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RZ358-606 RIZE Study

An Open-Label Multiple-Dose Study of RZ358 in Patients with Congenital Hyperinsulinism

**RIZE Data Call**
**May 1, 2022**

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May 2022

# Forward Looking Statements

Statements in this presentation that are not descriptions of historical facts are forward-looking statements relating to future events, and as such all forward-looking statements are made pursuant to the Securities Litigation Reform Act of 1995. Statements may contain certain forward-looking statements pertaining to future anticipated or projected plans, performance and developments, as well as other statements relating to future operations and results. Any statements in this presentation that are not statements of historical fact may be considered to be forward-looking statements. Words such as "may," "will," "expect," "believe," "anticipate," "estimate," "intends," "goal," "objective," "seek," "attempt," or variations of these or similar words, identify forward-looking statements.

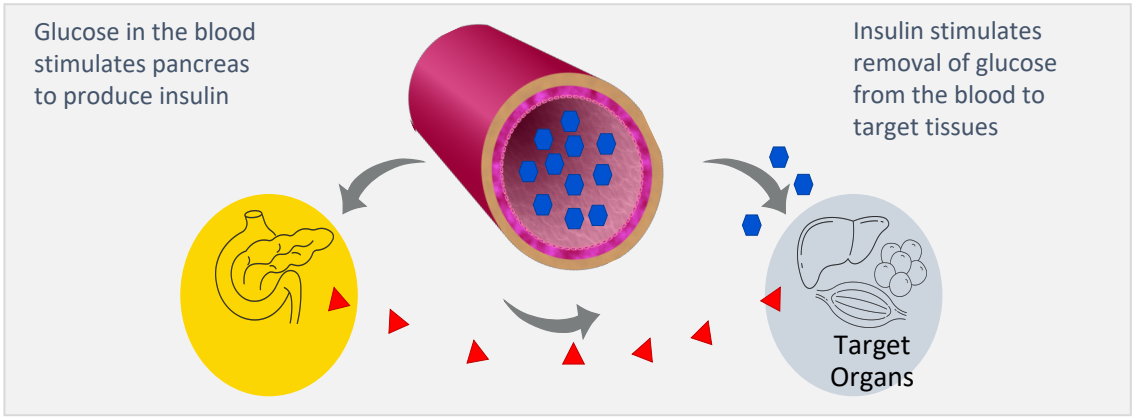
These forward-looking statements by their nature are estimates of future results only and involve substantial risks and uncertainties, including but not limited to risks associated with the uncertainty of clinical trial results, future financial results, additional financing requirements, development of new products, successful completion of the Company's proposed restructuring, the impact of competitive products or pricing, technological changes, the effect of economic conditions and other uncertainties detailed from time to time in our reports filed with the Securities and Exchange Commission.

Our actual results may differ materially from expectations based on the above factors and other factors more fully described in our public filings with the U.S. Securities and Exchange Commission, which can be reviewed at www.sec.gov

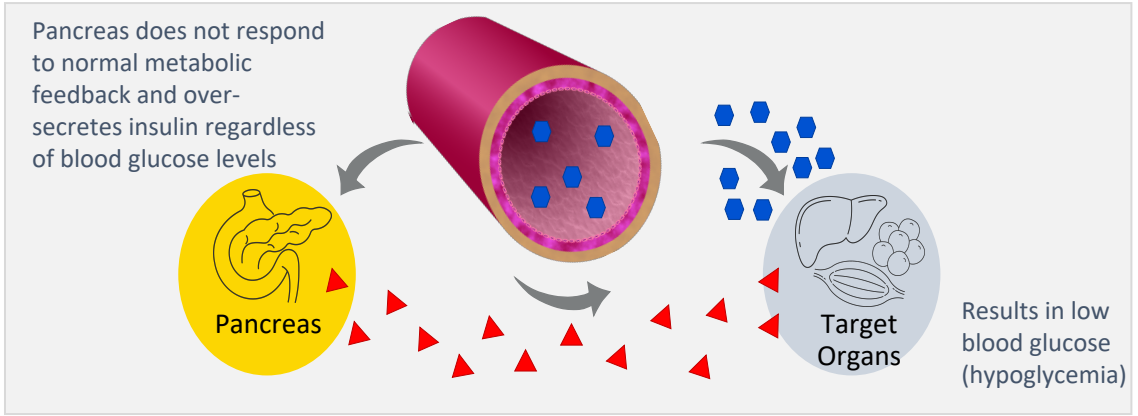
# Congenital Hyperinsulinism: Persistent Hypoglycemia Starves the Brain of Glucose

