Single Dose Studies of RZ358 in Patients with Congenital Hyperinsulinism:

Results of Population PK/PD Modeling and Simulation in Adult and Pediatric Patients

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REZOLUTE

Disclosures

- Presenting author (BR) is an employee and stock-option holder of Rezolute, Inc.*
- KJ was an employee and stockholder of Xoma, Corp**
- DE, YH, and LQ are employees of A2PG (pharmacometrics consultants to Rezolute, Inc.)
- SC is founding employee of A2PG and stock-option holder of Rezolute, Inc.

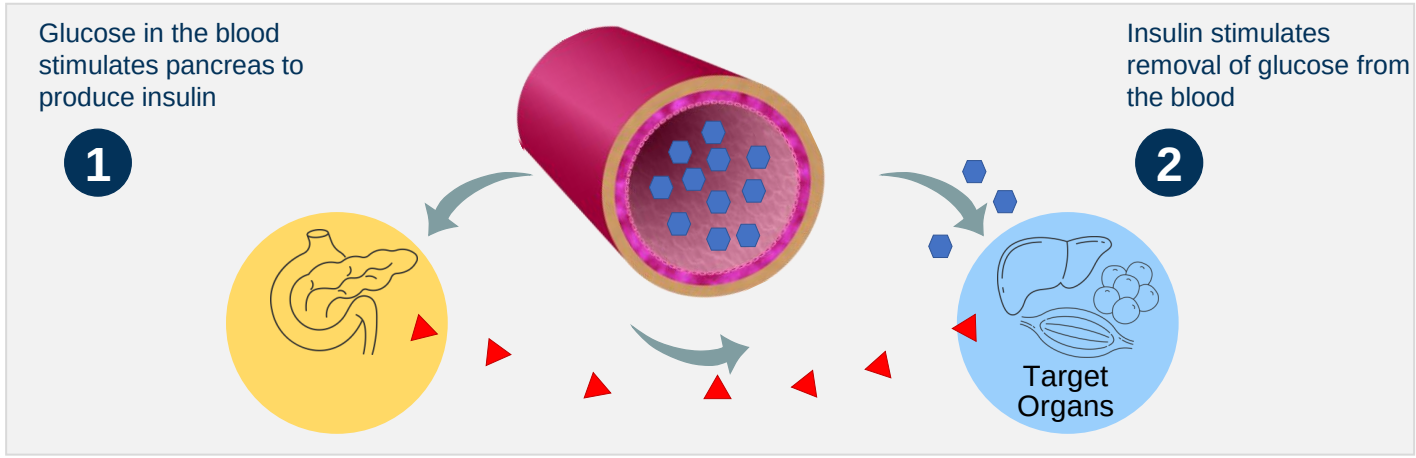
*Sponsor company with development/licensing rights to RZ358

**Discovered and developed RZ358 through out-licensing

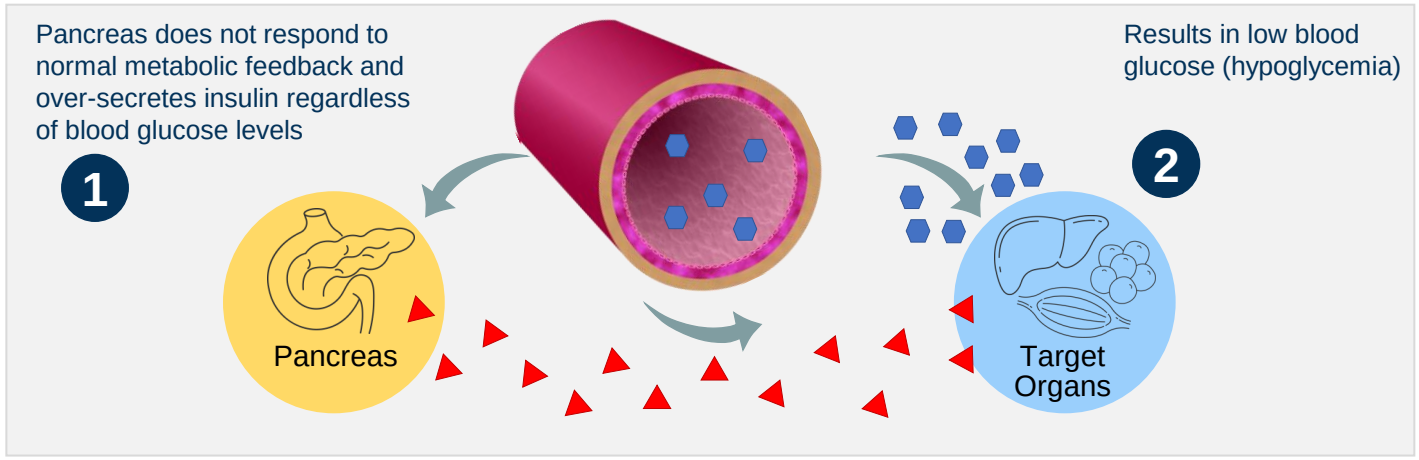
Congenital Hyperinsulinism (CHI): Background

