



PES PEDIATRIC ENDOCRINE SOCIETY

Ersodetug (RZ358) in Congenital Hyperinsulinism

Top-Line Results From a Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study (sunRIZE)

PES

Conflicts of Interest

Research support: Rezolute (related to this presentation); Hanmi Pharmaceuticals, Zealand Pharma A/S, Twist Biosciences, Ultragenyx, Moderna, and Rhythm Pharmaceuticals for studies not included in this presentation.

Consulting: Rezolute (related to this presentation); Zealand Pharma A/S, Ultragenyx, Fortress Biotech, Ligand Pharmaceuticals, Confo Therapeutics, AmideBio, Spruce Biosciences, Twist Bioscience, and Rhythm Pharmaceuticals not related to this presentation

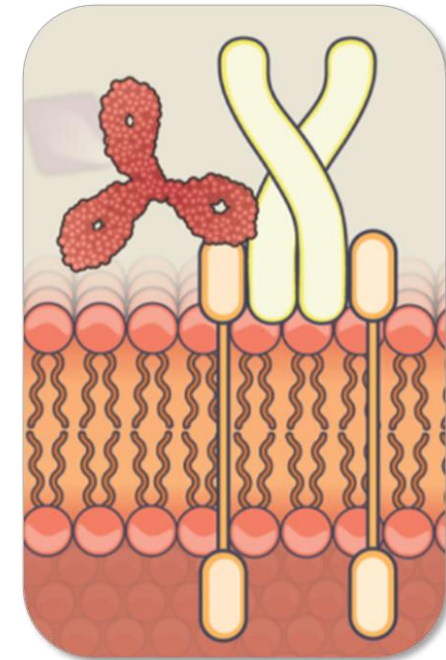
Background

Congenital Hyperinsulinism

- Most common cause of persistent, severe hypoglycemia in newborns, infants
- Estimated birth incidence of **1:28,000** (1:2600 in certain populations)
- Over **30** genetic loci identified
 - Most common are K-ATP channel mutations: *ABCC8* & *KCNJ11*
 - **30%** remain genetically unsolved
- Adverse neurodevelopmental outcomes have been shown to be as high as **50%**
- **60%** do not respond to the only approved therapy (diazoxide)

Ersodetug (RZ358)

- Insulin receptor modulating monoclonal antibody (IgG2)
- Allosterically binds to the insulin receptor in target tissue
- Does NOT block insulin binding
- Modulates insulin binding and signaling resulting in reduced glucose uptake from the bloodstream
- 30-min IV infusion given every 2-4 weeks
- Reductions in hypoglycemia of up to ~75% in open-label **Phase 2b (RIZE) study**



sunRIZE Study Design

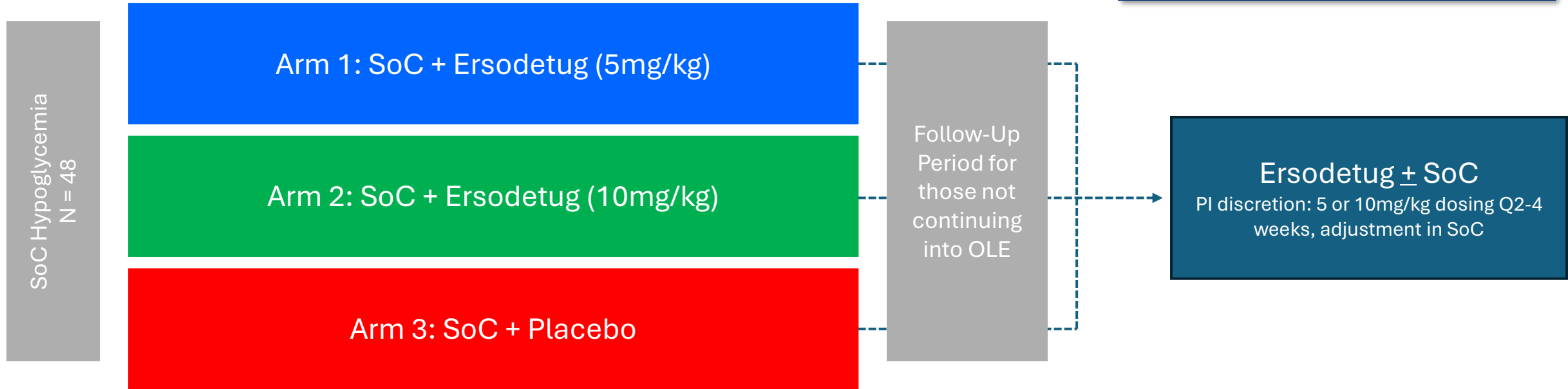
Screening <i>Up to 5 weeks</i>	Pivotal Treatment Period							FU Period	
	Biweekly Dosing			Monthly Dosing					
	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20		Week 24
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	EoT or OLE start	EoS