- Rare: 1 in 25,000 to 50,000 live births
- Characterized by excessive and uncontrolled pancreatic insulin secretion
- Most common cause of persistent hypoglycemia in infants and children
- Pediatric Endocrine Society recommends maintaining glucose above 70 mg/dL because low blood sugar:
  - Starves the brain of glucose
  - Creates risk of neurologic complications, coma, and death
- SOC inadequate; substantial unmet need
  - SOC therapies not developed for hyperinsulinism
  - Patients on SOC have substantial hypoglycemia
  - A ≥ 25% improvement in hypoglycemia from baseline is highly clinically meaningful and would be expected to translate to better outcomes for patients

## Normal Insulin-Glucose Feedback Loop




## Congenital HI




Insulin Glucose

# RIZE Study Summary

- Study was conducted primarily in a young pediatric population: average ~6.5 years of age
  - Diverse group of patients in the study across gender and genetics
  - Whether on SOC therapies, patients had to have substantial hypoglycemia to be enrolled
    - Patients enrolled had an average of 25% time in a hypoglycemic range at baseline
- RZ358 was generally safe and well-tolerated
- Expected RZ358 concentrations achieved
- Dose and exposure-dependent responses were observed
- RZ358 demonstrated:
  - ~50% improvement in hypoglycemia across all doses and cohorts
  - ~75% improvement in hypoglycemia at the 6 mg/kg and 9 mg/kg cohorts
    - These are the likely two dosing levels to be studied in Phase 3

# RZ358-606 RIZE Study

# A Phase 2b, Open-Label Multiple-Dose Study of RZ358 in Patients with Congenital Hyperinsulinism

## Topline Results

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# RZ358-606 Phase 2b (RIZE) Study Design

## Design

Open-label, repeat-dose study in 4 sequential ascending dosing cohorts (up to 8 patients per cohort)

## Population

CHI ≥ 2 years old with continued hypoglycemia on SOC, by specified continuous glucose monitoring (CGM) and self-monitored BG (SMBG) thresholds

## Duration

~26 weeks

- Screening – up to 5 weeks
- Treatment – 8 weeks
- Follow Up – 13 weeks

## Assessments / Endpoints

-Hypoglycemia Time by CGM
-Hypoglycemia events by CGM/BGM
-Time within range (70-180 mg/dL) by CGM

## Topline Results

Enable registrational Phase 3 planning and preparation for regulatory interactions

| Dosing Cohort | Dose Levels and Bi-Weekly Dosing Regimen (mg/kg) | | | |
|---|---|---|---|---|
| | Week 1 | Week 3 | Week 5 | Week 7 |
| **1** | 3 | 3 | 3 | 3 |
| **2** | 6 | 6 | 6 | 6 |
| **3** | 9 | 9 | 9 | 9 |
| **4** | 3 | 6 | 9 | 9 |

# Study Objectives and Endpoints

- Repeat-dose safety and pharmacokinetics (PK) in children
- Open-label, dose-ranging (3-9 mg/kg) to inform Phase 3
  - Dose or exposure-response relationship to validate the treatment effect
  - Fixed dose level(s) and dose regimen that optimize treatment and benefit across all patients
- Assessed glycemic efficacy across a range of CGM and BGM-based principle glycemic endpoints to inform Phase 3, including:
  - Time in Range (70-180mg/dL) [TIR] measured by continuous glucose monitoring (CGM)
  - Time in hypoglycemia measured by CGM
  - Hypoglycemia events measured by blood glucose monitoring (BGM)

# Patient Disposition and Study Status

| Disposition | N |
|---|---|
| Sites (Countries) that Enrolled | 12 (10) |
| Screened | 34 |
| Screen Failed | 11 |
| Enrolled | 23 |
| Completed Treatment and Efficacy Evaluable Period | 23 |
| Completed Study* (through 3-month follow-up) | 17 |
| Early Terminated | 0 |

