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A Single and Repeat-Dose Study of RZ358 in Patients with Post-Gastric Bypass Hypoglycemia (PGBH): Results of Population PK/PD Modeling

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ABSTRACT

PGBH is characterized by dysregulated hyperinsulinism (HI) and significant postprandial hypoglycemia and is not adequately served with existing therapies. RZ358 is a human monoclonal antibody which allosterically attenuates insulin (Ins) action at target cell insulin receptors (IR) during high Ins states. In previous clinical studies of induced (healthy volunteer [HV] Ins tolerance test) or intrinsic (congenital) HI, RZ358 exhibited favorable safety and PK, with consistent proof of concept (glucose normalization without hyperglycemia). Therefore, RZ358 may be beneficial in PGBH.

The present study is a Phase 2a, open-label, single ascending (3, 6, and 9 mg/kg) and repeat dose (3 mg/kg/week for 4 weeks) study of IV RZ358 in patients with PGBH (n=16 [M:2; F:14]). Serial measurements of RZ358 and biomarkers, and continuous glucose monitoring (CGM) were performed for up to 6 weeks. PK/PD modeling was conducted using NONMEM (v7.3) to describe RZ358 concentrations and exposure response (ER) relationships.

Other than gender, baseline (BL) characteristics were similar across the study. RZ358 was generally safe and well-tolerated with no discontinuations, deaths, or serious adverse reactions. The concentration data were well-described by the PK model, with dose-proportional exposures and PK that was comparable to that in HVs and CHI. The effective half-life was estimated as ~15 days. Concentration-dependent increases in Ins of up to 4-fold on Day 2 were observed, due to reduced clearance at IR, as supported by unchanged c-peptide. As further evidence of Ins attenuation at target tissues, increases in ketones and free fatty acids were observed. In the setting of a relatively normal overall BL, RZ358 resulted in modest and sustained glucose increases by CGM, creating an apparent saturable ER. Notably, patients with the most pronounced daytime (meal exposure period) hypoglycemia at BL had a persistent >50% improvement and near normalization of time in hypoglycemia (min/day <70 mg/dL) and time in target range (70-180 mg/dL), while the group with BL normoglycemia did not become hyperglycemic. The ER model well-described the glucose and Ins concentrations as a function of RZ358 concentrations and predicted that target RZ358 concentrations may be achieved with weekly administration of 3 mg/kg, or potentially less frequently at other doses.

Consistent with its mechanism of action, RZ358 increased glucose in a disease and exposure-dependent fashion, only when and to the extent needed. These properties make it uniquely suited as a potential novel and universal treatment for heterogenous and variable HI conditions such as PGBH. The validated PK/PD models have adequately described the PK and ER profile of RZ358 and inform future study design and dose selection. An 8-week Phase 2b study in CHI is currently underway and future studies in additional potential indications, including PGBH, are planned.

INTRODUCTION AND BACKGROUND

Post Gastric Bypass Hypoglycemia

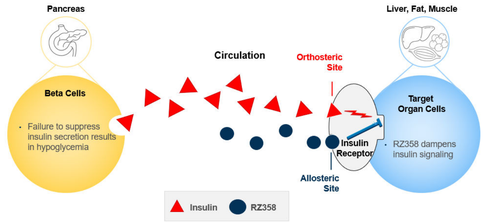
- Post gastric bypass hypoglycemia (PGBH), a complication of bariatric surgery, is characterized by low blood glucose that occurs postprandially due to hyperinsulinemia[1].
- The estimated 5-year incidence of PGBH exceeds 10%, with up to 3% having moderate to severe hypoglycemia requiring medical intervention[2].
- Possible mechanisms for hyperinsulinemia include expansion of beta-cell mass[1], enhanced beta-cell function and dysregulated insulin secretion[3], and other causes not related to the beta-cell[4].
- Complications from hypoglycemia can be life threatening, with the possibility of seizures and loss of conscience[2].

Limitations of Current Therapies

- Changes to nutritional uptake are often insufficient to control the disease[5].
- Existing pharmacological agents such as adacarbose, diazoxide, or somatostatin analogs are often not sufficiently effective, or aren't well-tolerated, and surgery is invasive and a last resort[5].

