Results from a Global, Multi-Center, Phase 2b Study (RIZE) in Congenital Hyperinsulinism: Characterization of a High Unmet Treatment Need and Glycemic Response to RZ358

Presenting Author: Hüseyin Demirbilek

ESPE 2022

DISCLOSURE STATEMENT

Dr. Hüseyin Demirbilek

✓ I have the following potential conflicts of interest to report:

- ✓ Research Contracts
- □ Consulting
- □ Employment in the Industry
- □ Stockholder of a healthcare company
- □ Owner of a healthcare company
- □ Other(s) – *NONE*

□ I declare that I have no potential conflict of interest.

Congenital Hyperinsulinism (HI)

Epidemiology

- Ultra-rare disease - 1 in 25,000 to 1 in 50,000 live births

Disease Characteristics

- At least 16 known genetic mutations
- 50% of patients with unknown genetics
- Dysregulated insulin secretion from pancreatic beta cells regardless of blood sugar levels

Persistent Hypoglycemia

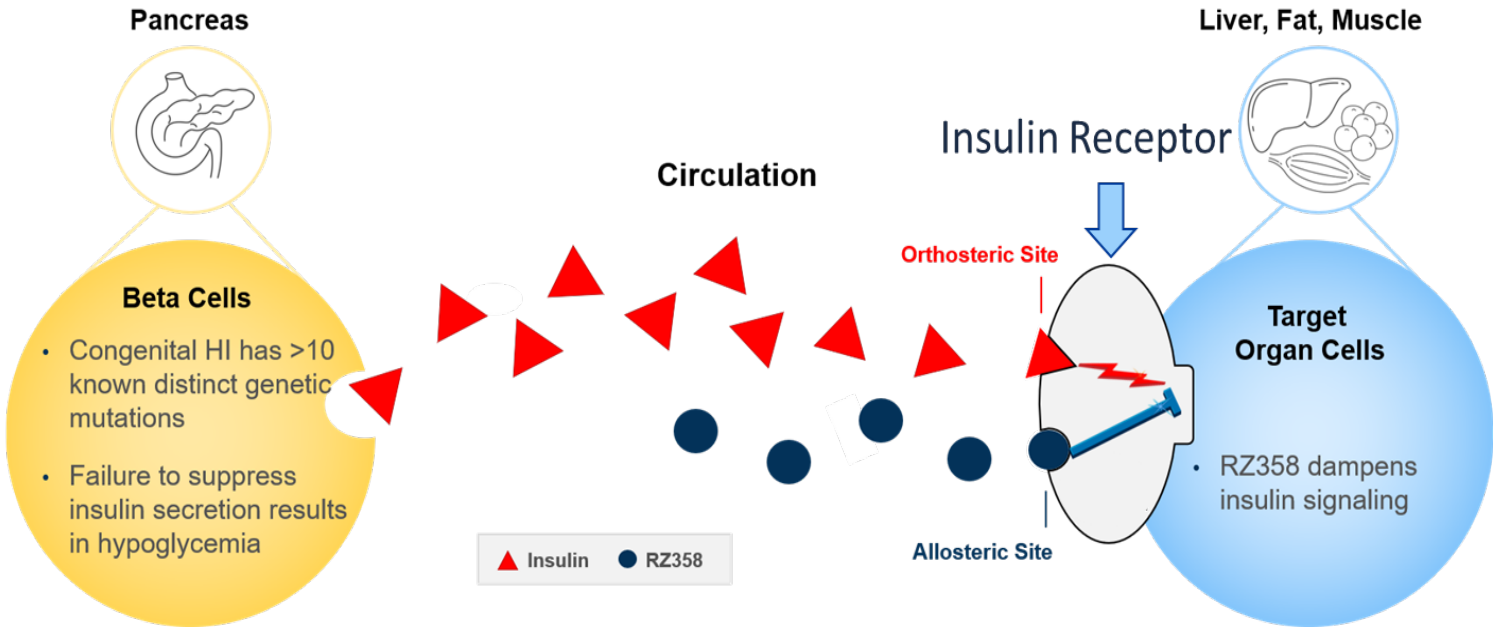
- Most common cause of persistent, recurrent hypoglycemia in infants and children
  - The HI brain starves in states of hypoglycemia as alternative fuels are also low
  - Signs are often difficult to recognize until life-threatening
  - If not detected early and properly treated, neurological complications, coma, and death can occur

