READY-TO-USE LIQUID GLUCAGON RESCUE PEN – A PHASE 3 STUDY OF PLASMA GLUCOSE RECOVERY IN PEDIATRIC PATIENTS WITH TYPE 1 DIABETES (T1D)

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ABSTRACT

OBJECTIVE: A novel ready-to-use, room-temperature-stable liquid glucagon rescue pen (GRP, Xeris Pharmaceuticals) auto-injector was evaluated for the treatment of insulin-induced hypoglycemia in pediatric subjects with age-specific doses.

METHOD: Three cohorts were studied, children ages 2 to <6 and 6 to <12 years received one dose of Xeris Rescue Pen 0.5 mg; adolescents ages 12 to <18 years received 0.5 and 1 mg doses of the Rescue Pen on two separate visits. Glucagon was dosed once plasma glucose (PG) was lowered to <80 mg/dL.

RESULT: A total of 31 children with T1D (ages 2 to <18 years) were studied. All evaluable participants had a glucose elevation of ≥25 mg/dL from baseline. Across age groups there were no notable differences with regards to mean glucose $AUC_{(0\text{-}90min)}$, C_{max} (199-208 mg/dL), and T_{max} (66-82 min). Plasma glucagon $AUC_{(0\text{-}90min)}$, C_{max}, and T_{max} were similar across the age groups. Across all age groups the mean increase in glucose at 15 minutes was 23.3±20.6 mg/dL, and at 20 minutes was 42.2±22.7 mg/dL. Mild and moderate nausea (43%) and vomiting (14%) were the most commonly reported adverse events. No serious adverse events occurred.

CONCLUSION: Currently available glucagon kits for treatment of severe hypoglycemia require a complex multi-step reconstitution process, making them difficult to administer in an emergency. A ready-to-use, easy, two-step administration GRP using a pre-measured pediatric glucagon dose has been developed and tested. Results from this Phase 3 study demonstrate that age-appropriate doses of GRP were effective and safe in pediatric participants and support the use of this ready-to-use liquid glucagon formulation for the treatment of severe hypoglycemia.

BACKGROUND

- The ADA recommends that glucagon be prescribed for all individuals at increased risk of clinically significant hypoglycemia for use in the event of an emergency
- The International Society for Pediatric and Adolescent Diabetes recommends age-specific dosing of glucagon for the rescue of severe hypoglycemia
- The majority of severe hypoglycemic events are treated on-site, outside of a healthcare facility
- Current available preparations require glucagon to be reconstituted in a complex multi-step process
- Dose calibration, based upon patient age, can be a difficult task to successfully complete

A novel ready-to-use stable liquid GRP is being developed for the rescue treatment of severe hypoglycemia. The key features of the GRP are:

- Ready-to-use: With its easy two-step administration process. There is no reconstitution required at the time of emergency. In a completed human factors study, 99% of trained and untrained users were able to successfully administer the full dose with GRP
- No dose calibration required: The GRP is provided in two pre-measured sizes, 0.5 mg for pediatric administration and 1 mg for adolescents and adults
- No visible needle: The needle in the GRP is not visible to the user
- Auto-locks: The device needle guard will auto-lock over the used needle, after use for safety
- Two-year room-temperature stability: No refrigeration is required at any time

METHODS

- This was a sequential efficacy and safety study in pediatric subjects with T1DM
- During the treatment phase, subjects ages 2 to <12 years completed a single treatment visit and received a 0.5 mg dose of GRP. Subjects ages 12 to <18 years received a 1 mg dose of GRP
- The procedure to evaluate the efficacy of GRP was performed through the induction of a low normal glycemic state by administration of insulin
- After a confirmatory plasma glucose of <80 mg/dL was verified, the subject was then treated with the age/weight appropriate dose of GRP subcutaneously in the upper arm, leg, or abdomen

RESULTS

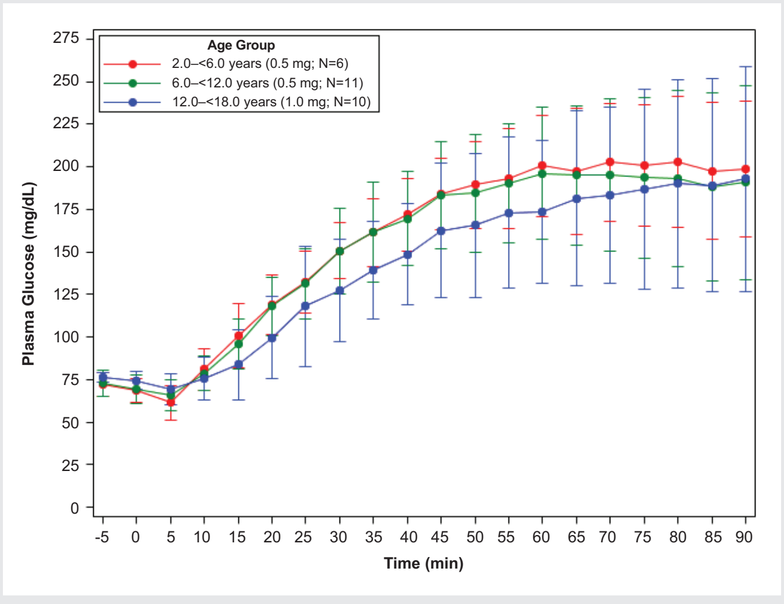
- Statistically significant increases in mean plasma glucose from baseline were observed across the 3 pediatric age groups. All evaluable patients achieved the target elevation of ≥25 mg/dL from baseline