RZ358 Background

Figure 1: Mechanism of RZ358



- RZ358 is a fully human IgG2 monoclonal antibody that binds with high affinity selectivity to an allosteric site of the insulin receptor, without competing or antagonizing insulin binding orthosterically[6].
- When levels are elevated, RZ358 dampens insulin effects into the physiologic range[6].
- In previous clinical studies of induced (healthy volunteer [HV] Insulin tolerance test) or intrinsic (congenital) HI, RZ358 exhibited favorable safety and PK, with consistent proof of concept (glucose normalization without hyperglycemia).

Study Objectives

- Phase 2a studies in patients with PGBH were completed to evaluate the efficacy and safety of RZ358 at various dosing regimens.
- A PK and empirical PK/PD model was developed to describe RZ358 plasma concentration-time profiles, as well as to explore the relationship between drug concentrations and glucose levels.

METHODS

Study Design Overview

Table 1: RZ358 Clinical Study Overview

Clinical Trial	Study	Study Design	Dose	Subjects on RZ-358	Subjects on Placebo	Population
Phase 1	X358601	Randomized, Double-Blind, placebo-controlled, single ascending dose (SAD)	0.1, 0.3, 1, 3 mg/kg	14	5	Healthy volunteer
	X358604	Randomized, Double-Blind, placebo-controlled, SAD	6, 9 mg/kg	8	2	
Phase 2a	X358602	Open-Label SAD	1, 3, 6, 9 mg/kg	10	0	Congenital Hyperinsulinism (CHI)
	X358605	Open-Label Repeat dose (x2 doses)	3 then 6 mg/kg	4	0	
	X358603	**Open-Label Part 1: SAD Part 2: repeat dose**	**Part 1: 3, 6, 9 mg/kg Part 2: 3 mg/kg weekly**	**Part 1: 12 Part 2: 4**	**0**	**Post-gastric Bypass hypoglycemia (PGBH)**

Assessments and Endpoints

- Continuous Glucose Monitoring (CGM) was utilized to measure interstitial glucose levels[7] with a frequency of 5 minutes during the Phase 2 clinical trials (including PGBH trial).
- CGM data was summarized by calculating a daily average or the daily percent time that glucose measurements are above or below key thresholds (i.e. 70 mg/dL).
- Other biomarkers such as plasma glucose, insulin, c-peptide, ketone bodies, and free fatty acids were measured in the fasting and postprandial state.

Population PK/PD Development

- The population PK analysis was performed using NONMEM 7.3 with pooled observations from all completed studies with RZ358, while the PK/PD modeling was conducted utilizing Phase 2 patient data (Table 1). The first-order conditional estimation method with interaction (FOCEI) was used to approximate the marginal likelihood facilitating estimation of the population model parameters.
- A 2-compartmental model with linear elimination was the starting point for PK base model development. Interindividual variability (IIV) of the PK parameters was incorporated, as well as residual variability to account for assay error, model misspecification, or other unexplained variability within a subject. Covariate effects were evaluated via backward elimination from a full PK model.

RESULTS

Demographics, Disposition, and Safety: Study 603 (PGBH)

- Study comprised 2 males and 14 females, with a body weight range of 62 to 112 kg, and an age range of 42 to 68 years
- One subject crossed over from 3 mg/kg to 9 mg/kg in Part 1
- RZ358 was generally safe and well-tolerated in PGBH patients with no discontinuations, deaths, or serious adverse reactions.

RESULTS (CONT.)

RZ358 Pharmacokinetics: Described by the Model, $t_{1/2}$ ~15 days

Fig. 1: Prediction corrected VPC for RZ-358 in study 603

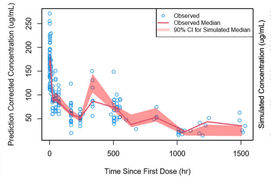


Fig.2: PK profile predictions utilizing the final 3-CMT model for a 75 kg reference subject

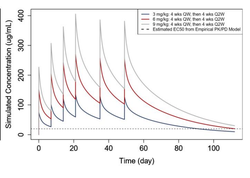


Table 2: Primary PK parameters for Final 3-CMT model

Primary Parameters	Estimates (Mean ± SE)	CV (%)	95% CI
Clearance (CL)	0.0089 ± 0.0003 (L/hr)	3.37	(0.0083, 0.0096)
Central Volume (V1)	2.7599 ± 0.0872 (L)	3.16	(2.5890, 2.9307)
Intercompartmental Clearance 2 (Q2)	0.0258 ± 0.0029 (L/hr)	11.24	(0.0200, 0.0315)
Peripheral Volume 2 (V2)	0.8704 ± 0.1524 (L)	17.51	(0.5717, 1.1691)
Intercompartmental Clearance 3 (Q3)	0.0127 ± 0.0016 (L/hr)	12.60	(0.0095, 0.0159)
Peripheral Volume 3 (V3)	2.2195 ± 0.1487 (L)	6.70	(1.9281, 2.5110)

