9-39 (Ex-9) have demonstrated that a single dose of Ex-9 can prevent postprandial hypoglycemia, normalize beta cell function, and reduce neuroglycopenic symptoms in patients with PBH. We present interim data from the first multi-dose, multi-day study aimed at evaluating the efficacy, tolerability, and pharmacokinetic profile of subcutaneous Ex-9 in patients with PBH.

In this Phase 2a, single-blind, multiple ascending dose study conducted at the Stanford University Clinical and Translational Research Unit, 11 participants underwent a baseline oral glucose tolerance test (OGTT) followed by random assignment to up to 3 days of BID subcutaneous doses of Ex-9 ranging from 0.05-0.45 mg/kg with a repeat OGTT on the final day of dosing. Treatment with Ex-9 reduced the magnitude of hypoglycemia at all dose levels. Participants receiving doses of ≥ 0.2 mg/kg did not require rescue, and on average achieved a 50 ± 13% reduction in peak insulin concentrations with a 44 ± 18% reduction in neuroglycopenic symptoms. These interim data provide preliminary evidence that multiple doses of Ex-9 prevent severe and symptomatic postprandial hypoglycemia in patients with PBH during OGTT.

Supported By: Eiger BioPharmaceuticals

5-LB

Differential Associations of Impaired Hypoglycemia Awareness and Severe Hypoglycemia with Cognition, Quality of Life, and Distress in T1D Adults

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Impaired hypoglycemia awareness (IHA) affects 20% to 40% of T1D patients and increases risk of severe hypoglycemia (SH). IHA has been associated with low concern about hypoglycemia, despite high risk of SH, and with reduced ability to change behavior to avoid future hypoglycemia. We assessed hypoglycemia awareness (HA) and sought correlations with cognition, quality of life (QoL), and distress in 85 T1D adults with HA and IHA. HA status was determined using the Gold Score (GS) and the Clarke score (CS), with ≥4=IHA for each. SH was evaluated by 2 questions (3 and 4) included in the CS. All subjects completed the Montreal Cognitive Assessment (global cognition); the INECO Frontal Screening (executive functions); the Diabetes Health Profile (DHP, QoL); and the Hospital Anxiety and Depression Scale. Participants' mean±SD age and diabetes duration were 38.4±12.5 and 19.1±11.7 years, respectively; 54.1% were male; median and interquartile ranges for GS and CS 3 [1-4] and 1 [0-3], respectively. 32% had IHA by GS and 17% by CS, the 2 scores correlating moderately (r_s=0.58, P < 0.001). 86% of IHA patients by CS vs. only 41% with IHA by GS had had SH in the past 6 months, with 50% vs. 19% reporting seizure, or parenteral treatment for SH in the last year and no reports of such SH in participants with IHA by GS only. Correlation analysis of the whole group showed that increased GS and CS associated with lower performance in naming subtest and higher barriers to activity in DHP. Only CS associated with higher psychological distress in DHP, and higher anxiety and depression, while 38% of subjects scoring positive for IHA with GS only had evidence of executive dysfunction.

In conclusion, people with T1D and IHA, at known high risk for SH, show evidence of impaired cognition and psychological distress. The association of a positive CS but not GS with increased psychological distress suggests the association may be driven by SH, while IHA alone may drive executive dysfunction.

6-LB

Racial Differences in Emergency Department Visits for Hypoglycemia in Older Insulin Recipients, 2004-2013