- Ultra-rare disease
- 1 in 2,500 to 1 in 50,000 live births
- Caused by one of 11 known mutations, leading to excessive insulin secretion
- Most common cause of persistent hypoglycemia in infants and children
- Increases risk of neurologic complications, coma, and death
- Signs/symptoms often not recognized until life-threatening
- Patients and families live in fear of hypoglycemia
- Existing therapies are suboptimal

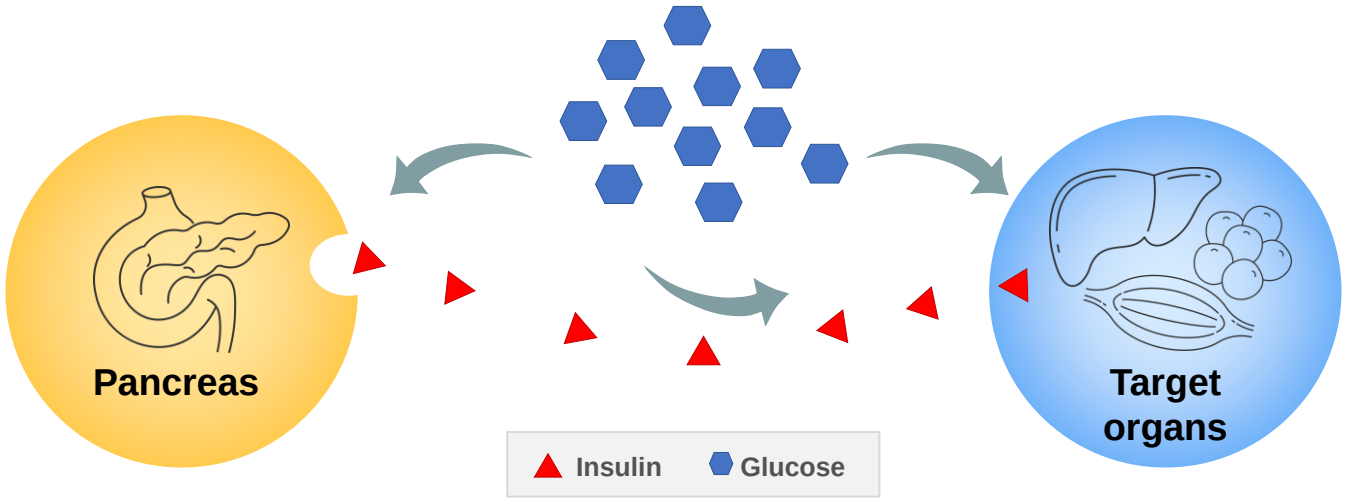
Normal Insulin-Glucose Feedback Loop



CHI

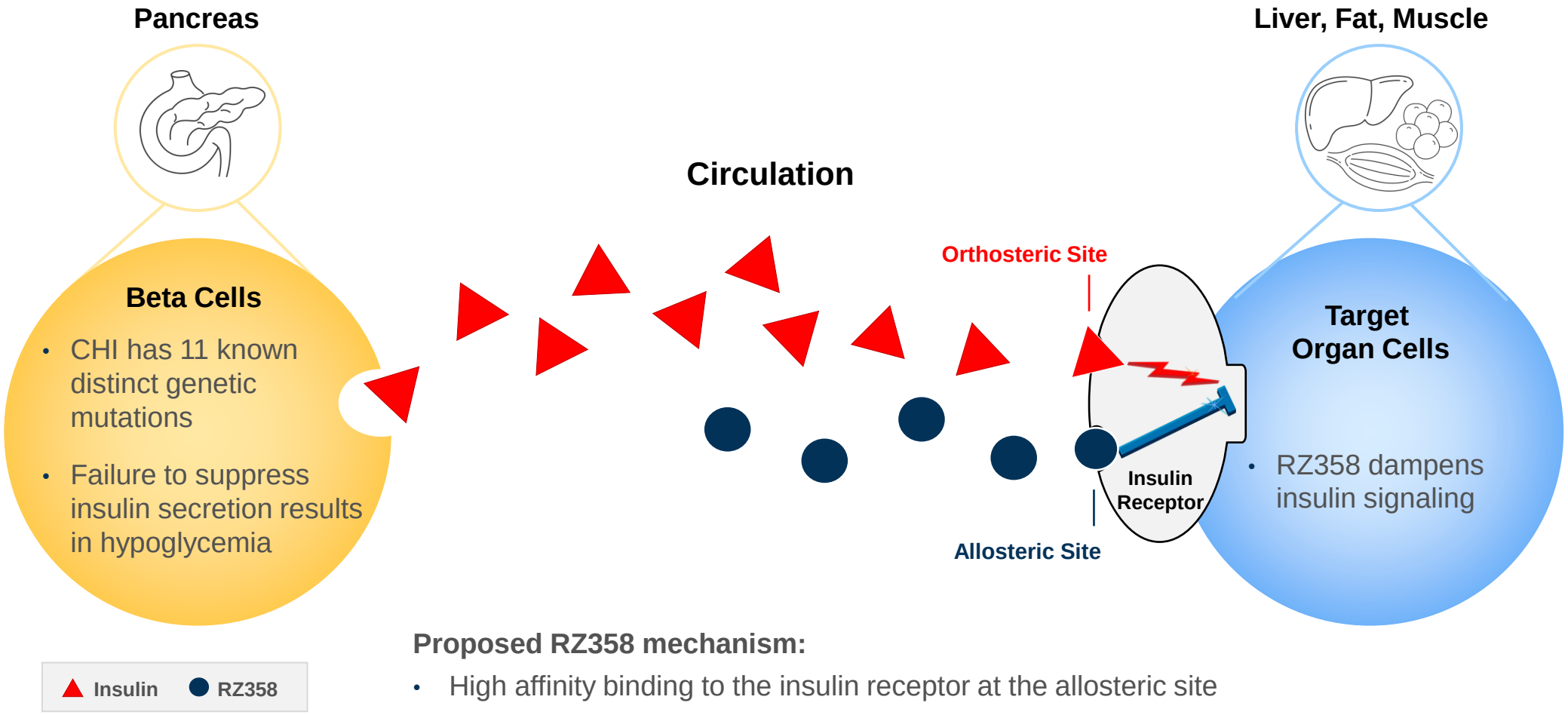


RZ358 Has Potential to Address Limitations of Current Standard of Care



	Current Standard of Care	RZ358
Targeting	Beta cells only	Insulin receptor/signal on insulin-dependent target organs
Development	Not developed for CHI	Tailored for CHI