Additional Model Features for 3 Compartment Model: Weight as covariate on CL, V1, and V3; Log additive residual error; Interindividual variability on CL, V1, V2, Q3

Assessment of PD Endpoints in PGBH Patients

Fig. 3: Plasma Glucose (Left) and Insulin (Right) before/after dosing with error bars representing 95% CI,*P<0.05 Unpaired t-test**

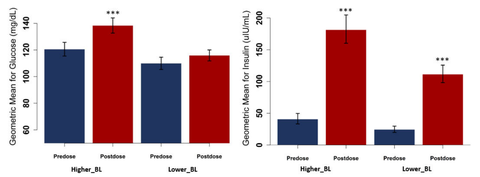
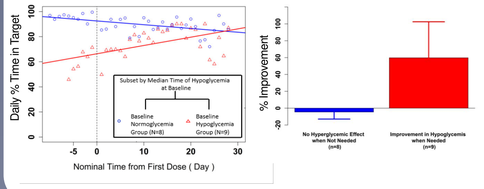


Fig. 4: Study 603 (PGBH) Median Daily (7:00 am to 11:00 pm) Percent Time in Glucose Target Range (70-180 mg/dL) (left) and Percent Improvement at Day 28 (right), by Baseline Hypoglycemia



RESULTS (CONT.)

PD Endpoints (Cont.) and Empirical PK/PD model of RZ358

Fig. 5: Percent of daily glucose AUC

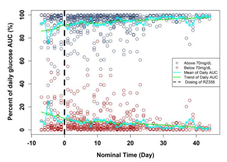


Fig.6: Empirical PK/PD Model

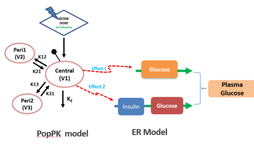
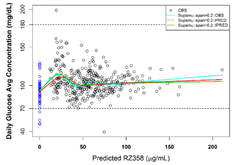


Table 3: Parameters in Empirical PK/PD model, with exposure predictions derived from a 3-CMT base model

Effects	Primary Parameters (Mean ± SE)
RZ358 on Glucose	GLU_BL1 = 91.8 ± 2.97 (mg/dL) E_{MAX_1} = 0.411 ± 0.0545 EC_{50_1} = 19.8 ± 11.4 (µg/mL)
RZ358 on Insulin	INS_BL =70.6 ± 9.90 (uIU/mL) E_{MAX_2} = 8.58 ± 0.00856 EC_{50_2} = 388 ± 118 (µg/mL)
Insulin on Glucose	GLU_BL2 = 130 (mg/dL, FIX) I_{MAX} = 0.151 (FIX) IC_{50} = 123 (µIU/mL, FIX) Gamma = 35.2 (FIX)

Fig. 7: PK/PD Model fitting plot of RZ358 on glucose in PGBH patients



CONCLUSIONS AND DISCUSSION

- Current therapies for PGBH have undesirable side effects and may be ineffective at controlling the disease, with surgery being the remaining option.
- RZ358 was generally safe and well-tolerated in PGBH patients with no discontinuations, deaths, or serious adverse reactions.
- RZ358 improves hypoglycemia without causing hyperglycemia (Fig. 4,5).
- RZ358 significantly increases plasma insulin by 4-fold due to reduced clearance of the IR, as supported by unchanged c-peptide (Fig.3). Increases in ketones and free fatty acids were also observed, as further biomarker evidence of decreased insulin activity (data not shown).
- The PK and PK/PD models generally described the data well (Fig. 1,7) and validate the applicability of the mechanism and therapeutic potential of RZ358 for treating hypoglycemia caused by varied conditions associated with hyperinsulinemia.
- 3 mg/kg once weekly of RZ358 may be sufficient to elicit effect (Fig.2), as the EC50 was estimated to be ~20 µg/mL.
- A Phase 2b study (RIZE) with RZ358 in patents with congenital HI is ongoing; Further studies in PGBH, as well as studies in insulinoma, are applicable and are being considered .

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