Open Label Extension
Long-term safety, efficacy durability, efficacy in monotherapy

Key Inclusion Criteria:

- Ages 3 months – 45 years*
- Biochemically established diagnosis of cHI
- Persistent hypoglycemia despite SoC
 - SMBG: ≥ 3 hypo (<70 mg/dL) per week
 - CGM: $\geq 8\%$ avg daily time <70 mg/dL

Double-Blind Comparator Control Groups*



*Initial 8 patients ages 3 months – 1 yr enrolled in open-label arm (making total planned enrollment 56)



2026 ANNUAL MEETING

EoT = end of treatment, EoS = end of study, FU = follow-up, OLE = open label extension, SMBG = self-monitored blood glucose, CGM = continuous glucose monitor, SoC = standard of care

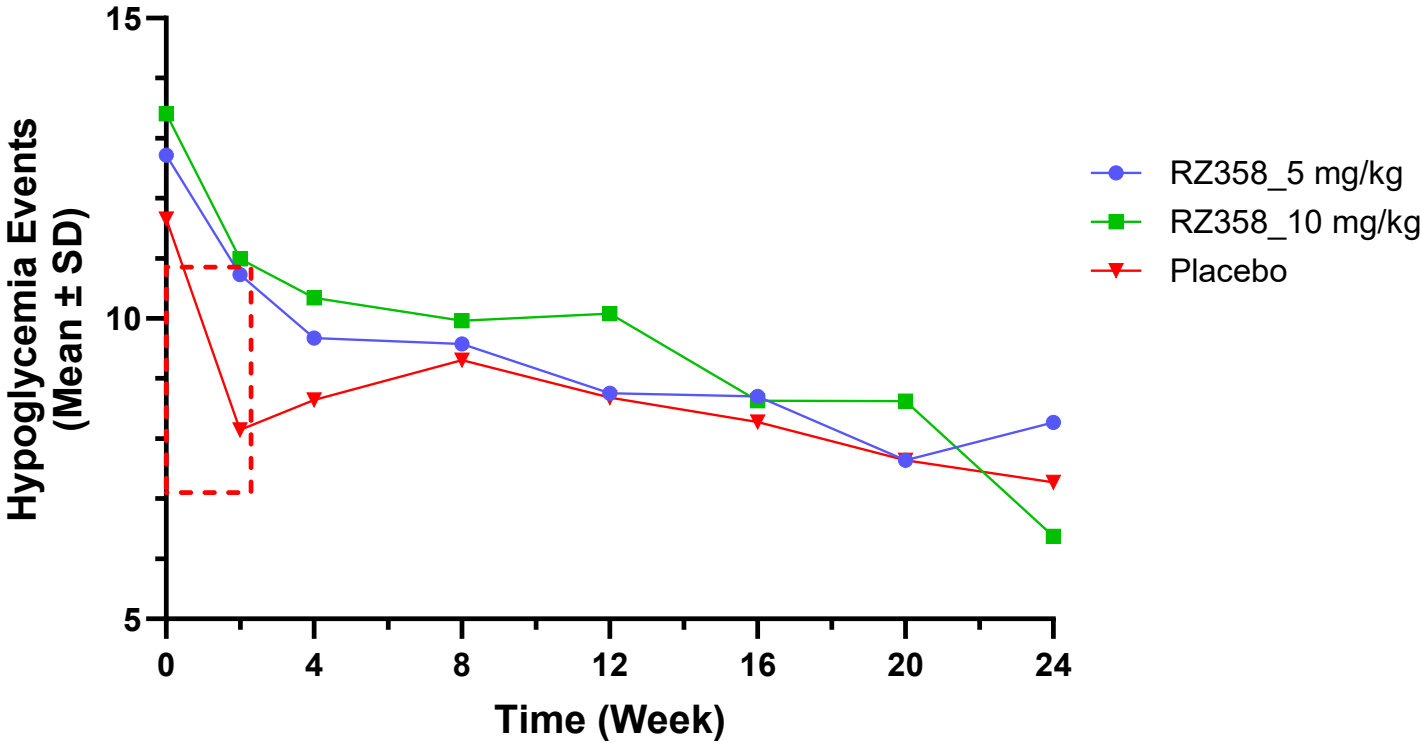
Enrolled Population (n=63) Baseline Characteristics

