A PHASE 3 COMPARISON OF A READY-TO-USE LIQUID GLUCAGON RESCUE PEN TO GLUCAGON EMERGENCY KIT FOR THE SYMPTOMATIC RELIEF OF SEVERE HYPOGLYCEMIA

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ABSTRACT

OBJECTIVE: A novel ready-to-use stable liquid Glucagon Rescue Pen (GRP; Xeris Pharmaceuticals) auto-injector, was evaluated for relief of symptoms during rescue treatment of severe hypoglycemia.

METHOD: A Phase 3 randomized, controlled, single-blind, crossover clinical trial enrolled 81 adults with T1D to compare subcutaneous 1 mg doses of the GRP versus Glucagon Emergency Kit (GEK; Eli Lilly) for the treatment of insulin-induced severe hypoglycemia in adults. Serial assessments of 4 autonomic, 4 neuroglycopenic, average total symptoms, and sensation of hypoglycemia were performed at each treatment visit.

RESULT: The mean time to symptom relief from the time receiving glucagon treatment was comparable between the GRP and GEK for autonomic symptoms (9.9±6.45 min and 9.8±6.86 min, p=NS), neuroglycopenic symptoms (10.3±8.92 min and 9.9±7.22 min, p=NS), average total symptoms scores (13.0±9.23 min and 11.9±7.57 min, p=NS), and mean time to resolution of the global feeling of hypoglycemia (11.6±6.51 min and 13.1±7.93 min, p=NS) from receiving glucagon. All subjects achieved successful plasma glucose recovery. The overall incidence of all adverse events (AEs) was comparable in both groups; the most commonly reported AE was mild to moderate nausea (GRP 38.2%, GEK 33.3%) and vomiting (GRP 26.3%, GEK 14.1%). No SAEs occurred related to GRP.

CONCLUSION: The prompt relief of neurologic symptoms is critical in the rescue of severe hypoglycemic emergencies. The GRP achieved both autonomic, neuroglycopenic, and average total symptom relief during induced severe hypoglycemia. GRP achieved successful plasma glucose recovery in a reliable manner, was safe and well tolerated, and had an incidence of nausea and vomiting comparable to GEK. These results demonstrate that ready-to-use GRP is a viable alternative to currently available GEK.

BACKGROUND

In 2014, the Department of Health and Human Services National Action Plan for Adverse Drug Event Prevention highlighted diabetes agent-associated hypoglycemia as one of its three primary concerns because of the increasing prevalence and urgency of the problem.

- Treatment-associated hypoglycemia in people with diabetes remains the major limiting factor in the glycemic management of T1D and T2D, affecting more than 5.6M people in the US
- Severe hypoglycemic events are extremely frightening for patients and caregivers and can result in seizure, coma and, if left untreated, death
- The majority of severe hypoglycemic events are treated outside of a healthcare facility. 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
- Although two emergency powdered glucagon kits are currently available to treat severe hypoglycemia, they can be difficult to successfully prepare – potentially delaying prompt and accurate treatment. Successful delivery of current glucagon kits ranges from 6-31%

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
- Stable at room temperature: No refrigeration is required at any time

METHODS

- This was a non-inferiority, randomized, controlled, single-blind, 2-treatment, 2-way crossover comparative efficacy and safety study in adult subjects with T1D
- The procedure to evaluate the efficacy of the GRP was performed through an insulin-induced hypoglycemia procedure, used to decrease a subject's plasma glucose to a target <50.0 mg/dL
- After a confirmatory plasma glucose of <50.0 mg/dL was obtained, the subject was treated subcutaneously (SC) in the abdomen with either 1 mg GEK or 1 mg GRP
- Plasma glucose levels were monitored post-dosing
- Subjects completed a questionnaire about symptoms of hypoglycemia during the hypoglycemia induction phase until resolution, after treatment with glucagon

RESULTS

- For a combined endpoint (where failure was defined as either blood glucose remained ≤70 mg/dL or increased <20 mg/dL throughout the 0 to 30 minute period from the administration of study drug), GRP was accepted as non-inferior to GEK

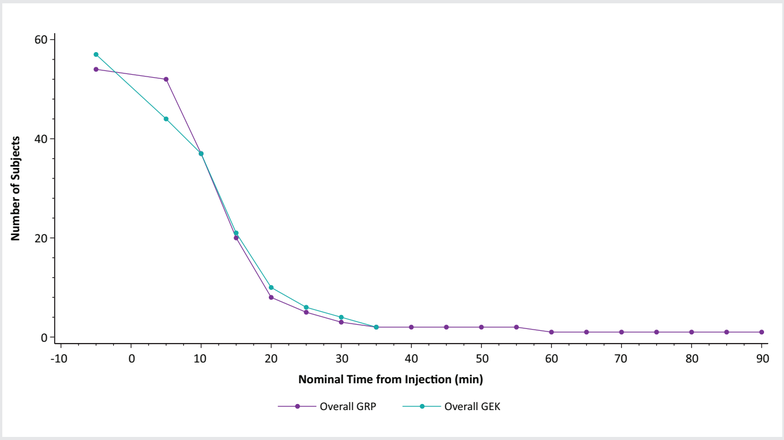
Clinical Comparison	Response Rate		
	GRP	GEK	p value
Subjects successfully rescued from induced hypoglycemia without other rescue therapy (e.g., D50)	100% (76/76)	100% (78/78)	N/A
Plasma glucose of >70 mg/dl or >20 mg/dl increase within 30 minutes of glucagon	100% (76/76)	100% (78/78)	N/A
Drug Preparation and Administration Time, mean ± SD (stopwatch, seconds)	27.3 ± 19.7	97.2 ± 45.1	p<0.0001
Mean Time to global resolution of hypoglycemia symptoms, minutes ± SD (from receiving glucagon)	11.6 ± 6.5	13.1 ± 7.9	p=NS
Mean Time to global resolution of hypoglycemia symptoms, minutes ± SD (from decision to dose)	12.7 ± 6.5	15.3 ± 8.0	p=0.02