Impact	Marginally effective, invasive, and/or significant AEs	Reversibly counteracts insulin only when insulin is elevated
Relevancy	Genetics-dependent narrow targeting	Potentially universal treatment

Unique Mechanism of RZ358 Attenuates Insulin Effects

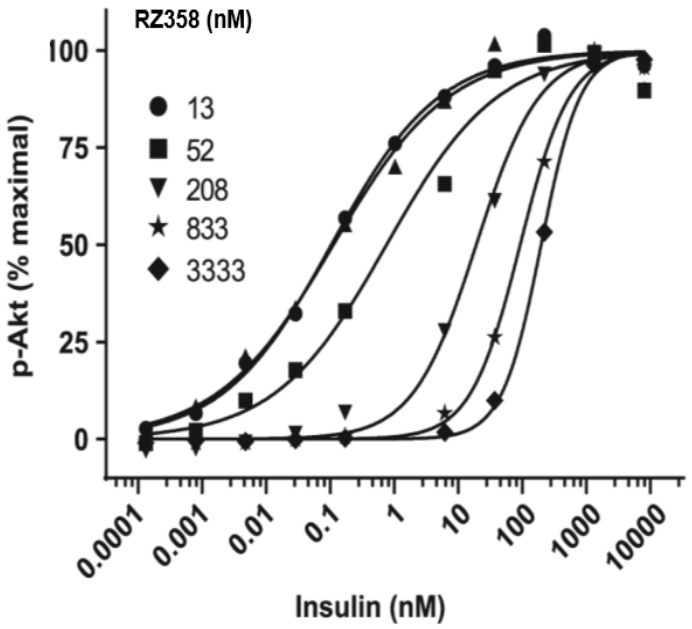


Proposed RZ358 mechanism:

- High affinity binding to the insulin receptor at the allosteric site
- High selectivity to the insulin receptor (no IGF-1 interaction)
- Insulin still binds and signals
- Dampens the insulin signal only when insulin is elevated

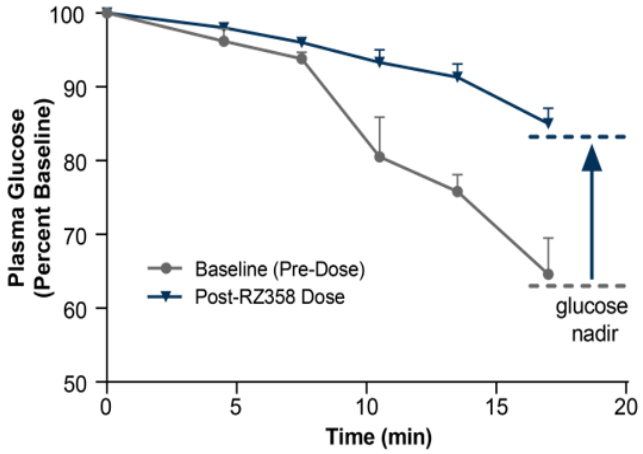
MAbs. 2014 Jan-Feb;6(1):262-72; J Diabetes Sci Technol. 2014 Jul;8(4):865-73

RZ358 In-Vitro and Human Proof of Mechanism

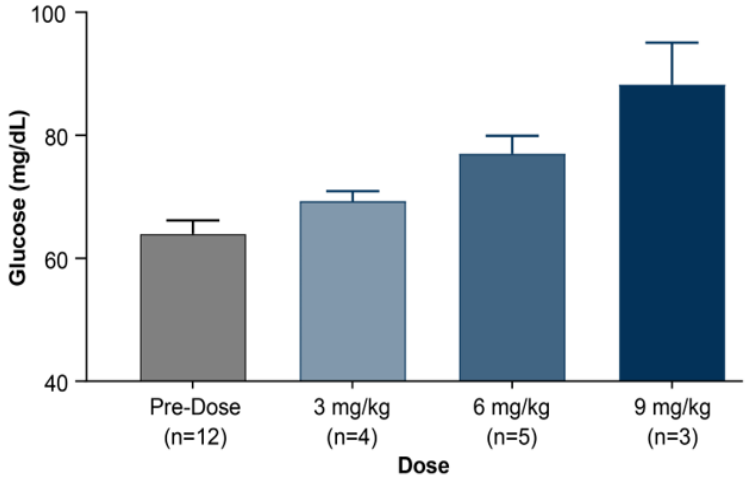


Phase 1 Insulin Tolerance Test (ITT)