Current Standard of Care (SOC)

- Existing therapies are suboptimal due to side effects and significant persistent hypoglycemia
- Lives of patients and families revolve around the avoidance and fear of hypoglycemia

RZ358: Novel Mechanism for the Treatment of Hyperinsulinism

- Humanized IgG2 monoclonal antibody
- Negative Allosteric Modulator: reversibly counteracts insulin at a distinct site at the Insulin Receptor
  - Discovered and developed specifically for hyperinsulinism
  - Downstream from pancreas, not genetics-dependent
- Administered as 30 min IV infusion every 2 weeks
- Clinical experience in 80+ participants: favorable PK/PD, no safety signals to date
- Phase 2b (RIZE) study data available



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

Design

-Open-label

-4 sequential dose cohorts (up to 8 patients/cohort)

-Every other week dosing

Key Eligibility Criteria

-CHI 2-45 years old

-Continued hypoglycemia on stable background SOC, confirmed by CGM and glucometer/BGM

Duration

~26 weeks

- Screening – up to 5 weeks
- Treatment – 8 weeks
- Follow Up – 3 months

Assessments / Endpoints

-Time in Hypoglycemia by CGM

-Hypoglycemia events by CGM/BGM

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

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

RIZE Study: Demographics and Baseline Characteristics

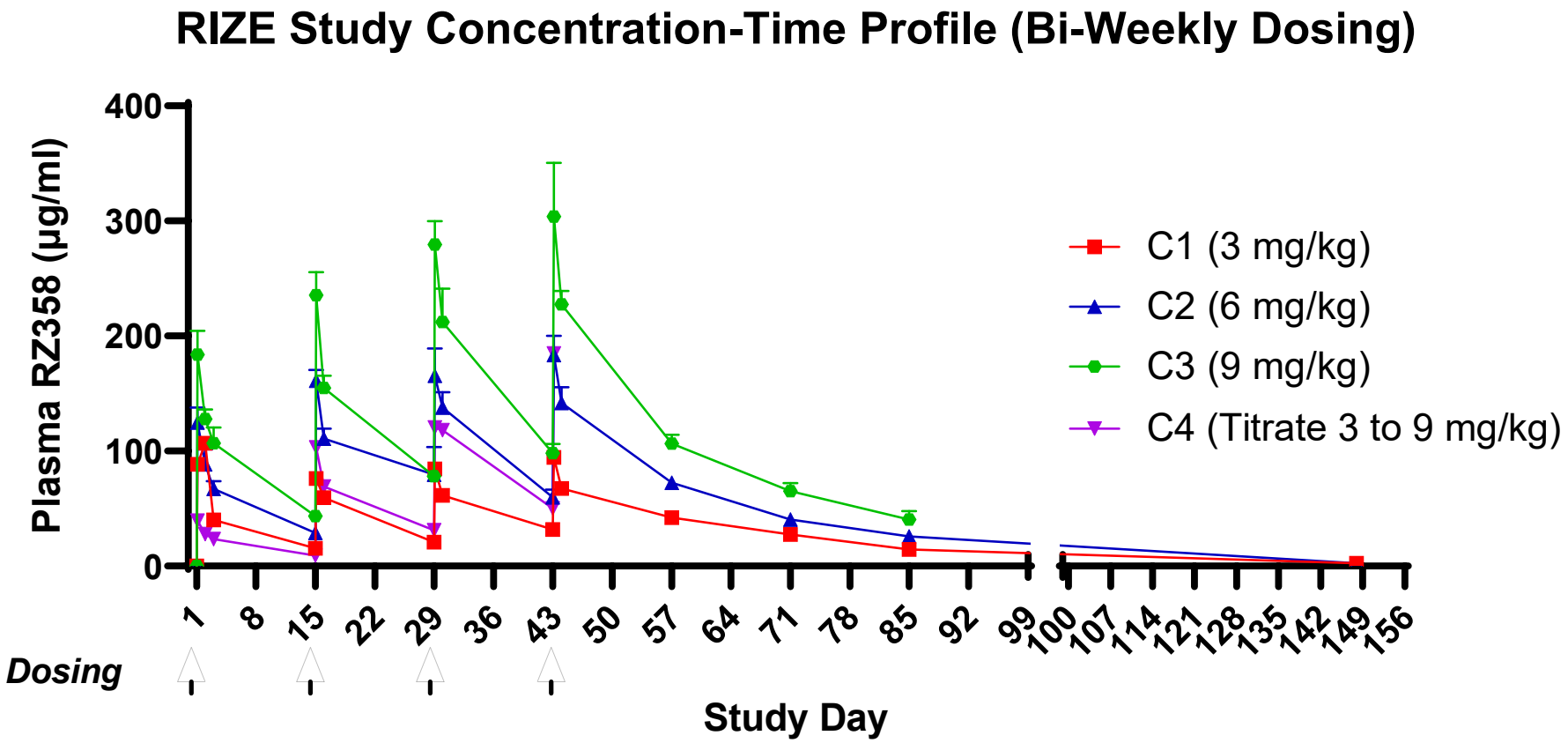
