in the study SAP.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Study Initiation Activities

The investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at a Pre-Study Visit by the Monitor (if necessary), an investigators' meeting, and during the Site Initiation Visit by the Monitor.

9.2 Training of Site Staff

The PI will ensure that everyone assisting with the clinical study is adequately informed about the protocol, the investigational product(s), and their study-related duties and functions. Furthermore, the investigator will maintain a list of qualified persons to whom the investigator has delegated study-related duties.

9.3 Documentation and Filing

9.3.1 CRF System

The Investigator and persons authorized by the Investigator will be instructed about how to complete the eCRF. Entries in the eCRF must only be made by the Investigator or persons authorized by the Investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site.

The investigator must ensure that all data entries in the eCRF are complete, accurate, legible and reported in a timely manner. Data reported on the eCRF should be consistent with the source documents or the discrepancies should be explained. Entries will be checked against appropriate source documentation by the Monitor.

9.3.2 List of Patients (patient identification log)

The Investigator will keep a confidential list of names of all patients participating in the study, so that the patients' records can be identified if necessary.

In addition, the Investigator will keep a list of all patients screened on a screening log to document identification of patients who were consented and entered study screening. If someone is not eligible to participate in the study, a reason should be provided.

9.3.3 Source Data

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

9.3.4 Protocol Deviations

The Investigator should document and explain any protocol deviations. The Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and IRB/EC in accordance with established IRB/EC policy and procedures.

The Sponsor will review all protocol deviations and assess whether any represent a serious breach in GCP guidelines and require reporting to health authorities. As per the Sponsor's or authorized designee's standard operating procedures, prospective requests to deviate from the protocol, including request to waive protocol eligibility criteria are not allowed.

Deviations from the protocol will be judged during the study and/or when an individual patient's eCRF is completed (monitored) and will be recorded as either major or minor.

Before analyzing the data, a data review meeting (DRM) will take place where protocol deviations will be classified (major/minor protocol deviations) for statistical analysis

9.3.5 Investigator Site File / Regulatory Binder

Before site initiation, the CRO will provide an Investigator Site File (ISF) to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements that are required for study initiation at the investigational site.

From that point onwards, the Investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the Monitor(s). These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to the local regulatory requirements and agreement with the study Sponsor.

Details pertaining to the retention and archiving of study documents are found in Section 10.4.

9.4 Monitoring

The Monitor is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the Monitor ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

Following the site prequalification and/or initiation of the study site, periodic monitoring visits will be conducted by Sponsor or their designee. The interval between monitoring visits will depend on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the investigator must grant direct access to the original patient's source documents.

The extent and nature of monitoring will be described in detail in the monitoring plan.

9.5 Audits and Inspections

Audits will be performed according to the corresponding audit program. The Sponsor's Quality Assurance Department or designee may visit the investigative site to audit the performance of the study, as well as all study documents. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the Monitor will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IECs/IRBs are possible at any time, even after the end of the study. The Investigator is to notify the Sponsor immediately of any such inspection. The Investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or Regulatory

Authorities, and will allow direct access to original source documents for monitoring, audits, and inspections.

10 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and investigator abide by the principles of the GCP guidelines of the ICH, and of the Declaration of Helsinki. The study also will be carried out in keeping with local legal requirements.

10.2 Informed Consent

Before the first study specific screening procedure can be performed each patients informed consent must be obtained (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country (i.e., the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 Code Federal Regulation [CFR] 50.25 [a] and [b], CFR 50.27, and CFR Part 56, Subpart A), and other applicable local regulations. This consent form must be approved by responsible IRB/IEC and must be signed and dated by the patient (or his/her legally authorized representative) and authorized consenter and retained by the investigator as part of the study records. The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the patient's medical records and eCRF.

The explicit wish of a minor, or mentally incapacitated adult, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be considered by the investigator.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB, and signed by all patients subsequently enrolled in the study, and potentially those currently enrolled in the study if applicable.

10.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local regulatory requirements. The Sponsor must ensure that all ethical and regulatory requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Regulatory Agency approval prior to implementation, in accordance with national regulations.

All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.4 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.5 Administrative Structure

This study will be sponsored and managed by Rezolute, Inc. The Sponsor will provide oversight of the CRO(s) managing the following; clinical operations, data, programming and statistical management, medical monitoring oversight and CGM device procurement including CGM data uploads and reporting. CRO(s) will provide study, site and patient management, global regulatory support, medical and site monitoring pharmacovigilance activities, device services and data management which includes both EDC and CGM data collection.

Randomization and drug distribution will occur through an RTSM system that is fully integrated into the EDC which will be used for data collection.

CGM data collection will be done through the internet in a software-as-a-service model. The software will provide a system-compliant audit trail of all relevant data collected and uploaded from the CGM device and all changes made within the data. Each activated site will upload the CGM device specific software to a workstation computer at the site enabling the site to be able to access and upload patient as often as needed throughout the duration of the CGM monitoring.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses).

10.6 Dose Escalation Review Committee

A Dose Escalation Review Committee will assess all available and relevant interim data from each cohort to determine the appropriateness of cohort escalation. The criteria for halting dose escalation are further specified in the protocol in Section 5.1.2.

10.7 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study;
- Failure to enroll patients at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

10.8 Confidentiality

Patient medical information obtained as part of this study is confidential. The use, transfer and disclosure of all personal information, including health related information, shall be in strict compliance with all applicable privacy laws. The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to CRO by their patient number allocated in the trial, not by name. Documents not to be submitted to CRO that identify the patient (e.g., the signed informed consent, patient identification list) must be maintained by the investigator as part of the ISF in a secure and confidential manner.

10.9 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by the Investigator and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.10 Publication of Data and Protection of Trade Secrets

Regardless of the outcome of the trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for disclosure of study results in appropriate government registries such as ClinicalTrials.gov and EudraCT, as applicable.

The Investigator must agree to submit for review and approval all manuscripts or abstracts/posters to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not be available to the Investigator.

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