**6 of the 23 enrolled patients are still in safety follow up period*

# Patient Demographics and Baseline Characteristics

| Parameter | Cohort 1: 3 mg/kg (N=4) | Cohort 2: 6 mg/kg (N=8) | Cohort 3: 9 mg/kg (N=8) | Cohort 4: 3-9 mg/g (N=3) | RZ358 Total (N=23) |
|---|---|---|---|---|---|
| **Age (Mean, Range)** | 5.8 (2-12) | 9.3 (2-22) | 5.8 (2-17) | 4.0 (2-6) | 6.7 (2-22); N=16 ages 2-6 |
| **Gender (n, M / F)** | 4 / 0 | 5 / 3 | 3 / 5 | 1 / 2 | 13 / 10 |
| **Genetics (n, kATP / Other / Unknown)** | 1 / 0 / 3 | 5 / 1 / 2 | 4 / 1 / 3 | 1 / 1 / 1 | 11 / 3 / 9 |
| **CHI Rx (n, %)** | 4 | 7 | 6 | 3 | 20 (87%) |
| Diazoxide | 2 | 3 | 1 | 2 | 8 (35%) |
| SSA (Long-acting/Short-Acting) | 2 / 0 | 1 / 2 | 3 / 4 | 1 / 0 | 7 / 6 (56%) |
| Other (inc 2+ meds, pancreatectomy, enteral feeding) | 0 | 2 | 6 | 1 | 9 (39%) |
| **% Time Hypoglycemia (<70 mg/dL) by CGM (Mean, Range, PP Population)** | 16 (12-20; n=4) | 22 (12-34; n=8) | 26 (6-86; n=7) | 29 (10-43) | 23 (6-86; n=22) |
| **Hypoglycemia Events / Wk by BGM (Mean, Range, PP Population)** | 10 (6-14; n=3) | 19 (5-78; n=8) | 17 (8-28; n=7) | 8 (5-11; n=3) | 16 (5-78; n=21) |

- Patients enrolled on stable background therapies had:
  - Clinically-significant, and in many cases, substantial residual hypoglycemia indicating an unmet treatment need
  - Some hyperglycemia (>180 mg/dL) at baseline

# RZ358 Was Generally Safe and Well Tolerated Across Doses

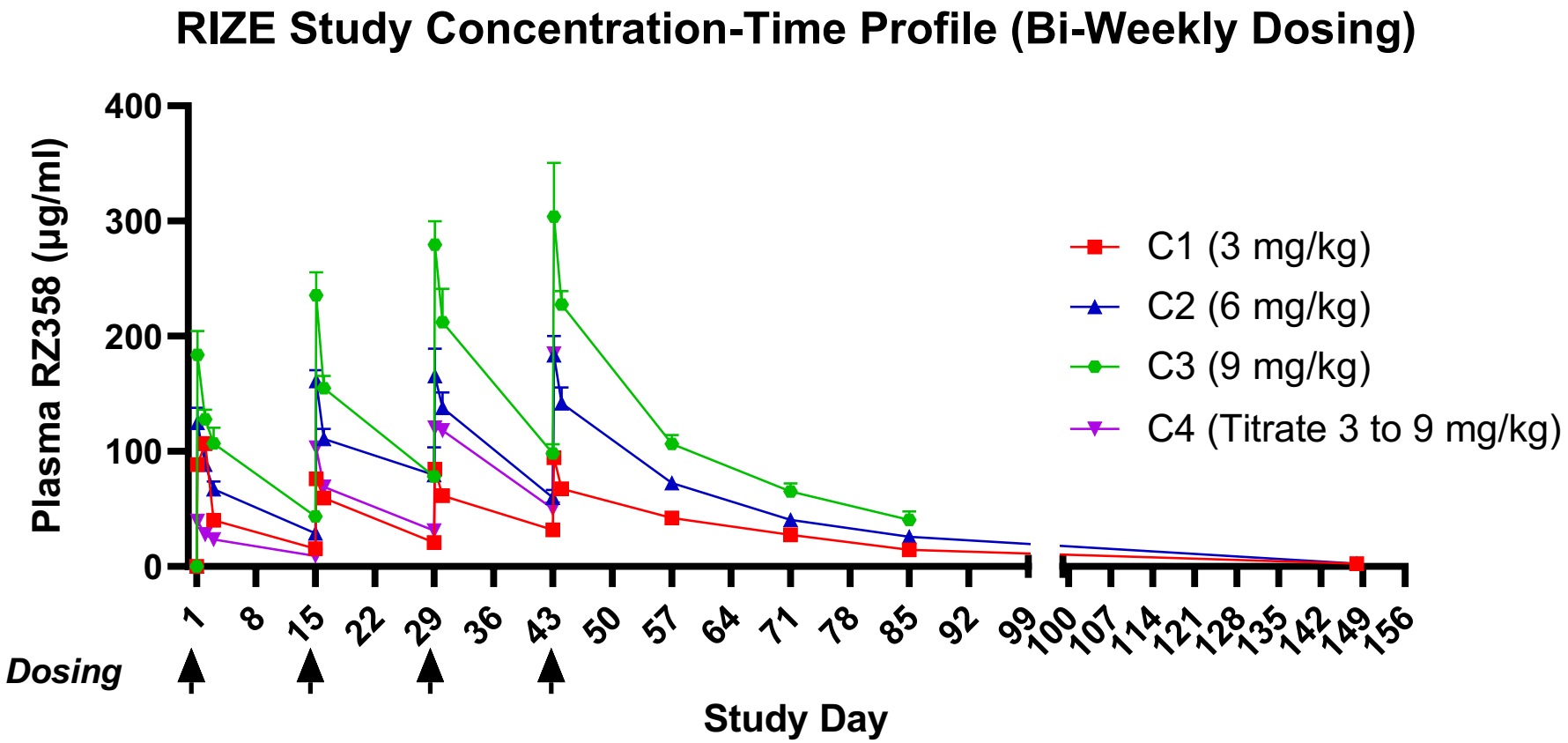
- No adverse drug reactions, AEs leading to study discontinuation, or dose-limiting toxicities
- In RZ358 treated subjects overall, 15 subjects (65%) experienced a total of 43 treatment-emergent AEs, compared to 10 subjects (43%) who experienced a total of 13 AEs outside of the defined treatment-emergent period (pre-treatment or >+42 days post-treatment)
  - No difference in time (or exposure)-adjusted AE rates
  - No dose-response
  - Generally mild and unrelated to study drug
  - No issues with GI tolerability
- Three patients experienced mild adverse events that were judged by Investigator(s) as related to study drug (hyperactivity, mild/transient infusion site rash, dizziness)
- Three patients experienced three unrelated SAEs (hospitalization), all deemed related to background conditions
- Mild hyperglycemia (>180 mg/dL) worsened from baseline in this patient group on SOC with some baseline hyperglycemia
- No increase from baseline in clinically relevant hyperglycemia (≥ 250 mg/dL) and no hyperglycemia AEs or adverse metabolic changes