Parameter	Cohort 1: 3 mg/kg (N=4)	Cohort 2: 6 mg/kg (N=8)	Cohort 3: 9 mg/kg (N=8)	Cohort 4: 3-9 mg/g (N=3)	RZ358 Total (N=23)
Age (Mean, Range)	5.8 (2-12)	9.3 (2-22)	5.8 (2-17)	4.0 (2-6)	6.7 (2-22); N=16 ages 2-6
Gender (n, M / F)	4 / 0	5 / 3	3 / 5	1 / 2	13 / 10
Genetics (n, kATP / Other / Unknown)	1 / 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)

- Study observations of persistent hypoglycemia on SOC confirm previous study outcome presented at ESPE2021
- 16 (70%) had seizure history; 5 (22%) reporting seizures within past 12 months.
- 14 (61%) reported hospitalizations within past year due to CHI-related complications.
- All 23 patients enrolled completed the study.

RZ358 Was Generally Safe and Well Tolerated Across Doses

- No adverse drug reactions, AEs leading to study discontinuation, or dose-limiting toxicities
- 15 subjects experienced a total of 43 treatment-emergent AEs
  - No dose-response
  - Generally mild and unrelated to study drug
- Three patients experienced mild TEAEs 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
- No increase from baseline in clinically relevant hyperglycemia (≥ 250 mg/dL) and no hyperglycemia AEs or adverse metabolic changes

RIZE Study Pharmcokinetics: 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)

RIZE Study: Significant Dose-Dependent Improvements in Hypoglycemia Events (BGM) and Time (CGM)

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)***	***-72% (p=0.1)***	***- 74% (p<0.05)***	***-20% (NS)***	***-71% (p=0.01)***