Parameter Category	RZ358 5 mg/kg (N=18)	RZ358 10 mg/kg (N=20)	Placebo (N=17)	Overall [+OLA] (N=63)
Age in years, mean (range)	3.4 (1-15 y)	3.9 (5 mo to 9 y)	4.0 (5 mo to 10 y)	3.4 (3 mo to 15 y)
Sex (n, F)	8 (44%)	10 (50%)	7 (41%)	31 (49%)
Genetics (n,% kATP / Other or Unknown)	13 (72%) / 5 (28%)	11 (55%) / 9 (45%)	15 (88%) / 2 (12%)	47 (75%) / 16 (25%)
Current SOC therapy	17 (94%)	18 (90%)	17 (100%)	60 (95%)
Diazoxide (n,%)	9 (50%)	11 (55%)	5 (29%)	26 (41%)
SSA (n,%)	10 (56%)	11 (55%)	14 (82%)	46 (73%)
Scheduled enteral tube feeding (n,%)	7 (39%)	7 (35%)	7 (41%)	24 (38%)
2+ therapies (n,%)	8 (44%)	9 (45%)	8 (47%)	29 (46%)
Pancreatectomy (n,%)	2 (11%)	3 (15%)	2 (12%)	8 (13%)
Pre-study Use of CGM (n, % yes)	8 (44%)	11 (55%)	9 (53%)	32 (51%)
cHI-Related Hospitalizations in Previous Year (n,%)	6 (33%)	12 (66%)	10 (59%)	32 (51%)
Mean (range) Hypoglycemia Events / Week by SMBG	12.7 (5-42.0)	13.4 (4-37)	11.7 (3-22)	12.6 (3-42)
Mean (range) % Time Hypoglycemia by CGM	23.1 (5-73)	20.0 (6-71)	13.0 (7-38)	19.1 (5-73)
Mean HbA1C (%), Range	4.96 (3.9-5.9)	5.01 (3.9-6.0)	5.32 (4.2-6.2)	---
~ Blood Glucose Conversion	(~99 mg/dL)	(~101 mg/dL)	(~111 mg/dL)	---
Mean Average Glucose by SMBG (mg/dL)	81	82	86	---
Mean (Range) Hypoglycemia Fear Survey (HFS) Worry Score	27.1	28.2	34.6	---

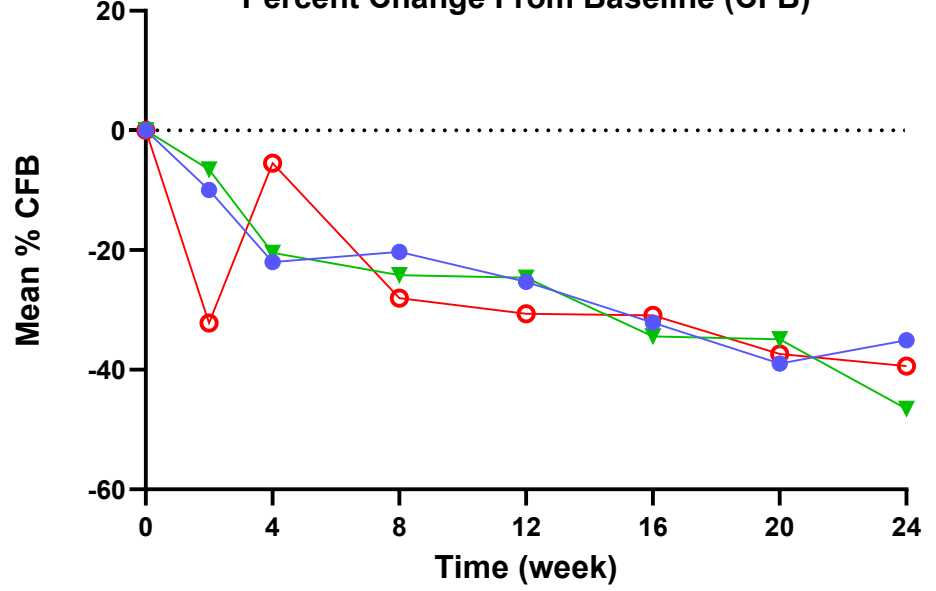
F= female, SOC = standard of care, SSA = somatostatin analog, CGM = continuous glucose monitor, SMBG = self-monitored blood glucose

Study Effect on Unblinded SMBG Occurred Early in Dosing: Primary Endpoint Not Met (Change in Avg Weekly Hypo Events by SMBG)

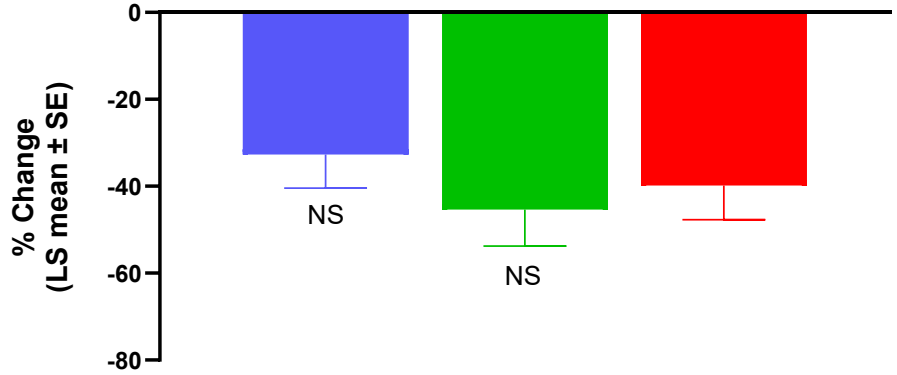
Observed Values



Percent Change From Baseline (CFB)



