PES

Ersodetug (RZ358) in Congenital Hyperinsulinism

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

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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

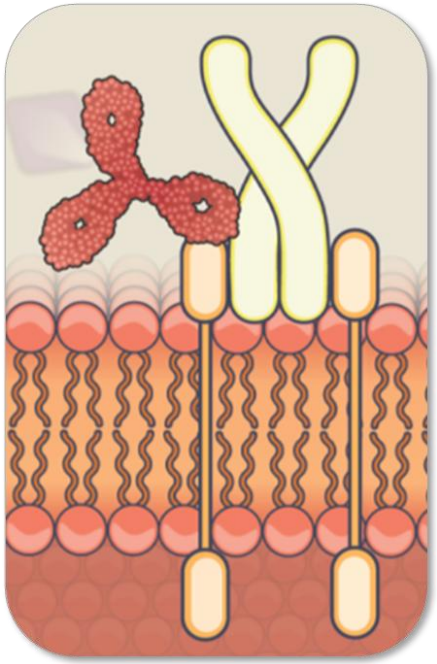
Background

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**



IV = intravenous, SMBG = self-monitored blood glucose, CGM = continuous glucose monitor

sunRIZE Study Design

Screening

Up to 5 weeks

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	Week 28
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: ≥8% avg daily time <70 mg/dL

Double-Blind Comparator Control Groups*

SoC Hypoglycemia N = 48

- Arm 1: SoC + Ersodetug (5mg/kg)
- Arm 2: SoC + Ersodetug (10mg/kg)
- Arm 3: SoC + Placebo

Follow-Up Period for those not continuing into OLE

→ **Ersodetug ± SoC**

PI discretion: 5 or 10mg/kg dosing Q2-4 weeks, adjustment in SoC

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

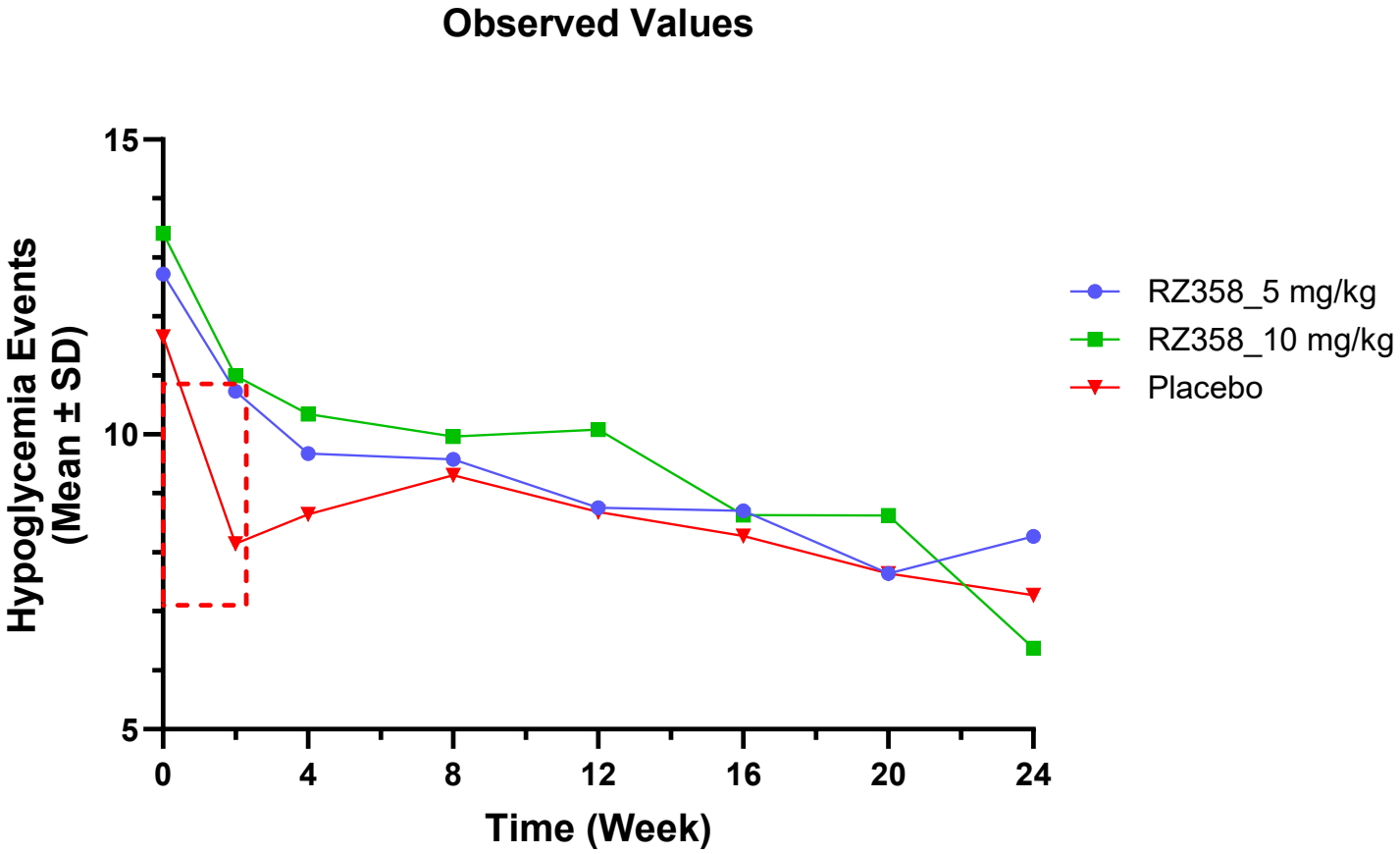
EoT = end of treatment, EoS = end of study, FU = follow-up, OLE = open label extension, SMBG = self-monitored blood glucose, CGM = continuous glucose monitor, SoC = standard of care