ITT
(Illustrated by 3 mg/kg on Day 5)



Glucose Nadir During ITT
(Cumulative Timepoints, By Dose)



- Conducted at: baseline and on Days 1, 2, 3, 5, 7, 11, and 22 at the 3, 6, and 9 mg/kg dose levels
- On each ITT day, insulin administered at T_0 and glucose measured serially until nadir (e.g. figure)
- RZ358 blunted insulin-induced hypoglycemia
- No hyperglycemia observed

- PK-PD (Dose-response) correlation observed
- Effect persisted for 2 weeks
- PK/PD model shows potential for 1-2x monthly dosing

Clinical Studies X358601 and X358604

Overview of RZ358 Clinical Studies (Contributing to Pop PK-PD Model)

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)

Pediatric Subjects:

- 2 subjects in each study: 602 and 605
- Ages 12-13 with weight range 29.9-61.3 kg

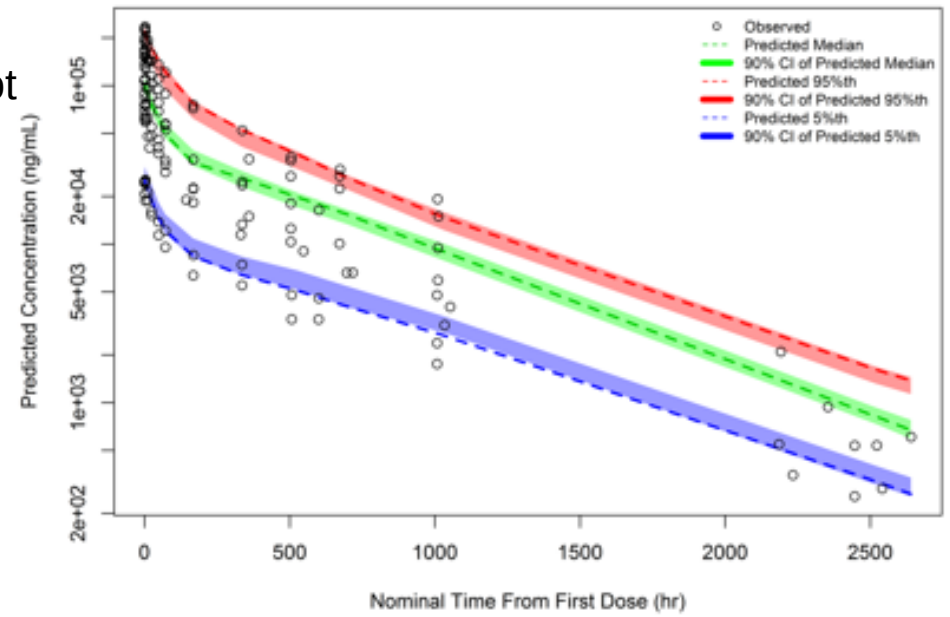
RZ358 Population Pharmacokinetics

- POPPK was performed with NONMEM software (Ver. 7.3) utilizing all clinical studies
- Final model: 2-CMT, first-order elimination, with WT as only covariate on CL and V terms
- Dose-proportional PK with effective half-life ~15 days.
- Patient population does not impact PK parameters
- Clinical data is described well by the model, as indicated by VPCs

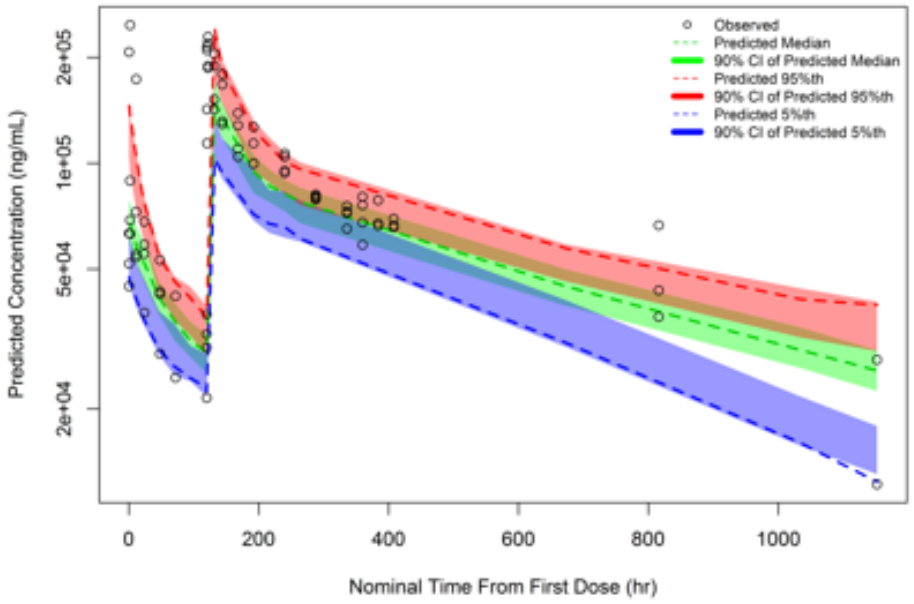
Primary Parameters	Estimates (Mean ± SE)	CV (%)	95% CI
CL	0.0091 ± 0.0003 (L/hr)	3.30	(0.0084 , 0.0097)
V1	2.83 ± 0.0836 (L)	2.95	(2.6673, 2.9952)
Q	0.0255 ± 0.0020 (L/hr)	7.84	(0.0216, 0.0294)
V2	2.8289 ± 0.1075 (L)	3.80	(2.6182, 3.0395)