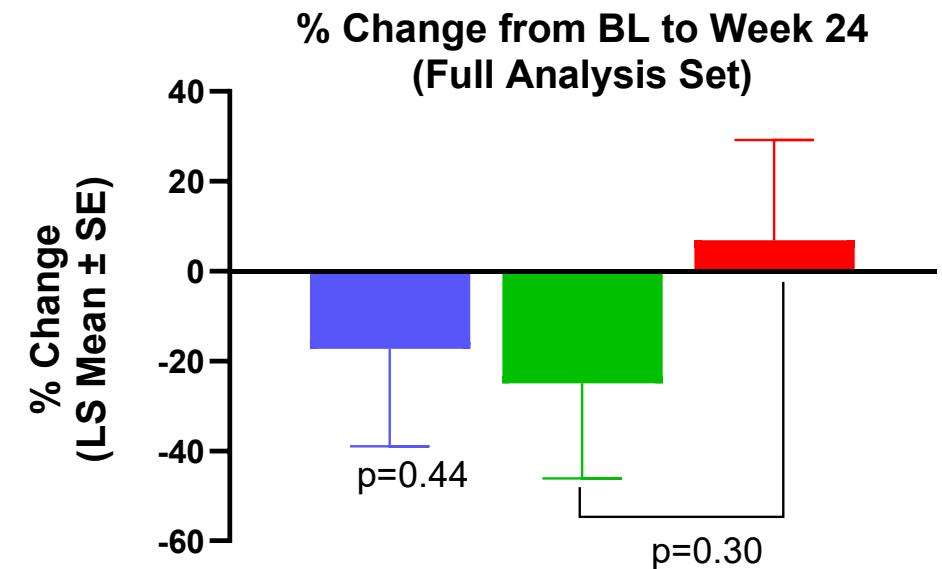
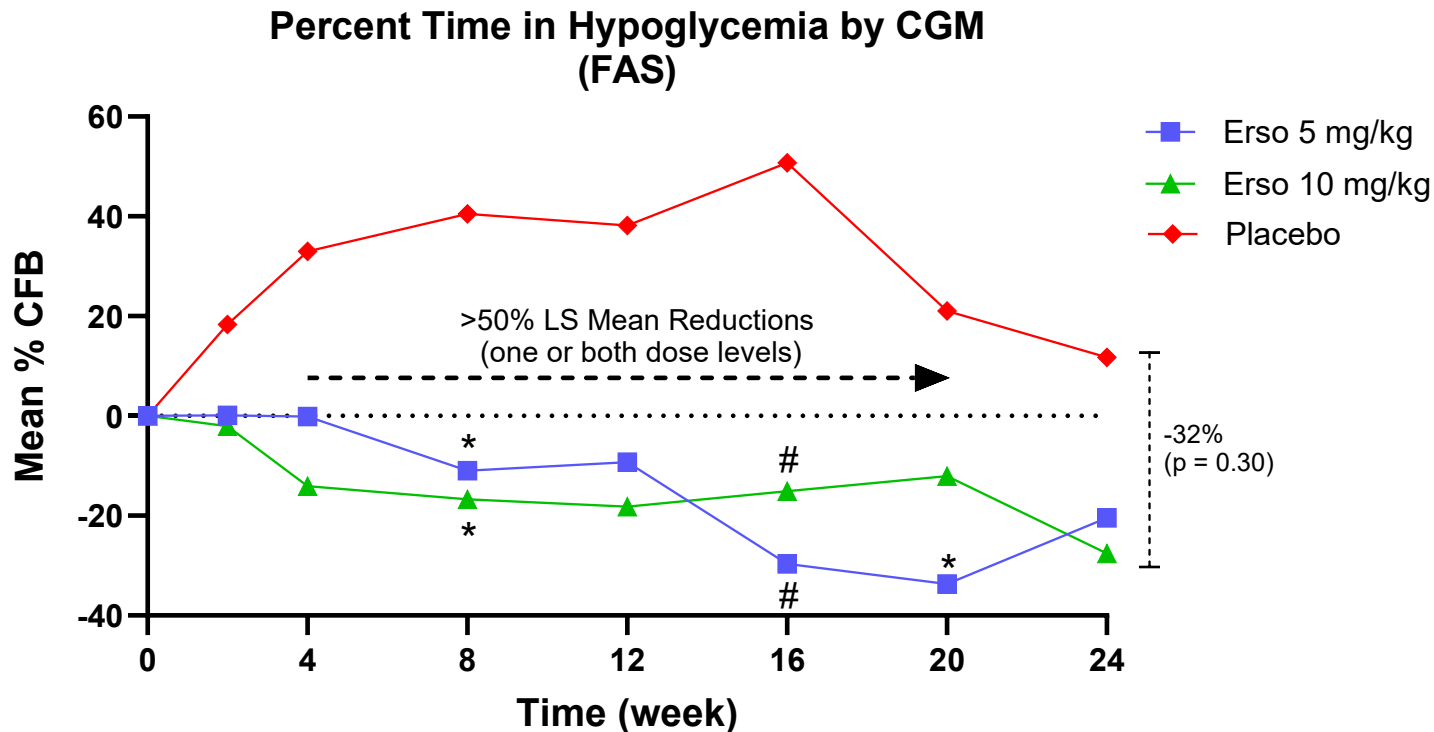
% Change from BL to EoT (Week 24)
Full Analysis Set