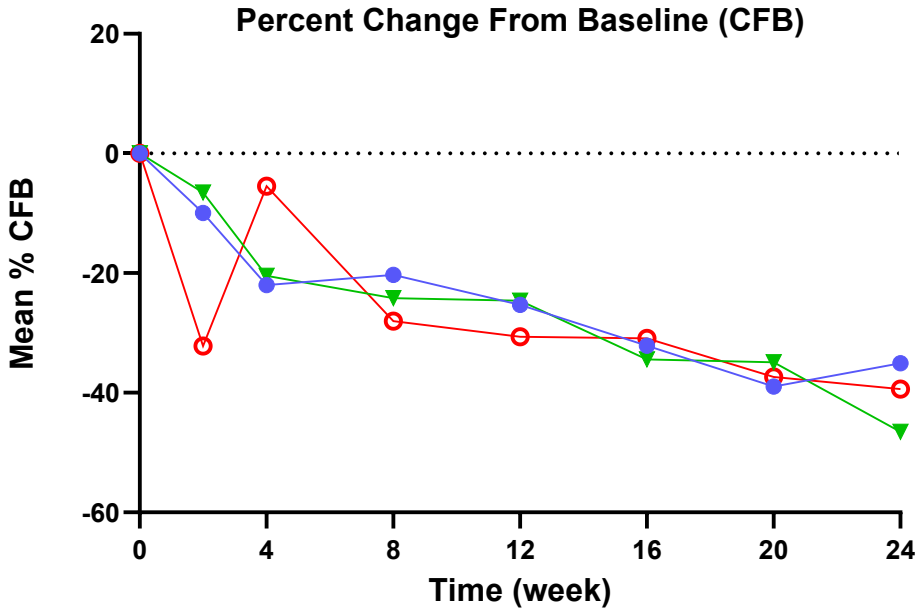
Enrolled Population (n=63) Baseline Characteristics

