REPEAT SUBCUTANEOUS DOSING OF EXENDIN 9-39 REDUCES HYPERINSULINEMIC HYPOGLYCEMIA AND NEUROGLYCOPENIC SYMPTOMS IN PATIENTS WITH POST-BARIATRIC HYPOGLYCEMIA

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ABSTRACT

Post-Bariatric Hypoglycemia (PBH) is a rare but serious complication of bariatric surgery manifested by frequent episodes of symptomatic postprandial hypoglycemia, for which there are no approved pharmacotherapies. A central role for exaggerated meal-induced secretion of the incretin hormone, glucagon-like peptide-1 (GLP-1) with dysregulated insulin secretion has been established, making GLP-1 receptor antagonism an attractive and targeted therapeutic approach. Studies evaluating intravenous (IV) infusion or subcutaneous (SC) injection of the GLP-1 receptor antagonist, exendin 9-39 (Ex 9-39) have demonstrated that a single dose can prevent postprandial hypoglycemia, normalize beta cell function, and reduce neuroglycopenic symptoms in patients with PBH during oral glucose tolerance testing (OGTT). This Phase 2, multiple-ascending dose (MAD) study conducted at Stanford University School of Medicine evaluated the efficacy, tolerability, and pharmacokinetic profile of two formulations of SC Ex 9-39 administered over up to 3 days BID in participants with PBH. We present interim results from the ongoing study. In Part A of this two-part study, 14 participants with PBH underwent a baseline OGTT followed by multiple ascending doses of up to 3 days of BID lyophilized (Lyo) Ex 9-39 with a repeat OGTT on the final day of dosing. In Part B, 5 participants underwent additional testing with 3 days of BID treatment with a novel liquid formulation (Liq) of Ex 9-39. Repeat dosing of both formulations of SC Ex 9-39 were well tolerated, improved postprandial hyperinsulinemic hypoglycemia, and reduced associated symptoms in patients with PBH in a dose-dependent manner. Liq Ex 9-39 improved postprandial metabolic and clinical parameters with comparable or greater efficiency than Lyo Ex 9-39 and appeared to confer greater exposure and duration of action. Liq Ex 9-39 represents a promising, convenient formulation for SC administration of Ex 9-39, and may provide an opportunity for lower and/or less frequent dosing.

BACKGROUND

Post-Bariatric Hypoglycemia (PBH) is a rare but serious complication of bariatric surgery manifested by frequent episodes of symptomatic postprandial hypoglycemia, for which there are no approved pharmacotherapies. A central role for exaggerated meal-induced secretion of the incretin hormone, glucagon-like peptide-1 (GLP-1) receptor antagonism an attractive and targeted therapeutic approach. Studies evaluating IV infusion (1,2) or SC injection (3) of the GLP-1 receptor antagonist, exendin 9-39 (Ex 9-39) have demonstrated that a single dose can prevent postprandial hypoglycemia, normalize beta cell function, and reduce neuroglycopenic symptoms in patients with PBH during OGTT. The current trial represents the first assessment of repeat dosing of SC Ex 9-39 and the first human data using a novel, proprietary liquid formulation. We present interim results (19 of 20 participants) from this investigation aimed at evaluating the efficacy, tolerability, and pharmacokinetic profile of multiple ascending doses of two formulations of SC Ex 9-39 administered over up to 3 days BID in participants with PBH.

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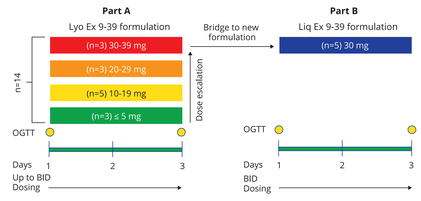
METHODS

Study Design and Procedures

Figure 1: Phase 2 MAD Study Scheme



This Phase 2 MAD study was conducted in two parts; Parts A and B. In Part A, 14 participants underwent a baseline OGTT, followed by up to 3 days of BID doses of a lyophilized (Lyo) formulation of SC Ex 9-39 ranging from 2.5 - 32 mg with a repeat OGTT on the final day of dosing. In Part B, 5 participants underwent a baseline OGTT, followed by 30 mg BID of a novel, liquid (Liq) formulation of Ex 9-39 with a repeat OGTT on Day 3 (Figure 1).