# Treatment Emergent Adverse Event Overview

| | Non-TEAE (Pre/42d Post-Rx) (n=23) | RZ358 3 mg/kg (n=4) | RZ358 6 mg/kg (n=8) | RZ358 9 mg/kg (n=8) | RZ358 Titrate (n=3) | RZ358 Total TEAE (n=23) |
|---|---|---|---|---|---|---|
| **Subjects with Adverse Events (AEs), n (%)** | 10 (43%) | 2 (50%) | 7 (87%) | 4 (50%) | 2 (50%) | 15 (65%) |
| Total AEs | 13 | 2 | 30# | 7 | 4 | 43 |
| **Subjects with Serious AEs (SAEs), n (%)** | 0 (0%) | 0 (0%) | 2 (25%) | 1 (13%) | 0 (0%) | 3 (13%) |
| Total SAEs | 0 | 0 | 2 | 1 | 0 | 3 |
| **Subjects with PI-Judged Related AEs, n (%)** | n/a | 0 (0%) | 2 (25%) | 1 (13%) | 0 (0%) | 3 (13%) |
| Total Related AEs | n/a | 0 | 3 | 1 | 0 | 4 |
| **Subjects with AEs by Severity, n (%)** | | | | | | |
| Grade 1 | 8 (35%) | 2 (50%) | 7 (87%) | 2 (25%) | 2 (50%) | 13 (57%) |
| Grade 2 | 2 (9%) | 0 (0%) | 3 (38%) | 1 (13%) | 0 (0%) | 4 (17%) |
| ≥ Grade 3 | 1 (4%) | 0 (0%) | 2 (25%) | 1 (13%) | 0 (0%) | 3 (13%) |
| **Subjects Discontinued due to AEs, n (%)** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

*# Majority of AEs in Cohort 2 were mild, judged unrelated to study drug, and experienced by 2 patients.*