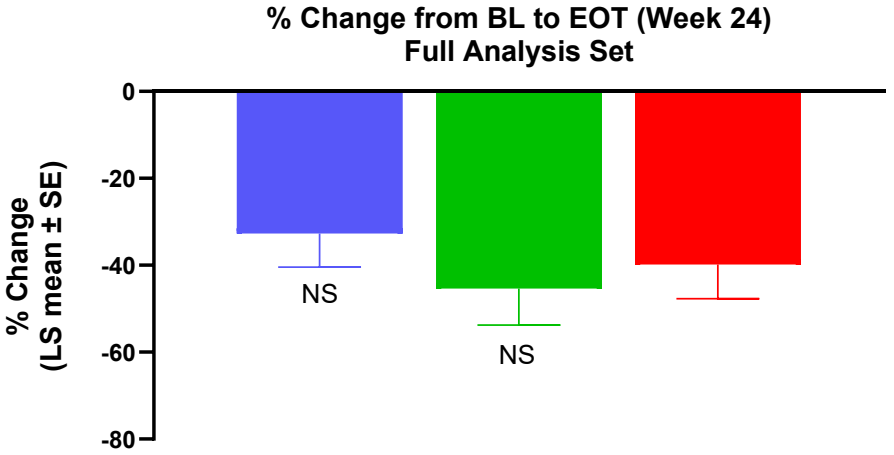
Parameter Category	RZ358 5 mg/kg (N=18)	RZ358 10 mg/kg (N=20)	Placebo (N=17)	Overall [+OLA] (N=63)
Age in years, mean (range)	3.4 (1-15 y)	3.9 (5 mo to 9 y)	4.0 (5 mo to 10 y)	3.4 (3 mo to 15 y)
Sex (n, F)	8 (44%)	10 (50%)	7 (41%)	31 (49%)
Genetics (n,% kATP / Other or Unknown)	13 (72%) / 5 (28%)	11 (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) **~ Blood Glucose Conversion**	4.96 (3.9-5.9) (~99 mg/dL)	5.01 (3.9-6.0) (~101 mg/dL)	***5.32*** (4.2-6.2) ***(~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)