Secondary Endpoint: Clinically Significant Reductions in Time in Hypoglycemia (CGM) not Stat. Sig. at Wk24/EOT

- Reductions of >50% compared to placebo with nominal statistical significance at the noted timepoints

- Not statistically significant at SAP-specified Week 24/EOT analysis window (-32%; p=0.30 at 10 mg/kg)



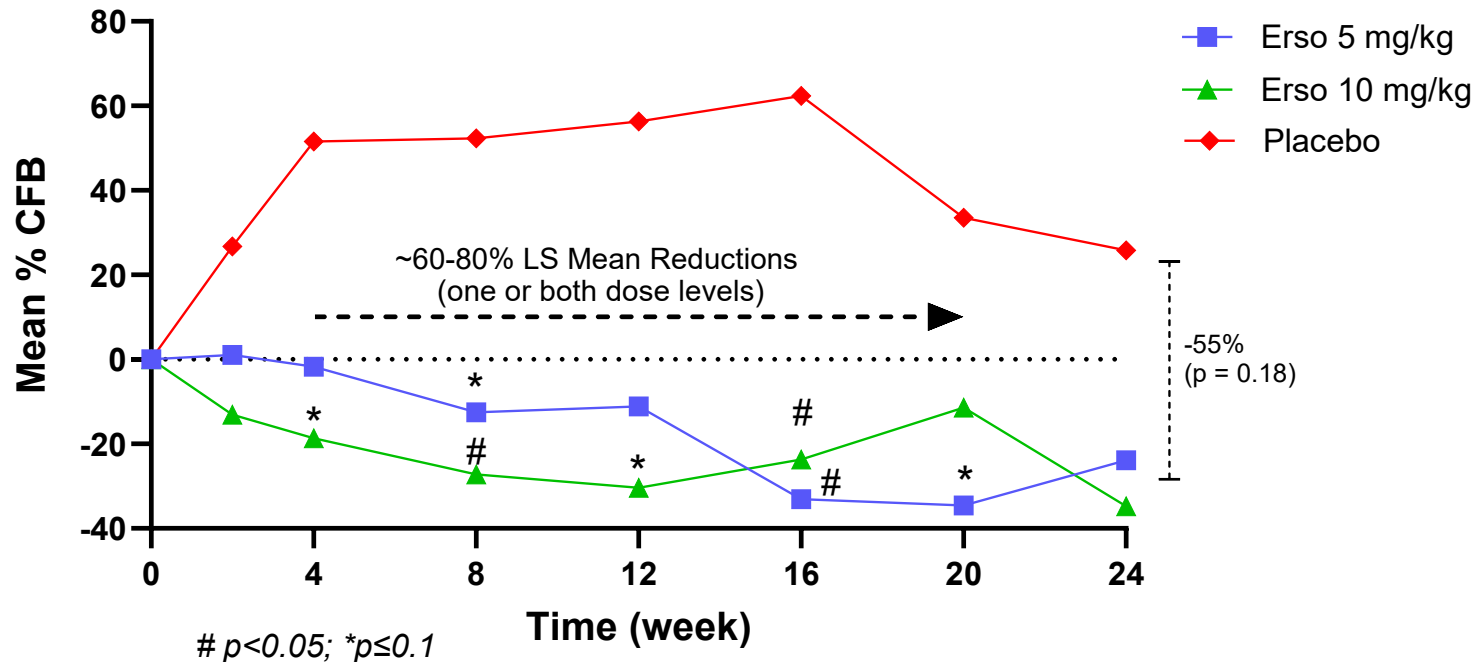
Significant reduction vs PBO ($p < 0.05$; both doses) at Week 16;