Key	
CI	Confidence interval
CL	Clearance
2-CMT	Two-Compartment
CV	Coefficient of Variation
NONMEM	NONlinear Mixed Effects Modeling
PK	Pharmacokinetics
POPPK	Population pharmacokinetics
Q	Rate of clearance
VPC	Visual predictive check
V	Volume
WT	Weight

VPC- Final Model_STUDY 602



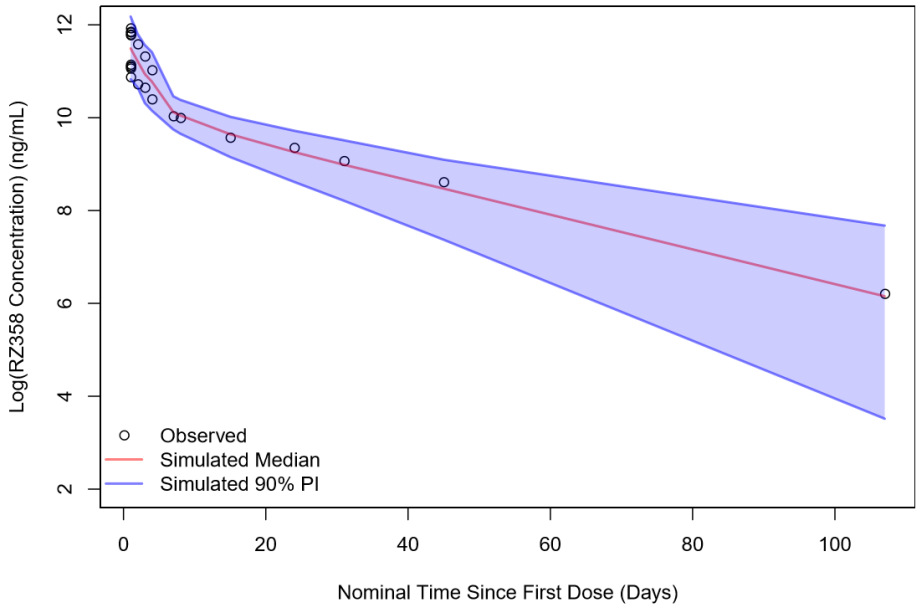
VPC- Final Model_STUDY 605



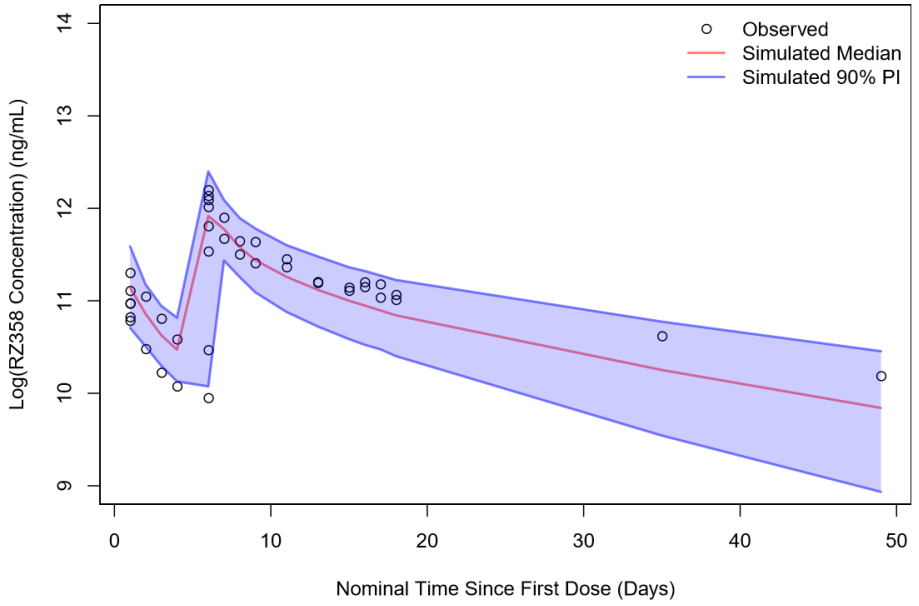
RZ358 Pediatric Pharmacokinetics

- Allometric scaling of adult CL and V adequately described pediatric PK through use of simulation
  - 1000 sets of simulated pediatric PK profiles generated from the scaled base model parameters
- Observed pediatric concentrations generally fall within the 90% prediction interval of simulated values
- RZ358 exposure is higher in pediatric subjects when corrected for dose

Study 602



Study 605



Key	
CI	Confidence interval
CL	Clearance
2-CMT	Two-Compartment
CV	Covariance
NONMEM	NONlinear Mixed Effects Modeling
PK	Pharmacokinetics
POPPK	Population pharmacokinetics
Q	Rate of clearance
VPC	Visual predictive check
V	Volume
WT	Weight