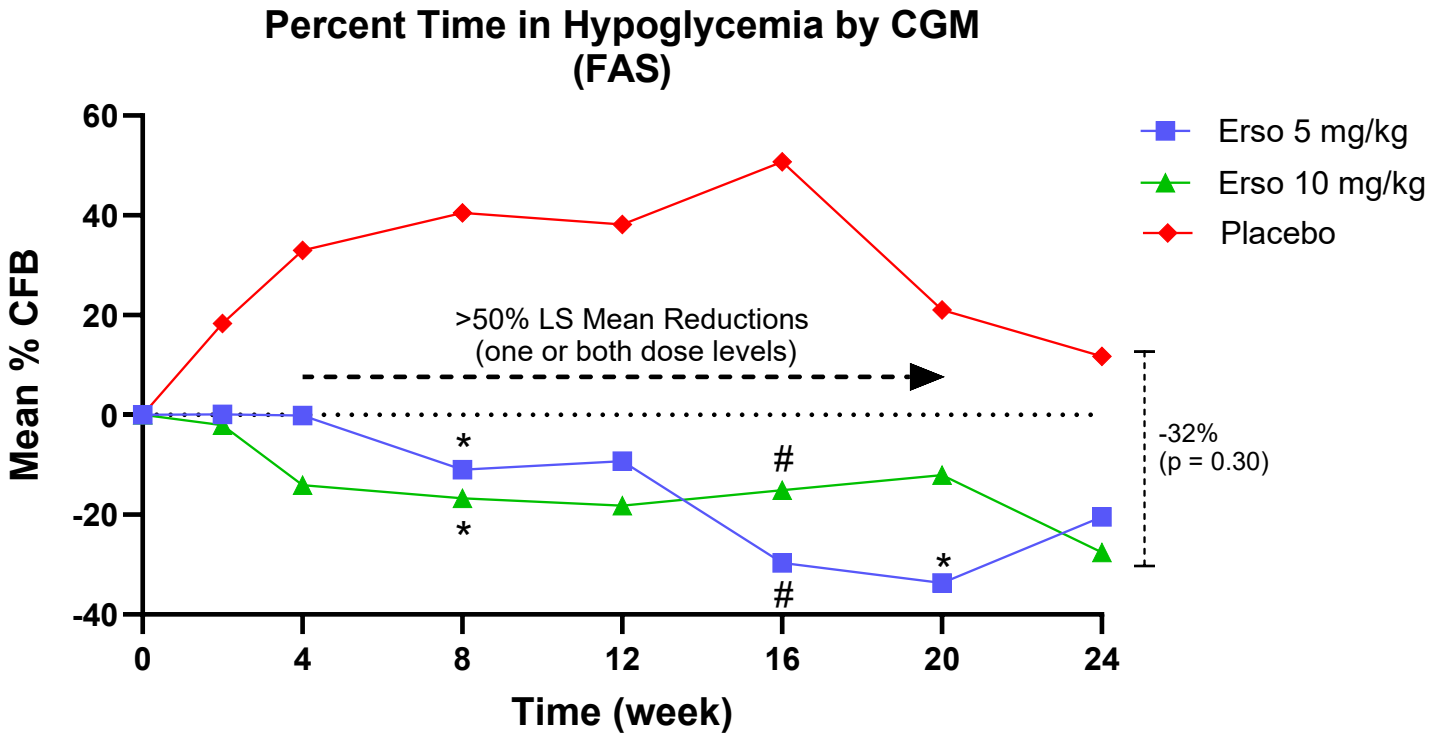


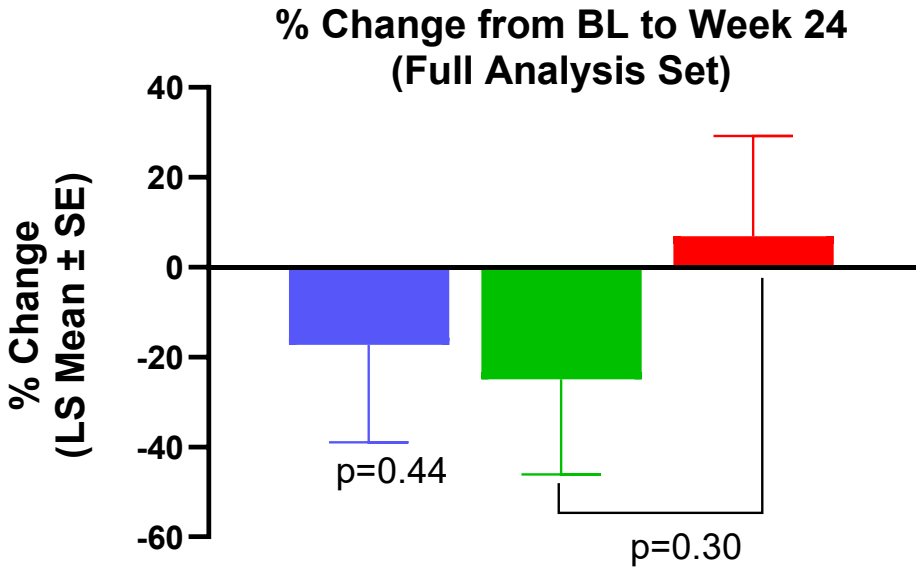


SMBG = self-monitored blood glucose, BL = baseline, EoT = end of treatment

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)