* $p \leq 0.1$ at Weeks 8 (both doses) and 20 (5 mg/kg)

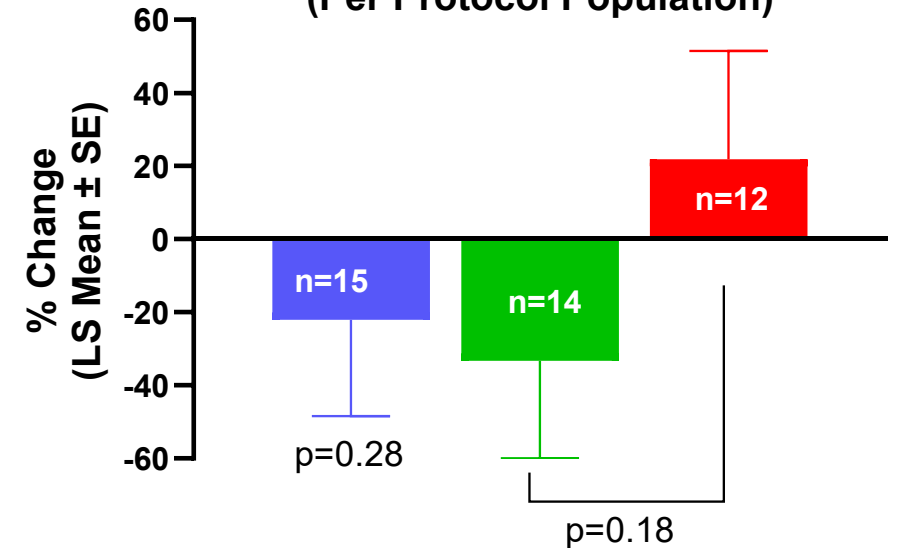
Time in Hypoglycemia Reductions (CGM) More Significant in the Per Protocol Set (PPS)* (n=41)

- Reductions of ~60-80% compared to placebo with nominal statistical significance at the noted timepoints
- Not statistically significant at SAP-specified Week 24/EOT analysis window (-55%; p=0.18 at 10 mg/kg)

Average Daily % Time in Hypoglycemia by CGM Per Protocol Population



% Change from BL to Week 24 (Per Protocol Population)