- Mean plasma glucose at the time of receiving glucagon:
  - GRP: 47.4 ± 0.22 mg/dL (SEM)
  - GEK: 47.7 ± 0.18 mg/dL (SEM)
- GRP 1 mg was similar to GEK 1 mg in terms of the key endpoints: glucose C_{max}, T_{max}, and AUC (0-90)

Neuro

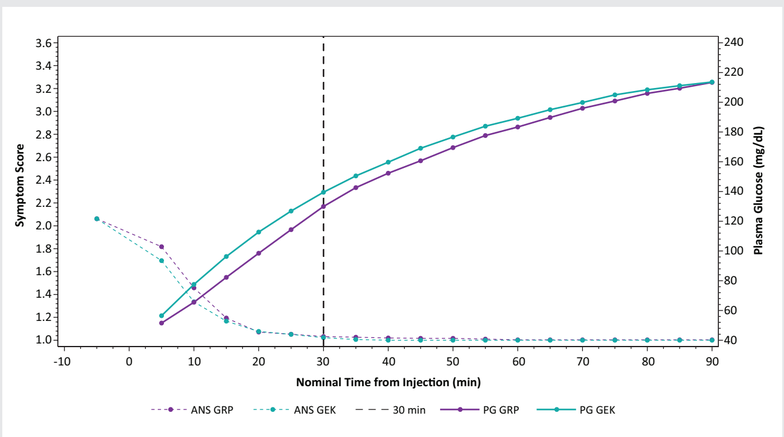
- As expected for both GRP and GEK, as plasma glucose levels increased, mean hypoglycemia symptom scores decreased
- Symptoms begin to resolve as early as 5 minutes

Number of Subjects with an Average Neuroglycopenic Score >1 by Time Intent-to-Treat Population

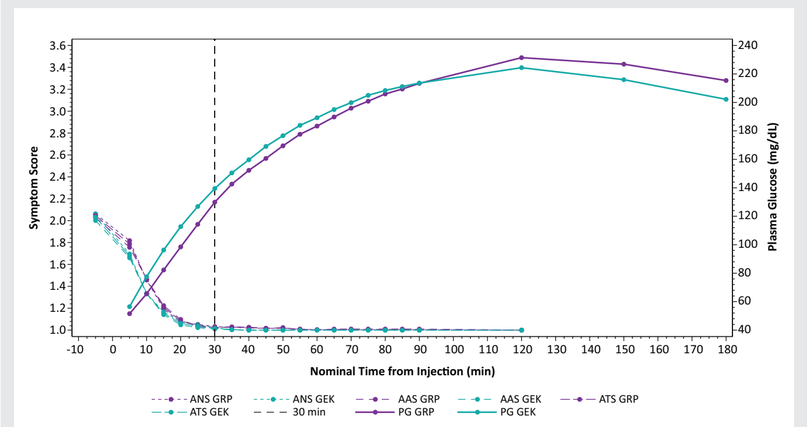


- The mean time to global resolution of hypoglycemia symptoms was statistically different between GRP and GEK from the decision to dose glucagon, 12.7 minutes and 15.3 minutes, respectively, (p=0.02). This may be in part due to the faster preparation and administration time of GRP.
- Symptom relief was comparable between GRP and GEK for both neurologic symptom scores with a median time of approximately 15 minutes across symptoms from decision to dose (p=NS for all assessments), GRP and GEK, respectively.

Mean Plasma Glucose Concentration and Average Neuroglycopenic Symptom Score Profiles by Time and Treatment Intent-to-Treat Population



Mean Plasma Glucose Concentration and Hypoglycemia Symptom Score Profiles by Time and Treatment Intent-to-Treat Population



- The most commonly reported AE considered related to study drug for subjects receiving GRP and GEK was nausea, followed by vomiting, and headache
- With GRP, all AEs were judged to be mild or moderate, and there were no SAEs
- No subjects were discontinued due to an AE, and there were no deaths in the study
- Both GRP and GEK were generally safe and well tolerated

Subjects Reporting Adverse Events Related to Study Medication by Treatment and Preferred Term (Safety Population)

Treatment-Emergent Adverse Events by Preferred Term	GRP N=76 N(%)	GEK N=78 N(%)
Nausea	29 (38.2%)	26 (33.3%)
Vomiting	20 (26.3%)	11 (14.1%)
Headache	6 (7.9%)	4 (5.1%)

CONCLUSION

GRP achieved successful plasma glucose recovery in a reliable manner, was safe and well tolerated, and had an incidence of nausea and vomiting comparable to GEK. The prompt relief of neurologic symptoms is critical in the rescue of severe hypoglycemic emergencies. The GRP achieved both autonomic, neuroglycopenic, and average total symptom relief during induced severe hypoglycemia. Time to global resolution of hypoglycemia symptoms was faster with GRP in comparison to GEK. The results of this Phase 3 clinically study demonstrate that ready-to-use GRP is a viable alternative to currently available GEK.

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