RZ358 Brings CHI Patients into Glucose Target Range

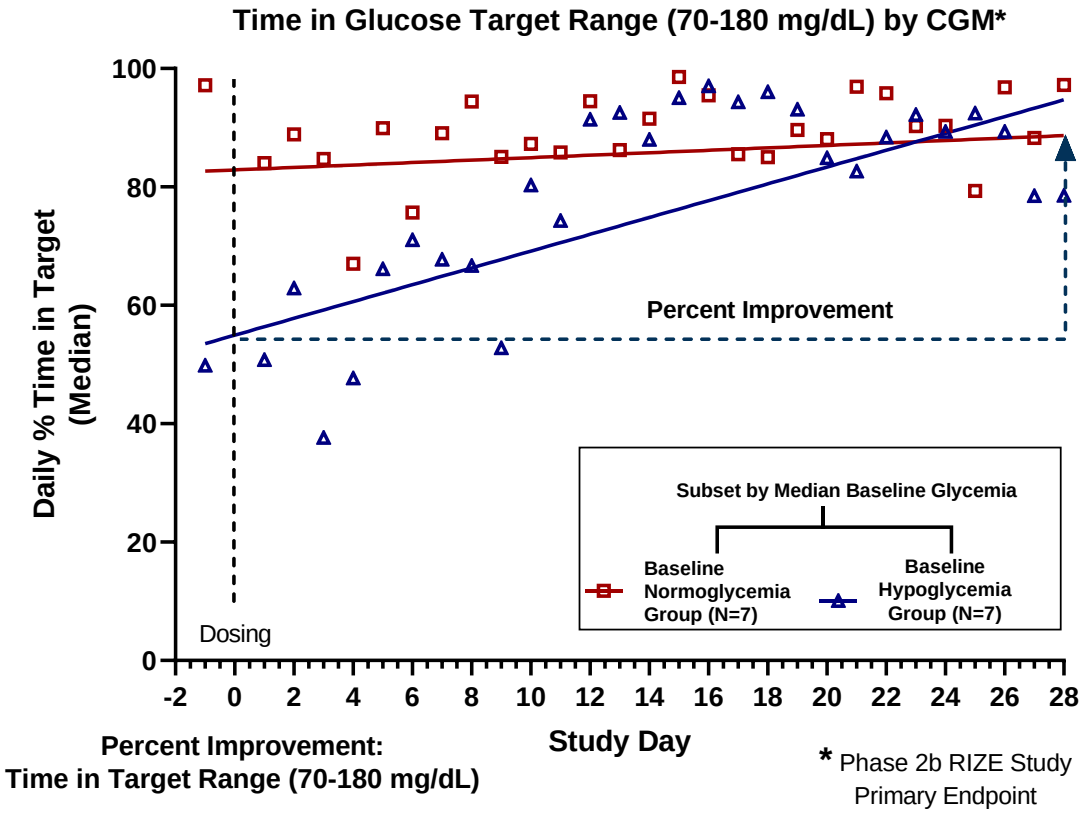
Design

- Single IV doses of 1 to 9 mg/kg in patients with CHI
- 14 patients; ages ≥ 12 in Europe and ≥ 18 in the US
- CHI patients by subgroup (median):
  - normal baseline glucose (n=7)
  - hypoglycemic at baseline (n=7)

Results

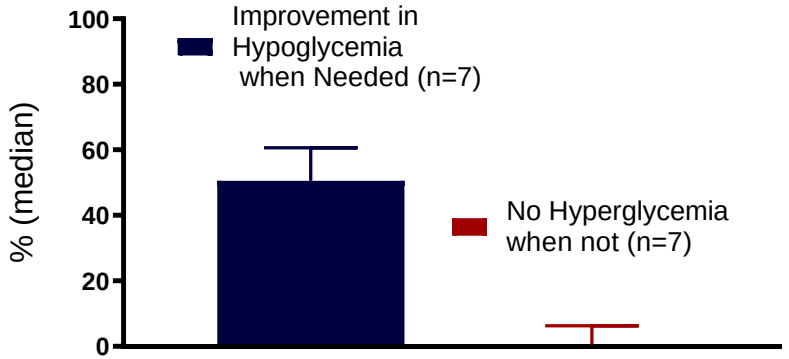
After a single dose of RZ358:

- 50% improvement for patients with baseline hypoglycemia
  - Achieved glucose normalization by 2 weeks
- No hyperglycemia in patients with normal baseline glucose
  - Confirmation of mechanism of action
- Effect persisted for 4 weeks, consistent with Phase 1 PK/PD
- Safe and well-tolerated
- Establishes strong proof of concept
- Informed Phase 2b entry criteria and endpoints



Percent Improvement: Time in Target Range (70-180 mg/dL)