Changes in Glucose and Side Effects

Glucagon Dose	0.5 mg dose		1 mg dose
Subject Ages (years)	2 to <6	6 to <12	12 to <18
n	7	13	11
% with >25 mg/dL rise from baseline	100	100	100
Mean Glucose C_{max} (mg/dL ± SD)	202 ± 36	216 ± 51	199 ± 57
Mean Glucose T_{max} (minutes ± SD)	67 ± 11	69 ± 15	81 ± 15
Mean $AUC_{0\text{-}90min}$ (mg/dL x minutes ± SD)	14440 ± 2114	14392 ± 2698	13105 ± 3026
Glucose at baseline (mg/dL ± SD)	68 ± 8	72 ± 8	76 ± 4
Glucose at 30 minutes (mg/dL ± SD)	150 ± 15	156 ± 27	130 ± 30
Time to rise in plasma glucose ≥25 mg/dL (minutes ± SD)	16.4 ± 3.8	16.2 ± 4.6	23.6 ± 9.5
% with nausea	43	54	36
% with emesis	14	23	18

- Across age groups there were no notable differences with regards to mean glucose AUC (0-90 m), C_{max}, and T_{max}. Plasma glucagon AUC (0-240 m), C_{max}, and T_{max} were similar across the age groups

Mean Plasma Glucose Over Time by Age Group



Note: For complete data only. Complete data was defined as no missing glucose value at any time point.
Note: Error bars are ± standard deviation.

- Nausea and vomiting were the most commonly reported AEs. No SAEs occurred. No safety concerns were noted with respect to vital signs measurements or physical examinations
- Administration site AEs (injection site discomfort and injection site reaction) were not frequently reported in this study
- The majority of instances of injection site discomfort were observed to be short in duration regardless of the dose or administration site of GRP
- The Faces Pain Scale – Revised (FPS-R) pain scores, associated with these injections were low across each age group and at each time point. At 30 minutes, scores ranged from 0.5 to 1.2 on a 10 point scale
- Instances of erythema and edema were frequently observed at 10 and 30 minutes following GRP administration in each age group, however mean and median Modified Draize Scale scores were at the low end of the scale

Incidence of Erythema After Administration of GRP by Age Group

		Incidence of Erythema*					
		10 Minutes		30 Minutes		180 Minutes	
Age Group	GRP Dose	n	%	n	%	n	%
2 to <6 years (N=7)	0.5 mg	4	57.1	2	28.6	0	0.0
6 to <12 years (N=13)	0.5 mg	8	61.5	7	53.8	0	0.0
12 to <18 years (N=11)	1 mg	5	45.5	6	54.5	1	9.1

*Erythema formation was defined as Modified Draize Scale score for erythema >0.

Incidence of Edema After Administration of GRP by Age Group

		Incidence of Edema*					
		10 Minutes		30 Minutes		180 Minutes	
Age Group	GRP Dose	n	%	n	%	n	%
2 to <6 years (N=7)	0.5 mg	3	42.9	3	42.9	1	16.7
6 to <12 years (N=13)	0.5 mg	9	69.2	8	61.5	4	30.8
12 to <18 years (N=11)	1 mg	5	45.5	5	45.5	1	9.1

*Edema formation was defined as Modified Draize Scale score for edema >0.

Incidence of Any Injection Site Discomfort by Age Group

		Incidence of Any Injection Site Discomfort*					
		10 Minutes		30 Minutes		180 Minutes	
Age Group	GRP Dose	n	%	n	%	n	%
2 to <6 years (N=7)	0.5 mg	6	85.7	1	14.3	1	14.3
6 to <12 years (N=13)	0.5 mg	8	61.5	6	46.2	1	7.7
12 to <18 years (N=11)	1 mg	7	63.6	2	18.2	0	0.0

*Any injection site discomfort was defined as Faces Pain Scale–Revised (FPS-R) score >0.

CONCLUSION

The Phase 3 clinical study results demonstrate that GRP consistently corrected insulin-induced hypoglycemia in pediatric subjects with type 1 diabetes, within the recommended ISPAD Guidelines. GRP is an effective, safe, and well tolerated rescue treatment for hypoglycemia in pediatric patients.

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