An Analysis of Overnight Hypoglycemia in Patients with Congenital Hyperinsulinism: Results from the RZ358-606 (RIZE) Study

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I. BACKGROUND

The hallmark of congenital hyperinsulinism (cHI) is hypoketotic hypoglycemia, putting those affected at risk of neurologic sequelae. In particular, the overnight fasting period is a vulnerable time, during which undetected hypoglycemia can lead to short and long-term adverse neurologic outcomes. Consistent disruptions from overnight hypoglycemia lead to poor patient/caregiver quality of life and negatively impact school/work productivity.

RZ358 is a monoclonal antibody that allosterically and reversibly binds the insulin receptor, thereby decreasing excessive insulin action.

II. OBJECTIVE

While primary and key secondary glycemic endpoints (weekly events and daily percent time) from the RZ358-606 (RIZE) study have been previously reported, this analysis highlights the continuous glucose monitor (CGM)-based clinically-relevant overnight (12-8 am) glycemic endpoints of average hypoglycemia time (<70 mg/kg) and average glucose level.

III. METHODOLOGY

RIZE, a global, open-label phase 2b study of RZ358 in participants with cHI ≥2 years old experiencing persistent hypoglycemia despite standard of care (SOC), enrolled 23 participants (57% M; mean age 6.7y [2-22]). Participants remained on stable background therapy (e.g. diazoxide, somatostatin) and received RZ358 biweekly for 8 weeks, in 4 sequential dose cohorts of 3-9 mg/kg (n=3-8 per cohort). Glucose was measured using Dexcom G6® and glycemic endpoints were evaluated during the 2-week period following the last dose (end of treatment (EOT) evaluable period) and compared to baseline (analysis by Wilcoxon rank sign test; SAS 9.3®).

Table 1. Median Overnight Percent Time Below 70mg/dL by CGM, Per Protocol Population*

	3mg/kg n=4	6mg/kg n=8	9mg/kg n=7*	3-9mg/kg n=3	Pooled n=22
Baseline	16.8	15.3	11.8	47.9	13.6
EOT	14.5	5.8	3	19.7	6.7
				Net Change	5.5
				% Change	52.1% (p=0.001)

Table 2. Median 8-hour (Midnight to 8AM) Average Glucose Values (in mg/dL) by CGM, Per Protocol Population*

	3mg/kg n=4	6mg/kg n=8	9mg/kg n=7*	3-9mg/kg n=3	Pooled n=22
Baseline	94.5	102.4	100.3	95.9	98.7
EOT	95.9	121.4	121.9	111.6	112.8
				Net Change	17.8 (p<0.001)

* One participant at 9 mg/kg was excluded from the per protocol analyses for stopping background therapy while on study.

IV. RESULTS/FINDINGS

Across all dose levels, baseline overnight hypoglycemia time (13.6% time [65 min]) improved by a median of 52% (p=0.001), as shown in Table 1. Reduction in hypoglycemia was dose-dependent with the highest dose cohort (9mg/kg) achieving the lowest residual hypoglycemia (~3 percent time) following the 8-week treatment period. Reflecting the upward shift in glucose curves generally seen in RIZE participants, Table 2 illustrates the average overnight glucose increased from 99 mg/dL at baseline to 113 mg/dL at end of treatment (p<0.001) across the Per Protocol Population studied (n=22).

V. REAL-LIFE IMPLICATIONS

Parents caring for children with cHI, a condition defined by severe, unpredictable hypoglycemia around the clock, often report lack of sleep[1] due to fear of potentially unrecognized hypoglycemia during the sleeping hours and the consequences of untreated hypoglycemia, such as neurologic damage or death, that leads to frequent nightly glucose monitoring and interventions to avoid low glucose levels. Minimizing hypoglycemia during the vulnerable overnight period not only offers safety for the child but also promotes undisturbed sleep for the entire family. Better sleep is associated with improved quality of life for both participants and their families, reduced caregiver burden, and enhanced child and caregiver performance at school and work.

References: 1. Banerjee, I., Raskin, J., Arnoux, JB. et al. Congenital hyperinsulinism in infancy and childhood: challenges, unmet needs and the perspective of patients and families. Orphanet J Rare Dis 2022; 17(1): 61.

VI. CONCLUSION

RZ358 led to a substantial reduction in overnight hypoglycemia in participants with cHI in the RIZE study. These and previously reported results suggest that RZ358 has the potential to be a safe and effective therapy to treat all forms of cHI. A Phase 3 study is underway.