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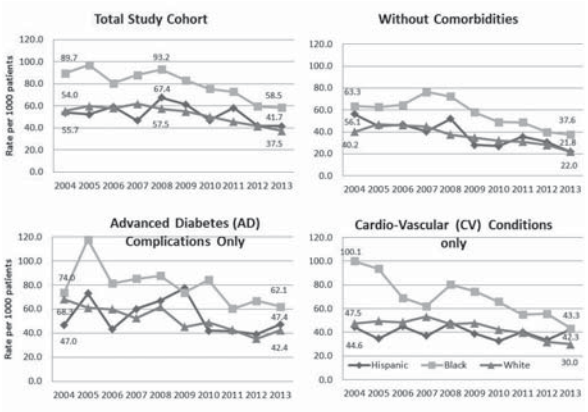
We evaluated annual trends in emergency department (ED) visits for hypoglycemia (HYPO) in veterans receiving Veteran Health Administration (VHA) care using linked VHA and Medicare databases. Patients on insulin and ≥65 years were stratified by race/ethnicity and four comorbidity categories (cardio-vascular (CV), advanced diabetes complications (AD), diminished life expectancy, and mental health/neurologic). Patients on insulin increased from 55,882 (11.2% of older diabetes patients) in 2004 to 100,175 (15.5%) in 2013. 80-82% were white, 10-11% black, 5-6% Hispanic, and <2% women. 79-83% had ≥1 comorbidity categories: AD only: 8-9%, CV only: 24-29%, AD and CV only: 16-21%. Cumulative ED visits were 37,494 (3,266-4,056/year) for 24,760 (2,563-3,266/year) unique patients; 5,094 (14%) events had subsequent hospitalization. Rates declined from 2008 for all races/ethnicity (rate ratio: 0.65; 95% CI=0.62-0.68 from a Poisson regression). Blacks had higher rates than whites (58.5 vs. 37.5 events per 1,000 patients in 2013). Compared to those without comorbidities (24.4 in 2013), rates were 46.4 for AD only, 31.3 for CV only, 49.6 for AD and CV only, and 70.1 for having 3 or 4 comorbidity categories in 2013. Racial differences persisted in all comorbid categories despite marked declines in HYPO_ED rates. We propose case management for high risk patients, especially minority groups.

Figure.



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7-LB

Prediction of Hypoglycemia during Aerobic Exercise in Individuals with Type 1 Diabetes Using Decision Trees

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Individuals with type 1 diabetes (T1D) indicate the fear of exercise related hypoglycemia as the major barrier to regular physical activity. There is currently no validated prediction algorithm that can help these individuals ascertain the risk of hypoglycemia prior to the start of aerobic exercise. We developed and evaluated 3 separate prediction algorithms with increasing levels of complexity to identify the risk of hypoglycemia at the start of exercise. A metadata set was used from over 130 observations of in-clinic aerobic exercise in 37 adults with T1D from 3 different studies (17M; weight, 72±12 kg; age, 33±6 years) to train and validate the prediction algorithms. Subjects performed either moderate or mild aerobic exercise at different times of the day (morning, midafternoon, or late afternoon) and exercised for durations ranging from 25 min to 45 min. We developed and tested the following three prediction algorithms using a ten-fold cross-validation approach and included anthropomorphic, exercise, glucose and insulin features. Model 1: Simple decision tree model. Model 2: Complex decision tree model. Model 3: Random forest model for use in automated insulin delivery systems

Table.

Classifier	Number of features	Accuracy (%)	Sensitivity (%)	Specificity (%)
Model 1	2	80.00	72.92	84.15
Model 2	5	83.85	85.42	82.93
Model 3	8	97.69	100	96.34

After further validation, these models could potentially be used by both artificial pancreas and decision support systems to help people with T1D avoid exercise related hypoglycemia.

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8-LB

Suppressed Catecholamine Release following Recurrent Hypoglycemia Involves Altered Adrenal Function

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Insulin-induced hypoglycemia activates the counter-regulatory response (CRR), a hormonal and neuronal mechanism that restores euglycemia. A major component of the CRR is the release of epinephrine from neuroendocrine chromaffin cells in the adrenal medulla. Epinephrine acts on a variety of target tissues including the liver and adipose tissue to increase glucose production. However, with repeated activation of the CRR, epinephrine release becomes progressively impaired. Although the reasons are not clear this could involve central or peripheral mechanisms or a combination of the two. To determine whether the altered CRR involves a change in adrenal function we quantified catecholamine release from chromaffin cells from (i) control mice; (ii) mice exposed to one episode of insulin-induced hypoglycemia (IIH: blood glucose < 60 mg/dl) and (iii) mice exposed to three episodes of insulin-induced hypoglycemia. Catecholamine release was evoked optogenetically from single chromaffin cells in vitro isolated from THcre x ChR (tdTomato) mice. Secretion was triggered by a train of light flashes and