In both parts, metabolic, clinical and pharmacokinetic responses were evaluated, and tolerability and safety were monitored. Determination of dose levels and frequency were based upon interim review of PK, PD and safety data. Symptoms of hypoglycemia were assessed during OGTT by use of the Edinburgh Hypoglycemia Symptom Scale (EHSS) (4,5). At a plasma glucose of ≤ 50 mg/dL the OGTT was stopped with investigator rescue by IV dextrose.

Study Participants

Eligible participants were men and women, ages 18 to 65 years, who had undergone Roux-en-Y gastric bypass (RYGB) surgery at least 12 months prior, with a documented history of Whipple's triad, with inappropriately elevated insulin concentrations (> 3 µU/mL) at the time of hypoglycemia (≤ 55 mg/dL) and a minimum of one symptomatic episode per month by patient report.

Table 1: Participant Baseline Characteristics

	FORMULATION	
Characteristic	**Lyo Ex 9-39**	**Liq Ex 9-39**
Number of participants	N=14	N=5
Age (years)	45 ± 3.5	51 ± 2.9
Sex (male/female)	0 / 13	0 / 5
Pre-surgical BMI (kg/m^2)	48 ± 2.1	50 ± 2.4
Post-surgical BMI (kg/m^2)	28 ± 1.0	30 ± 2.3
Post-surgical time to hypoglycemia (years)	2.0 ± 0.5	1.8 ± 0.9
Post-surgical time with hypoglycemia (years)	6.6 ± 1.2	8.4 ± 1.1
History of T2D (yes/no)	3 / 10	1 / 5
HOMA-IR (U)	35 ± 6	40 ± 9
Percent with postprandial BG ≤ 50 mg/dL at least daily	54	60
Percent with neuroglycopenic symptoms at least daily	54	60

BMI = body mass index; BG = blood glucose; HOMA-IR = homeostatic model assessment of insulin resistance; T2D = type 2 diabetes

RESULTS

Metabolic and Clinical Responses

Part A:
Treatment with Lyo Ex 9-39 reduced the presence and degree of hypoglycemia at all dose levels. Participants receiving doses of ≥ 18 mg did not require IV dextrose rescue. A dose-response relationship was observed for Lyo Ex 9-39 with incrementally increasing improvements in glucose nadir, insulin peak and symptom score (Figure 2 and Table 2). The top two dose cohorts who on average received approximately 30 mg Lyo Ex 9-39 BID over 3 days, demonstrated a mean 37% increase in glucose nadir, 50% reduction in peak insulin concentrations, and 50% reduction in overall hypoglycemia symptom score, with a 50% reduction in neuroglycopenic symptoms (Figure 3A/C and Table 2). All doses were well tolerated with only mild headache or nausea reported, and no drug related adverse events (DRAEs) observed. On the basis of interim efficacy, safety and tolerability results, a fixed dose of 30 mg BID of Liq Ex 9-39 was selected for Part B.

Part B:
Treatment with BID doses of 30 mg Liq Ex 9-39 raised the postprandial glucose nadir during OGTT on the 3rd day of dosing in all participants evaluated, with no one requiring IV dextrose rescue. On average, participants achieved a 49% increase in glucose nadir, a 58% reduction in peak insulin concentrations and a 56% reduction in overall hypoglycemia symptom score, with a 12% reduction in neuroglycopenic symptoms (Figure 2, Figure 3B/D and Table 2). All doses were well tolerated with no DRAEs observed.

Table 2: Mean Metabolic and Pharmacokinetic Responses to OGTT on Final Day of Dosing by Dose and Formulation