# Dose-Dependent and Predictable Drug Concentrations



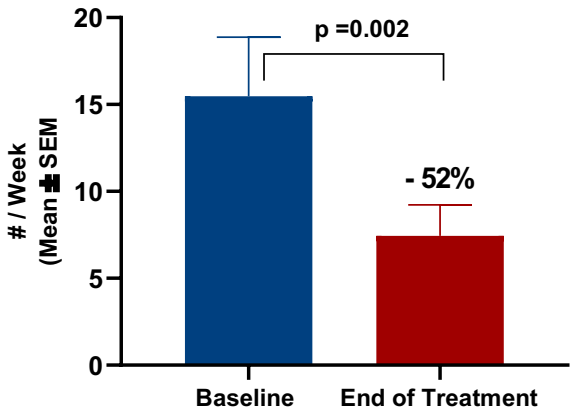

- Dependable concentrations independent of congenital HI patient factors (absorption, PO aversion, GI tolerability, etc)
- Half-Life > 2 weeks
- No apparent age dependencies
- Well below exposures in monkey toxicology studies (≥ 4-fold margin at highest dose)

# Topline Glycemic Results: Far Exceeded Expectations

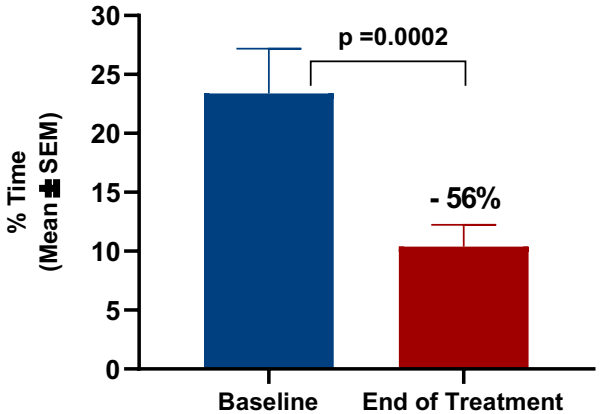
- Low starting dose (3 mg/kg) was selected for safety with minimal expectations for efficacy
  - Notably, an improvement in hypoglycemia of ~25% was achieved
- Improvements in hypoglycemia of ~75% at the mid (6 mg/kg) and top doses (9 mg/kg) and a high patient response rate
  - Improvements were comparable between both BGM (hypoglycemia events) and CGM (hypoglycemia time)
- Better than expected hypoglycemia correction resulted in an increase from baseline in mild, self-limiting, non-clinically meaningful hyperglycemia in patients taking background therapies
  - TIR (70-180 mg/dL) by CGM improved 8% across all doses, 16% at the top dose, and more significantly (>25%) in patients without baseline hyperglycemia on SOC
- Clear dose-response observed
- Results demonstrate that RZ358 can be administered at fixed dose levels with the potential to be an effective combination or monotherapy in all patients with congenital and syndromic HI

# Expectations of ≥ 25% Hypoglycemia Correction (Time and Events) Were Met and Exceeded Across Multiple Metrics

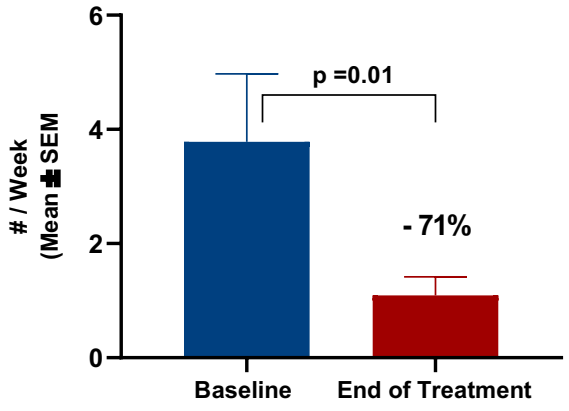
**Hypoglycemia Event Rate by BGM**
**(Events Per Week <70 mg/dL) [N=21]**



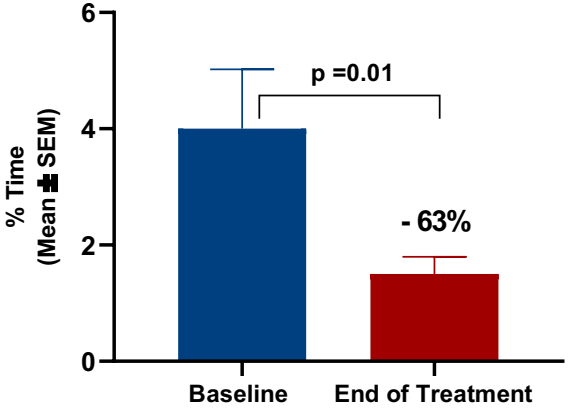

**Hypoglycemia Duration by CGM**
**(Percent Time <70 mg/dL) [N=22]**




**Severe Hypoglycemia Event Rate by BGM**
**(Events Per Week <50 mg/dL) [N=21]**




**Severe Hypoglycemia Duration by CGM**
**(Percent Time <50 mg/dL) [N=22]**

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# Highly Significant Dose-Dependent Improvements in Hypoglycemia Events (BGM) and Time (CGM) Exceeded Study Expectations