* Phase 2b RIZE Study Primary Endpoint

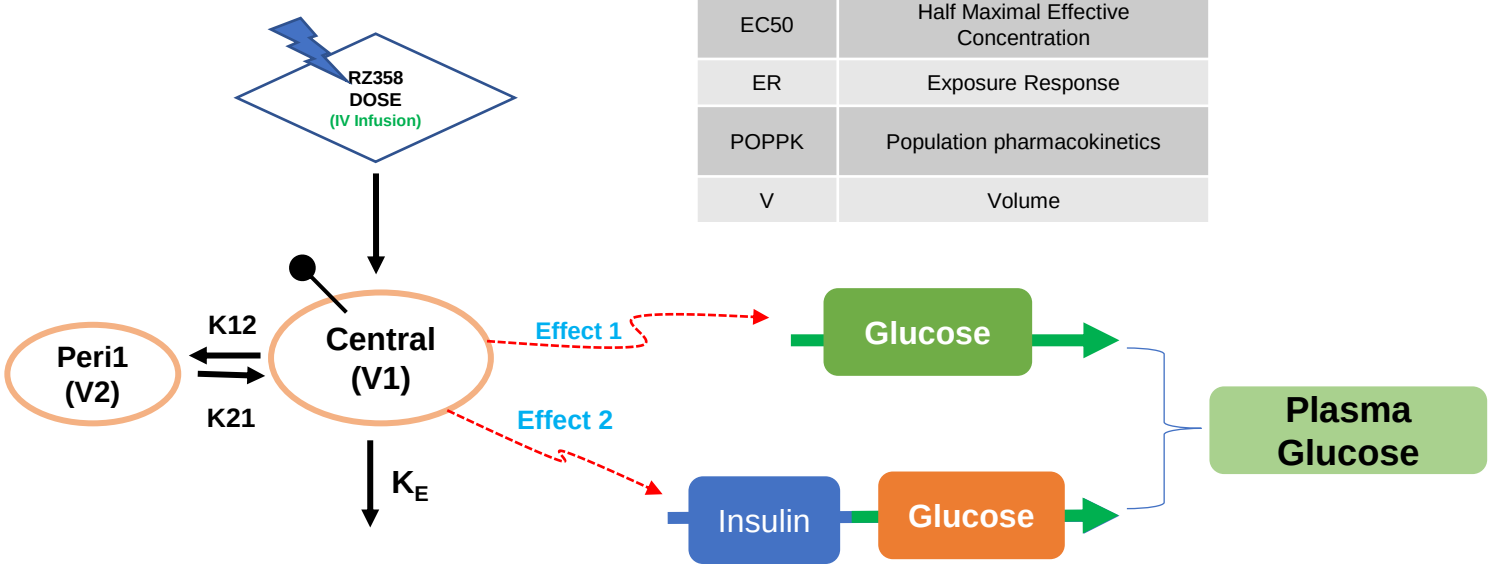


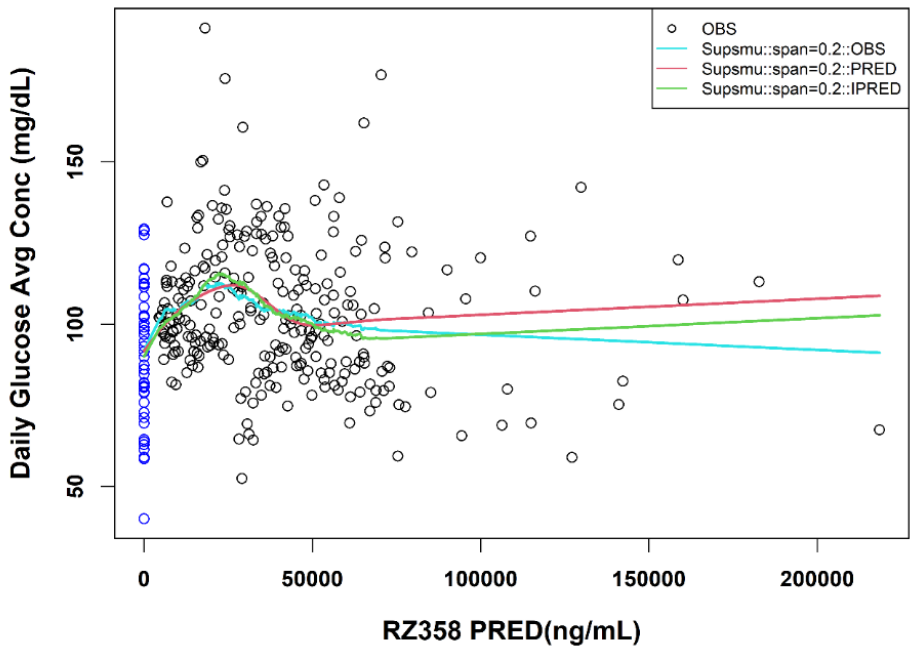
Key	
CGM	Continuous Glucose Monitoring
CHI	Congenital Hyperinsulinism

Clinical Study X358605; EudraCT Number: 2016-001275-80
Clinical Study X358602; EudraCT Number: EUDRACT 2015-002847-32

Empirical Exposure Response Model Characterizes RZ358 Target Concentrations

Key	
EC50	Half Maximal Effective Concentration
ER	Exposure Response
POPPK	Population pharmacokinetics
V	Volume