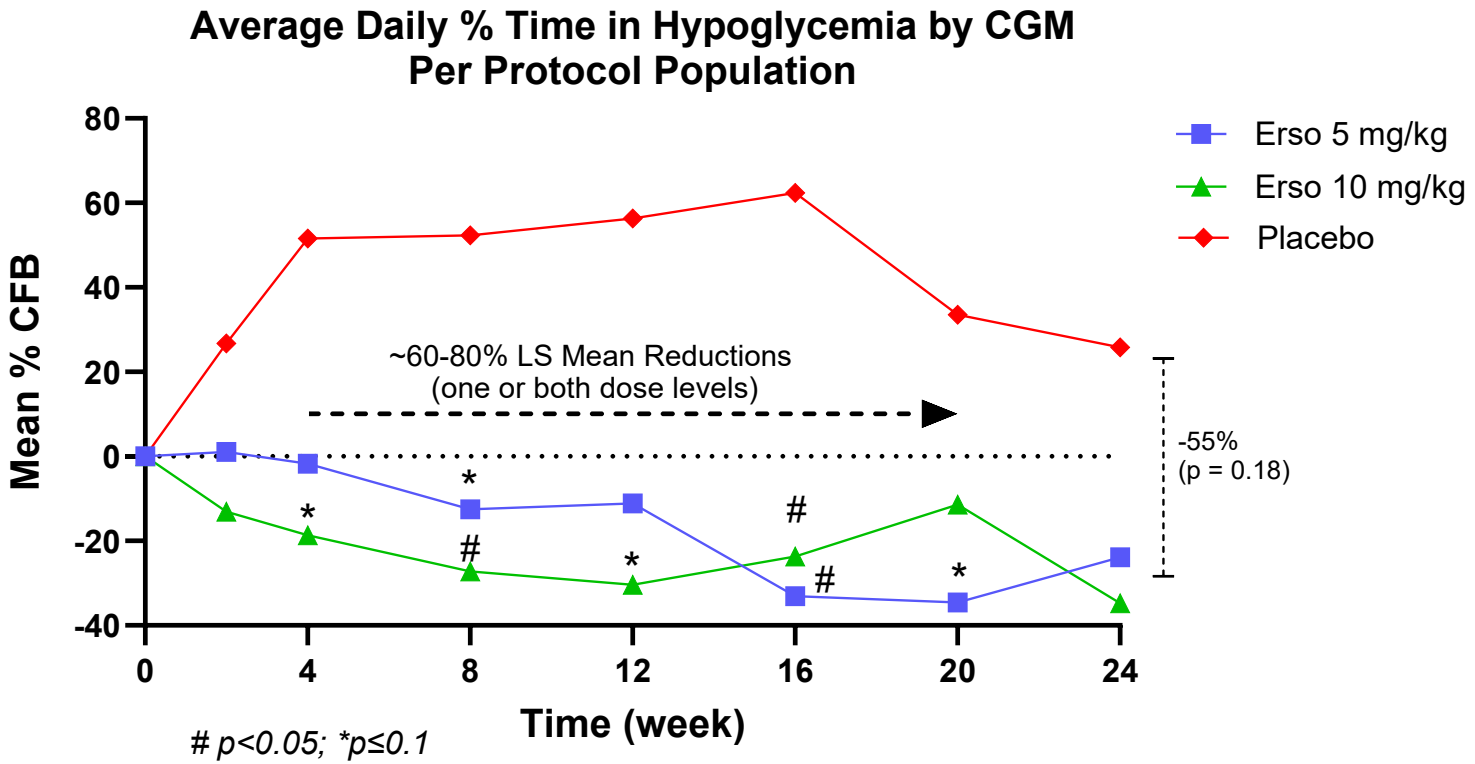


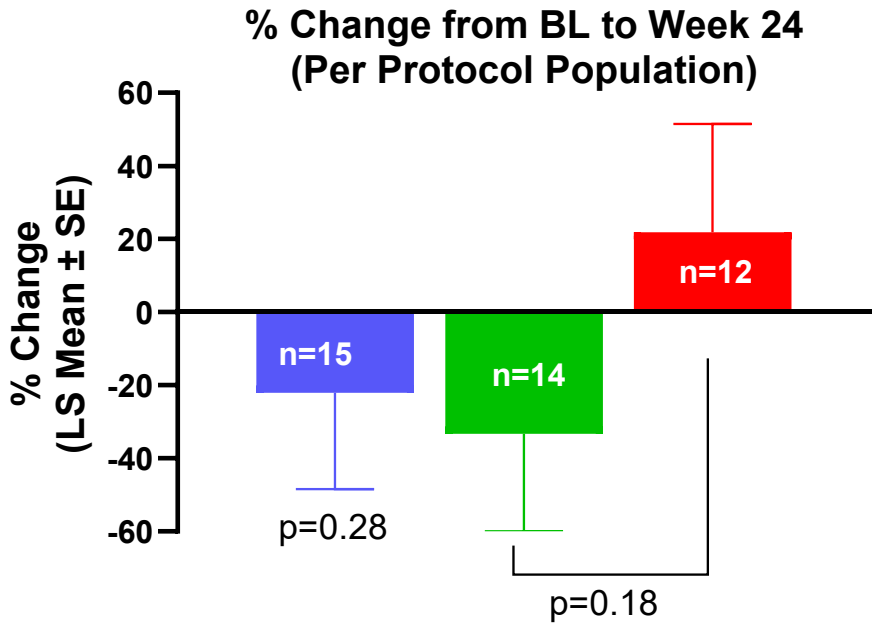
 # Significant reduction vs PBO (p<0.05; both doses) at Week 16;
**p≤0.1 at Weeks 8 (both doses) and 20 (5 mg/kg)*