| Mean (Range) | RZ358 3 mg/kg (n=4) # | RZ358 6 mg/kg (n=8) | RZ358 9 mg/kg (n=7) ^ | RZ358 Titrate (3-9 mg/kg) (n=3) | RZ358 Total Pooled (n=22) |
|---|---|---|---|---|---|
| **Time in Hypoglycemia (<70 mg/dL) by CGM (%)** | | | | | |
| Baseline | 16.1 | 22.2 | 26.5 | 29.1 | 23.3 (6-86) |
| End of Treatment | 10.5 | 9.2 | 9.4 | 15.8 | 10.4 (0.3-33) |
| ***% Change from BL (p-value)*** | ***-35% (p=0.05)*** | ***-59% (p<0.01)*** | ***-65% (p=0.07)*** ^ | ***-46% (p=0.10)*** | **-56% (p=0.0002)** |
| **Time in Severe Hypoglycemia (<50 mg/dL) by CGM (%)** | | | | | |
| Baseline | 1.8 | 5.1 | 4.3 | 3.3 | 3.9 (0-21) |
| End of Treatment | 1.3 | 1.4 | 1.7 | 1.6 | 1.5 (0-5) |
| ***% Change from BL (p-value)*** | ***-25% (NS)*** | ***-73% (p<0.05)*** | ***-61% (NS)*** ^ | ***-52% (NS)*** | **-63% (p=0.01)** |
| **Hypoglycemia Events (<70 mg/dL) by BGM (events/week)** | | | | | |
| Baseline | 10.1 | 19.2 | 16.7 | 8.0 | 15.5 (4.5-77.8) |
| End of Treatment | 7.8 | 9.9 | 5.3 | 5.3 | 7.5 (0-30.3) |
| ***% Change from BL (p-value)*** | ***-22% (NS)*** | ***-48% (p=0.1)*** | ***- 68% (p<0.01)*** | ***-34% (p<0.05)*** | ***-52% (p=0.002)*** |
| **Severe Hypoglycemia Events (<50 mg/dL) by BGM (events/week)** | | | | | |
| Baseline | 1.6 | 5.5 | 4.2 | 0.5 | 3.8 (0.5-23.8) |
| End of Treatment | 1.5 | 1.2 | 1.1 | 0.4 | 1.1 (0-5.5) |
| ***% Change from BL (p-value)*** | ***-8% (NS)*** | ***-77% (p=0.1)*** | ***- 74% (p<0.05)*** | ***-20% (NS)*** | ***-71% (p=0.01)*** |

# One patient at 3 mg/kg was excluded from the per protocol BGM analyses for failing to meet pre-specified minimum glucometer testing

^ One patient at 9 mg/kg was excluded from the per protocol CGM and BGM analyses for stopping background therapy while on study; Two 2 year-old patients in 9 mg/kg group wore CGM on the arm which may have impacted their results, but were included in analysis

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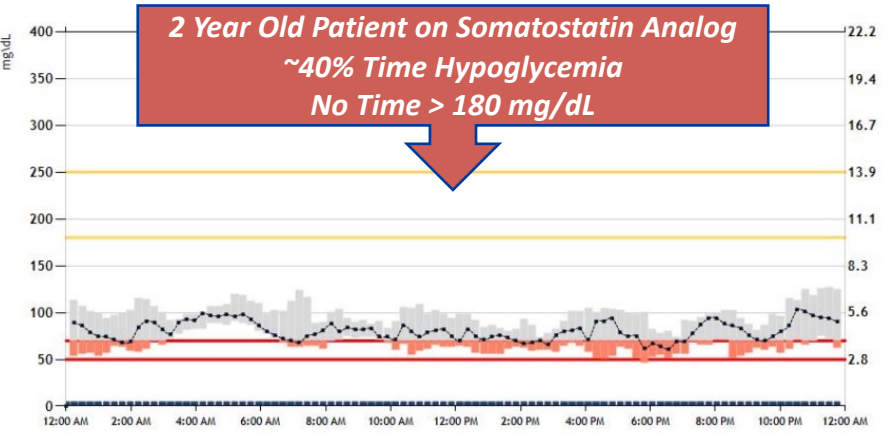
# High Patient Response Rate at Clinically-Relevant Correction Thresholds