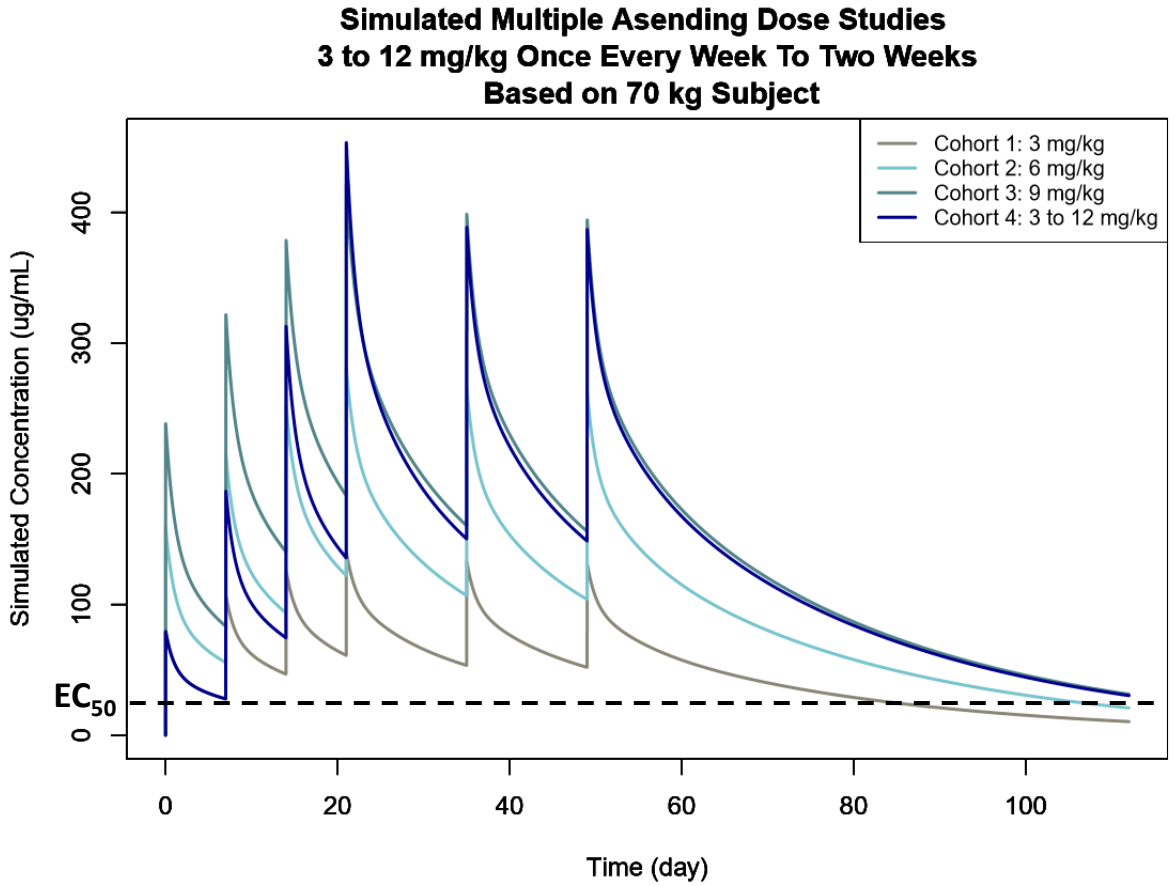
Effects	THETAs	ETAs
RZ358 on Glucose	GLU_BL1 = 91.8 ± 2.97 (mg/dL) E_{MAX} = 0.411 ± 0.0545 EC_{50} = 19.8 ± 11.4 (µg/mL)	GLU_BL1= 0.0149 E_{MAX}= 0 FIX EC_{50}= 0.00202
RZ358 on Insulin	INS_BL =70.6 ± 9.90 (µIU/mL) E_{MAX} = 8.58 ± 0.00856 EC_{50} = 388 ± 118 (µg/mL)	INS_BL= 0 FIX E_{MAX}= 0 FIX EC_{50}=0.000592
Insulin on Glucose	GLU_BL2 = GLU_BL1 E_{max} = 0.151 (FIX) EC_{50} = 123 (µIU/mL, FIX) Gamma = 35.2 (FIX)	E_{max}= 0 FIX EC_{50}= 0 FIX

Two opposing effects dictate plasma glucose levels:

- **Effect 1:** Attenuation of insulin signal increases glucose
- **Effect 2:** Drug-induced decrease in insulin clearance decreases glucose

Summary and Conclusions

- CHI is a devastating childhood disease with severe neurological outcomes and suboptimal therapies
- RZ358, as an allosteric modulator of the insulin receptor, is ideally suited as a potential universal treatment for CHI
- RZ358 was generally safe and well tolerated in clinical trials to date
- Population PK has provided the means of adequately describing pediatric concentration profiles through use of allometric scaling factors
- Exposure response (ER) modeling has demonstrated that the efficacy of RZ358 is dependent on both disease severity and exposure (dose), consistent with allosteric MOA.
- Model output (effective concentrations) suggests that 3 mg/kg may be a sufficiently effective dose (see figure)
- A Phase 2b multiple dose study is underway, to refine the dosing regimen



Based on EC_{50}, 3 mg/kg weekly expected to elicit a drug effect

Acknowledgements

- Phase 2a Study Investigators and their Teams:
  - Diva DeLeon (CHOP, USA)
  - Indi Banerjee (Royal Manchester Children's; Manchester, UK)
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- LifeSci Communications

Questions?