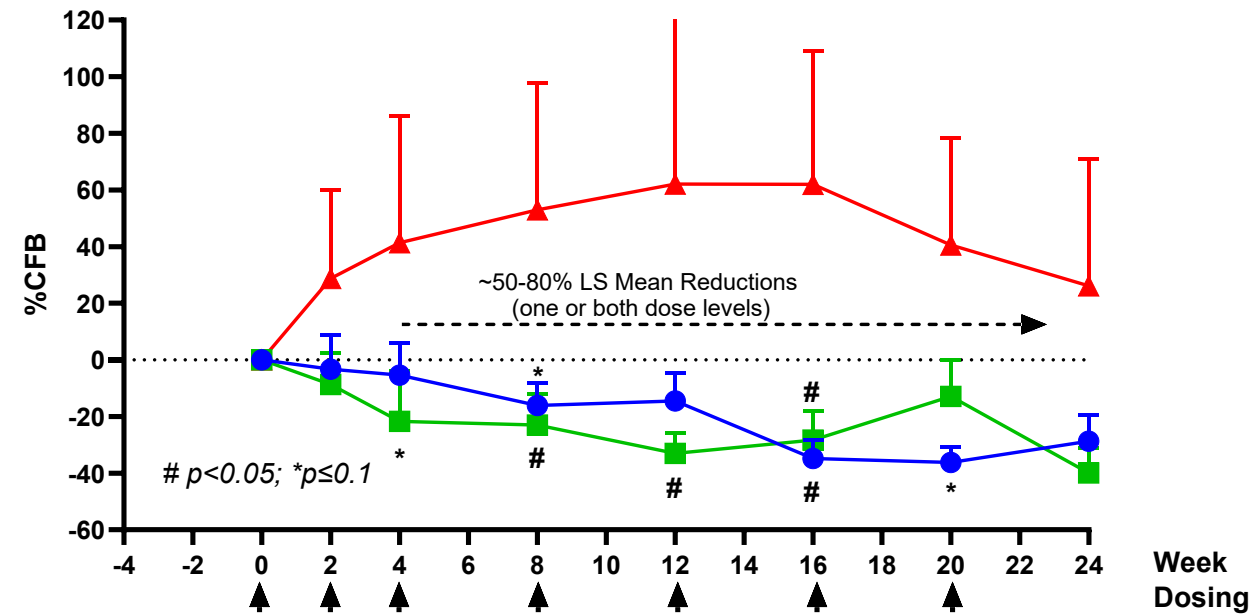
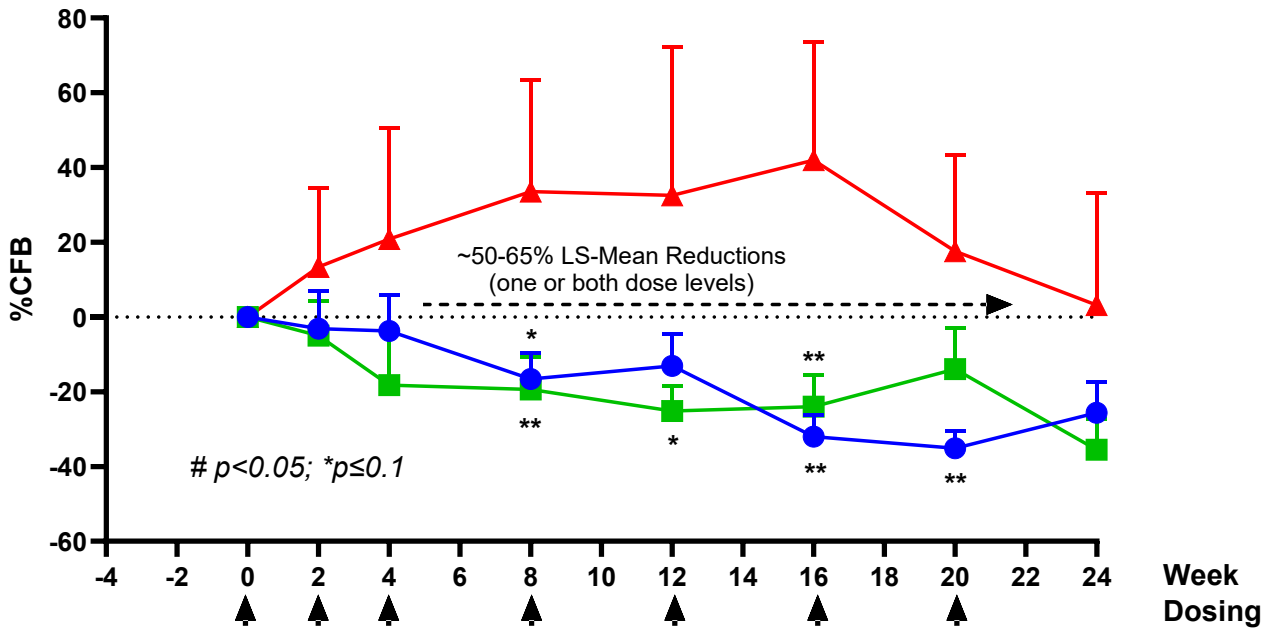


*Per-Protocol Set (PPS): Defined in blinded fashion prior to database lock and excludes participants with below threshold SMBG/CGM data collection, significant escalation in background SOC, and early discontinuations.

Reduction in Average Weekly Hypoglycemia Events by CGM in FAS & PPS Populations (Pre-Specified Endpoint)

Full Analysis Set (FAS)

Per Protocol Set (PPS)