| Responders N (%) | RZ358 3 mg/kg (n=4) # | RZ358 6 mg/kg (n=8) | RZ358 9 mg/kg (n=7) ^ | RZ358 Titrate 3-9 mg/kg (n=3) | RZ358 Total (n=22) |
|---|---|---|---|---|---|
| | | | | | |
| **≥25% Correction of Hypoglycemia** | | | | | |
| **Severe (<50 mg/dL)** | 3 (75%) | 7 (88%) | 7 (100%) | 2 (67%) | 19 (86%) |
| **Overall (<70 mg/dL)** | 3 (75%) | 7 (88%) | 7 (100%) | 3 (100%) | 20 (91%) |
| | | | | | |
| **≥50% Correction of Hypoglycemia** | | | | | |
| **Severe (<50 mg/dL)** | 3 (75%) | 6 (75%) | 7 (100%) | 2 (67%) | 18 (82%) |
| **Overall (<70 mg/dL)** | 1 (25%) | 7 (88%) | 7 (100%) | 1 (33%) | 16 (73%) |
| | | | | | |
| **≥75% Correction of Hypoglycemia** | | | | | |
| **Severe (<50 mg/dL)** | 1 (25%) | 5 (63%) | 6 (86%) | 2 (67%) | 14 (64%) |
| **Overall (<70 mg/dL)** | 1 (25%) | 3 (38%) | 5 (71%) | 1 (33%) | 10 (45%) |

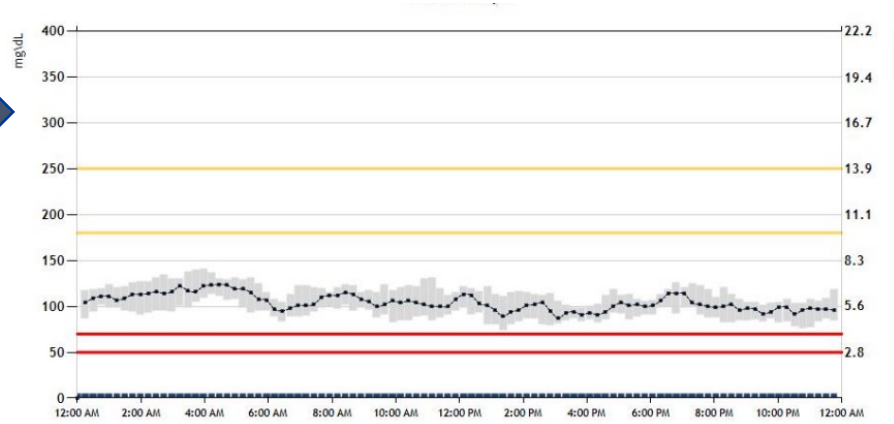
# Potential for RZ358 to be an Effective Monotherapy Treatment

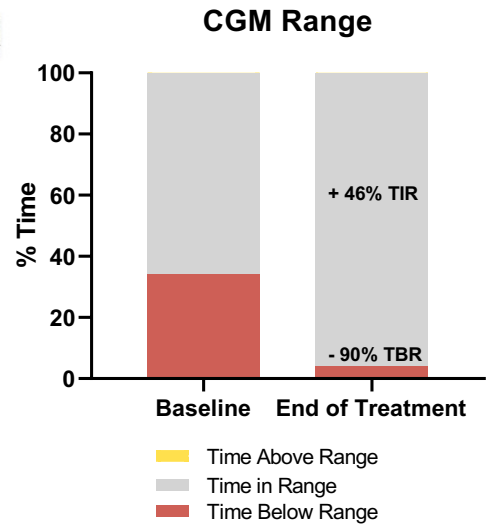
*2 Year Old Patient on Somatostatin Analog*
*~40% Time Hypoglycemia*
*No Time > 180 mg/dL*




+ RZ358
(6 mg/kg)