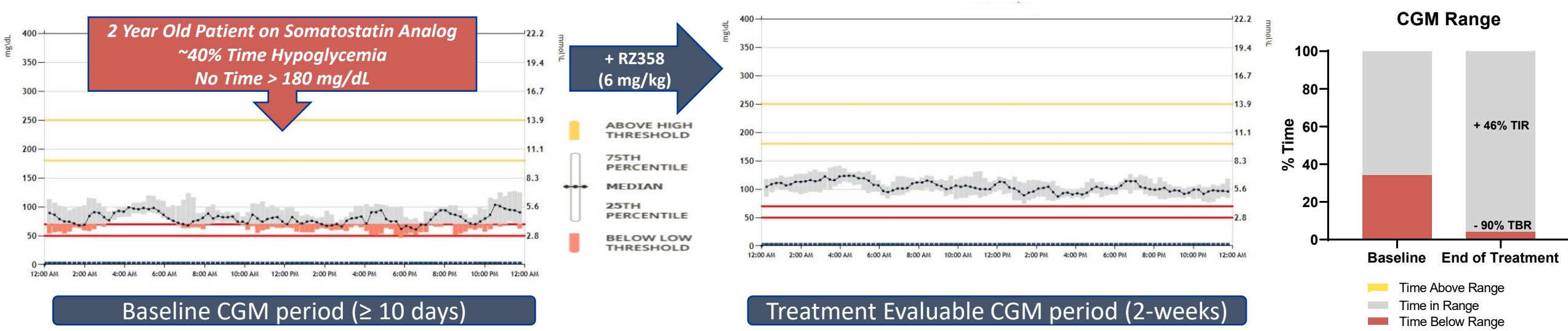
One patient at 3 mg/kg was excluded from the per protocol BGM analyses for failing to meet pre-specified minimum glucometer testing

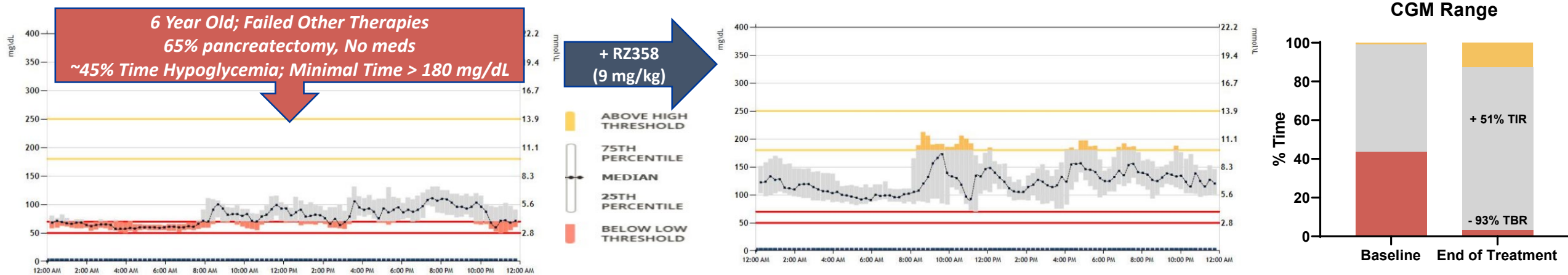
^ One patient at 9 mg/kg was excluded from the per protocol CGM and BGM analyses for stopping background therapy while on study;
Two 2 year-old patients in 9 mg/kg group used CGM sensor on arm [less accurate and discordant from BGM], but were included in analysis

RIZE Study: 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%)

RIZE Study: Potential for RZ358 to be an Effective Monotherapy Treatment





RIZE Study Summary of Outcomes

- 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
  - Add-on to SOC therapies
    - RIZE again showed that SOC therapies are suboptimal for some CHI patients
    - Patients enrolled had an average of ~25% time in a hypoglycemic range at baseline
- 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 was generally safe and well-tolerated
- Expected RZ358 concentrations achieved
- Dose and exposure-dependent responses were observed
  - 100% patient response rate with > 50% Hypoglycemia correction at the top dose

Acknowledgements:
- Patients & families who participated in RIZE
- Fellow investigators & authors
- Patient advocacy organizations whose work to support families, raise awareness and empower research that is foundational to finding better therapies and outcomes for those living with CHI.