● RZ358_5 mg/kg

■ RZ358_10 mg/kg

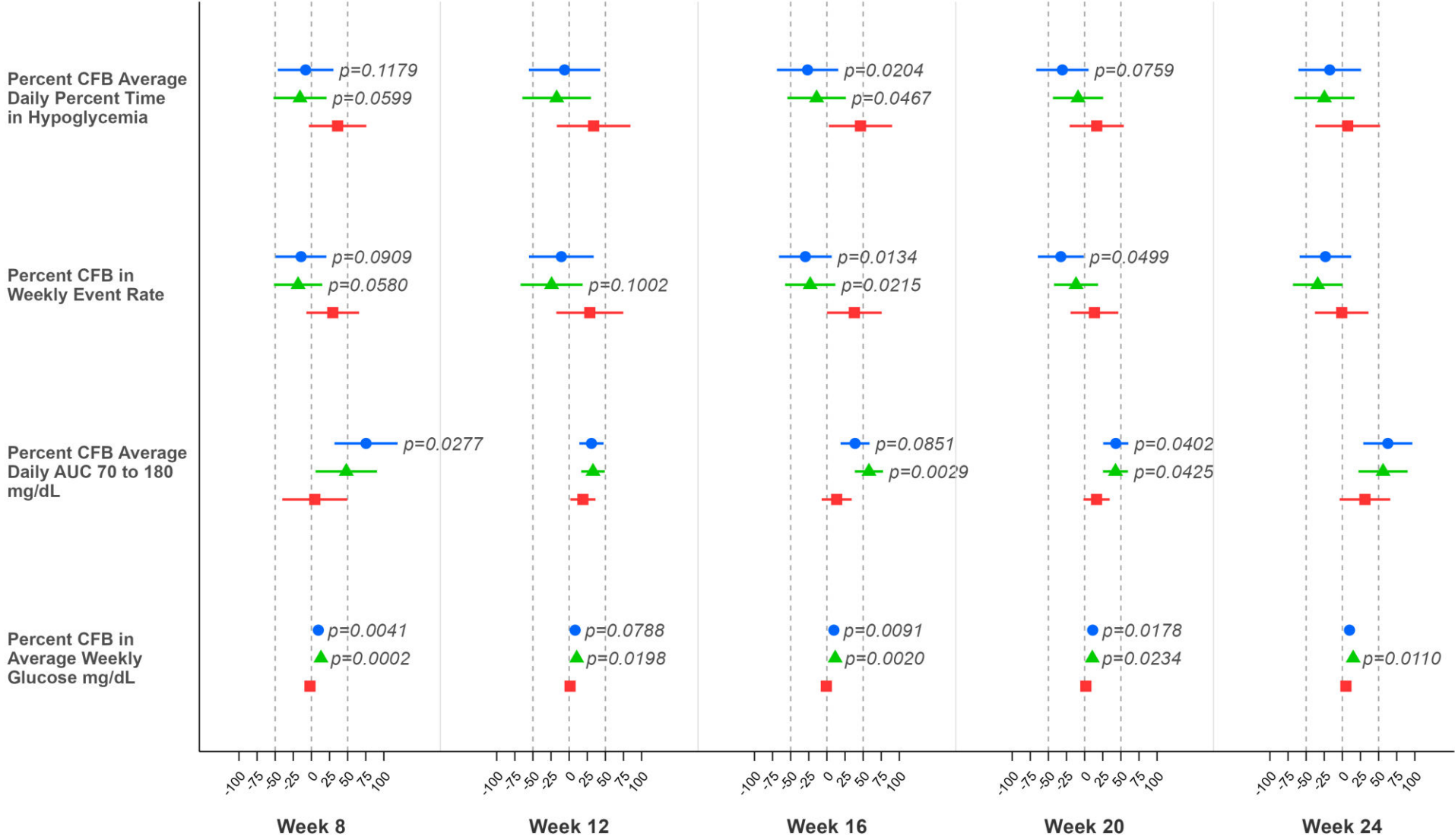
▲ Placebo

● RZ358_5 mg/kg

■ RZ358_10 mg/kg

▲ Placebo

Consistent and Clinically Relevant Glycemic Improvements Across Time & Multiple CGM Outcomes (LS-Mean [95% CI] Percent Change from Baseline; FAS Population)



Treatment ● RZ358 5 mg/kg ▲ RZ358 10 mg/kg ■ Placebo

Safety and Tolerability

- **Adverse events occurred in ~90% of participants at a comparable rate across treatment groups**
- **Adverse events with relationship to ersodetug (Adverse Drug Reactions)**
 - Excess hair growth (hypertrichosis) was commonly reported in ersodetug treated patients (~35%)
 - Mild and not dose-dependent
 - Led to discontinuation of study drug in 1 participant
 - Hypersensitivity reactions led to early discontinuation of study drug in 3 participants
 - Two participants with serious allergic reactions (including anaphylaxis)
 - Resolved quickly upon discontinuation of study drug
 - Overall program incidence of ~2%
- **No clinically-relevant hyperglycemia:**
 - Low rates of transient mild to moderate hyperglycemia without associated sequelae
 - No hyperglycemia AEs
- **Hepatic safety:** No signal by liver enzymes or ultrasound monitoring

Preliminary Observations from Ongoing OLE*

- **All 59** participants rolled-over into the open-label extension after the pivotal treatment period
 - 57 still ongoing
- Cumulative duration of OLE participation: **~6-24 months**
- **Glycemic improvement from baseline** across multiple endpoints (e.g. average glucose by SMBG, hypoglycemia events by SMBG, HbA1c)
 - Notably also in the rolled-over placebo participants compared to the controlled period of the study
- **Concurrent overall reduction in background SoC** (e.g, diazoxide, somatostatin analogs, and/or regular tube feeds)
 - Including discontinuation of other therapies and use of ersodetug in monotherapy in many instances
- **Favorable patient/family reported experiences overall**

Conclusions

- **Study Status**
 - Phase 3 pivotal study completed; OLE ongoing
- **Efficacy**
 - Primary endpoint (SMBG weekly hypoglycemia events) not met
 - Likely influenced by caregiver behavioral adaptations in hypoglycemia avoidance
 - CGM metrics showed consistent and clinically meaningful reductions in hypoglycemia
- **Safety**
 - Reassuring safety profile
 - 2% systemic hypersensitivity reactions
 - Mild hypertrichosis observed
- **Long-Term Experience**
 - Significant exposure experience with continued glycemic benefit
 - Compassionate use program available (~48 months exposure in EAP)