CGM = continuous glucose monitor, SAP = statistical analysis plan, FAS = full analysis set, CFB = change from baseline, PBO = placebo, BL = baseline

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)

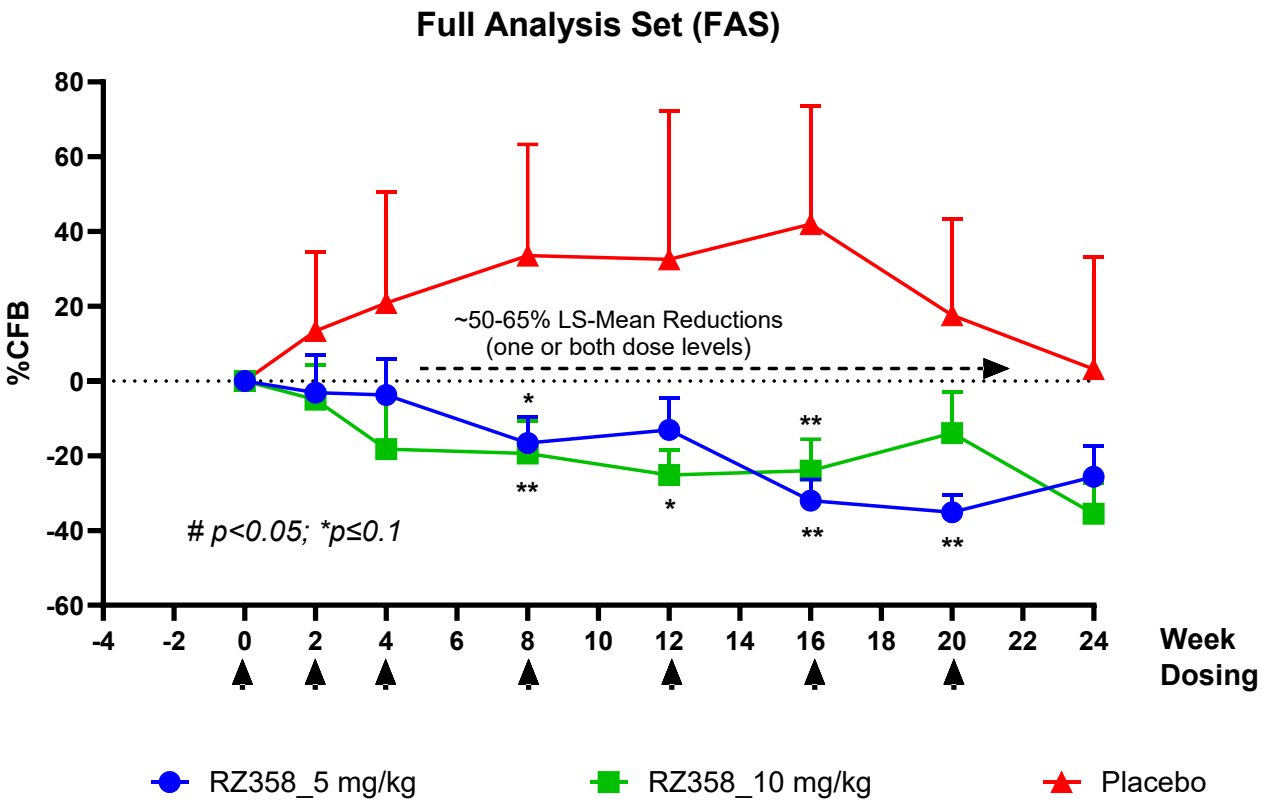


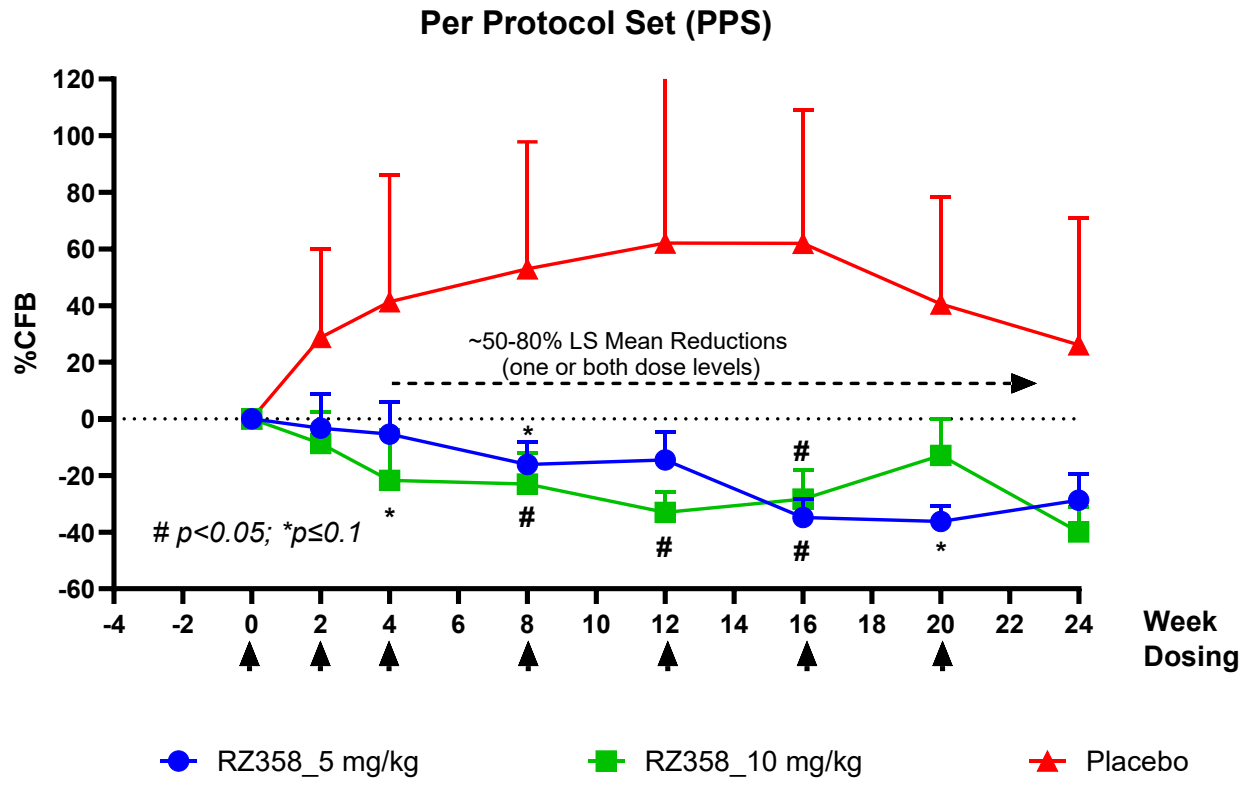


*Per-Protocol Set (PPS): Defined in blinded fashion prior to database lock and excludes participants with below threshold SMBG/CGM data collection, significant escalation in background SOC, and early discontinuations.

CGM = continuous glucose monitor, SAP = statistical analysis plan, EOT = end of treatment, CFB = change from baseline, BL = baseline, SMBG = self-monitored blood glucose, SOC = standard of care