ABOVE HIGH THRESHOLD
75TH PERCENTILE
MEDIAN
25TH PERCENTILE
BELOW LOW THRESHOLD

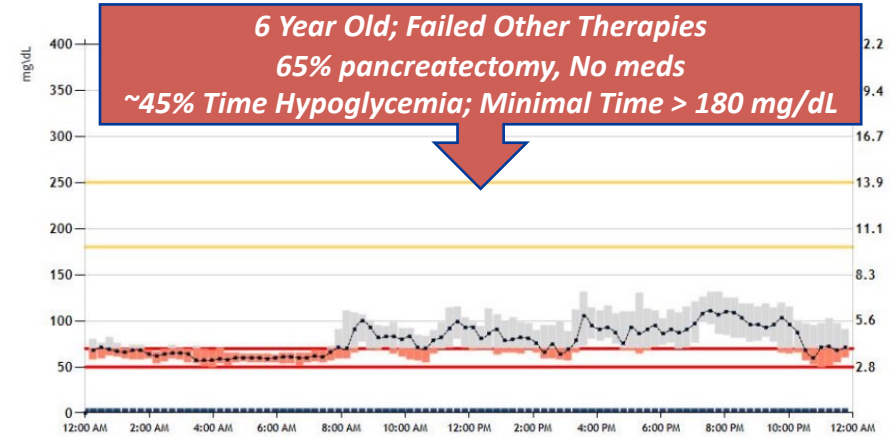



Baseline CGM period (≥ 10 days)

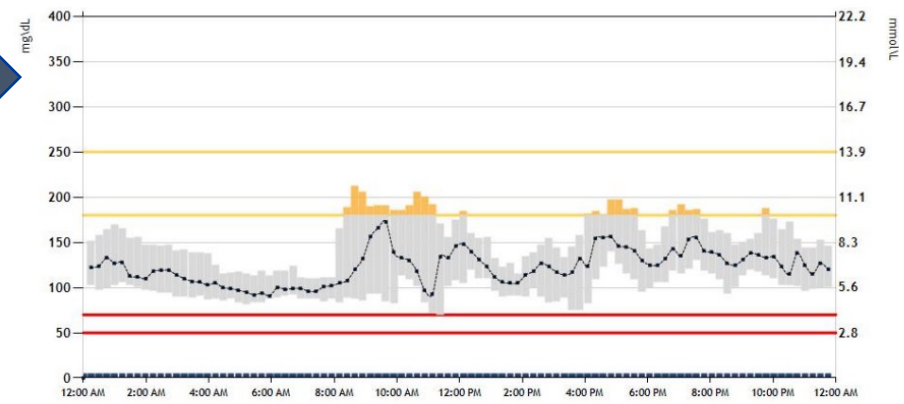
Treatment Evaluable CGM period (2-weeks)

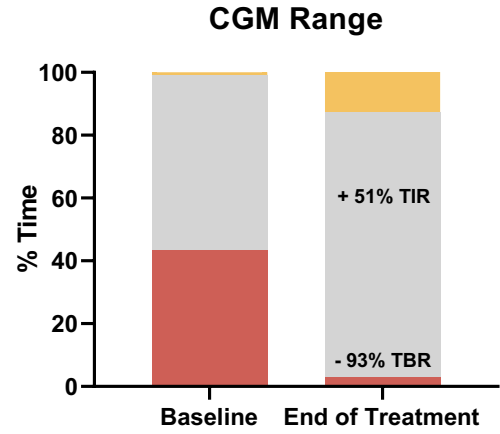
*6 Year Old; Failed Other Therapies*
*65% pancreatectomy, No meds*
*~45% Time Hypoglycemia; Minimal Time > 180 mg/dL*




+ RZ358
(9 mg/kg)

ABOVE HIGH THRESHOLD
75TH PERCENTILE
MEDIAN
25TH PERCENTILE
BELOW LOW THRESHOLD

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# Summary of Results

- RZ358 was safe and effective in a diverse group of congenital HI patients (across age, gender, and genetics) who had continued hypoglycemia and some hyperglycemia on background SOC
- Improvements in hypoglycemia of ~75% at the mid (6 mg/kg) and top doses (9 mg/kg) and a high patient response rate
  - Improvements were comparable by both BGM (hypoglycemia events) and CGM (hypoglycemia time)
- Better than expected hypoglycemia correction resulted in mild, self-limiting, non-clinically meaningful hyperglycemia in patients taking background therapies
  - TIR (70-180 mg/dL) by CGM improved 8% across all doses, 16% at the top dose, and more significantly (>25%) in patients without baseline hyperglycemia on SOC
- Clear dose-response observed
- Results demonstrate the potential for RZ358 to be an effective combination or monotherapy for patients with congenital and syndromic HI