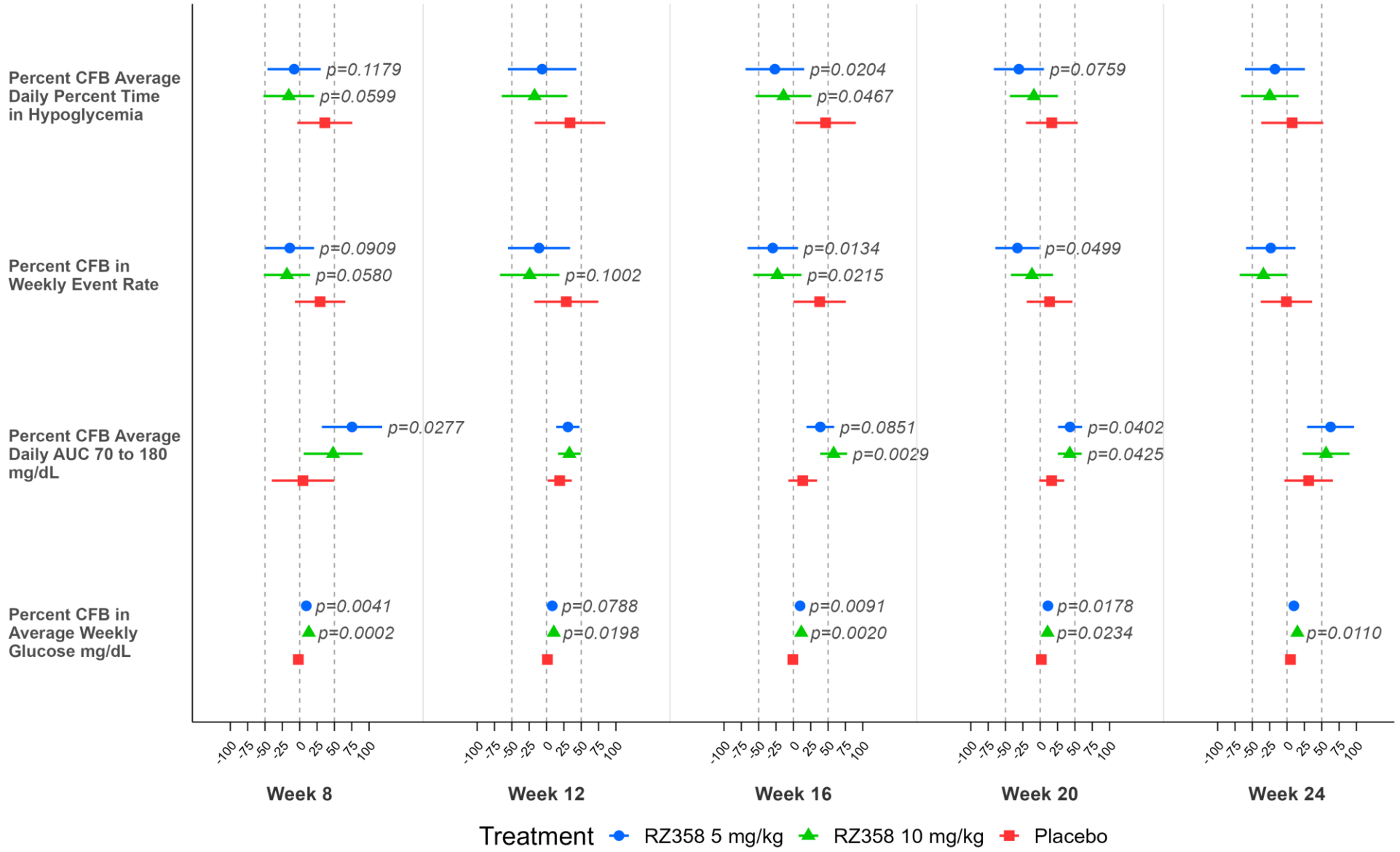
Reduction in Average Weekly Hypoglycemia Events by CGM in FAS & PPS Populations (Pre-Specified Endpoint)





CGM = continuous glucose monitor, FAS = full analysis set, PPS = per protocol set, CFB = change from baseline

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



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 sequalae
  - No hyperglycemia AEs
- **Hepatic safety**: No signal by liver enzymes or ultrasound monitoring

AE = adverse event, TEAE = treatment-emergent adverse event, SAE = serious adverse event

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**

** Data preliminary and in flux in ongoing OLE*

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)

OLE = open label extension, SMBG = self-monitored blood glucose, CGM = continuous glucose monitor, EAP = expanded access program