	FORMULATION				
Characteristic	**Lyo Ex 9-39**				**Liq Ex 9-39**
Dosing range	**≤ 5 mg**	**10-19 mg**	**20-29 mg**	**30-39 mg**	**30 mg**
Number of participants	3	5	3	3	5
Dose (mg/kg)	0.5 ± 0.1	0.15 ± 0.02	0.35 ± 0.04	0.46 ± 0.02	0.38 ± 0.03
Metabolic Responses					
Glucose (mg/dL)					
Nadir (mg/dL)	45 ± 4	46 ± 5	51 ± 2	59 ± 8	60 ± 7
% increase nadir	16	6	33	41	49
% increase AUC$_{90,180}$	42	23	57	101	73
Rescue required (yes/no)	Yes	Yes	No	No	No
Insulin (µU/mL)					
% reduction peak	-1	31	32	67	58
% reduction AUC$_{0,60}$	-20	44	26	68	56
Pharmacokinetic Responses					
Cmax (ng/mL)	61 ±12	156 ± 24	228 ± 33	331 ± 72	359 ± 87
Tmax (min)	270 ± 17	252 ± 7	240 ± 35	190 ± 26	396 ± 82
AUC$_{0,720}$ (min ng/mL)	21151 ± 5702	46485 ± 7105	7798 ± 13522	113872 ± 22599	142971 ± 26449

Pharmacokinetic Responses

Part A:
Increasing doses of Lyo Ex 9-39 resulted in incrementally increased Ex 9-39 exposure, as demonstrated by Cmax and 12-hour AUC concentrations (Figure 4 and Table 2).

Part B:
Equivalent doses administered on a mg/kg basis of Liq vs Lyo Ex 9-39 yielded a higher Cmax, a higher 12-hour AUC and a later T-max. Liq Ex 9-39 resulted in higher trough plasma concentrations on the final day of dosing and demonstrated a more sustained absorption profile than comparable doses of Lyo Ex 9-39 (Figure 4 and Table 2).

Figure 2: Metabolic and Clinical Improvements in Response to OGTT by Dose and Formulation

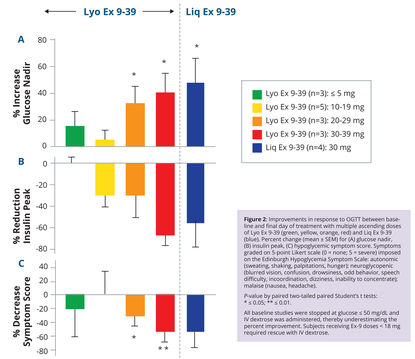
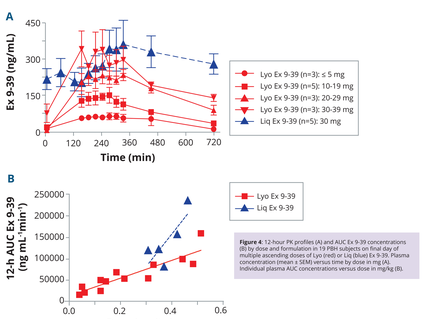


Figure 2: Improvements in response to OGTT between baseline and final day of treatment with multiple ascending doses of Lyo Ex 9-39 (green, yellow, orange, red) and Liq Ex 9-39 (blue). Percent change (mean ± SEM) for (A) glucose nadir, (B) insulin peak, (C) hypoglycemic symptom score. Symptoms graded on 5-point Likert scale (0 = none; 5 = severe) imposed on the Edinburgh Hypoglycemia Symptom Scale: autonomic (sweating, shaking, palpitations, hunger); neuroglycopenic (blurred vision, confusion, drowsiness, odd behavior, speech difficulty, incoordination, dizziness, inability to concentrate); malaise (nausea, headache).

P-value by paired two-tailed paired Student's *t* tests:
* ≤ 0.05; ** ≤ 0.01.

All baseline studies were stopped at glucose ≤ 50 mg/dL and IV dextrose was administered, thereby underestimating the percent improvement. Subjects receiving Ex-9 doses < 18 mg required rescue with IV dextrose.

Figure 4: Plasma Ex-9-39 Concentrations on Final Day of Treatment by Dose and Formulation



Lyo: R^2=0.8157; Liq: R^2=0.6247

Figure 4: 12-hour PK profiles (A) and AUC Ex 9-39 concentrations (B) by dose and formulation in 19 PBH subjects on final day of multiple ascending doses of Lyo (red) or Liq (blue) Ex 9-39. Plasma concentration (mean ± SEM) versus time by dose in mg (A). Individual plasma AUC concentrations versus dose in mg/kg (B).

Figure 3: Metabolic Responses to OGTT at Baseline and Final Day of Treatment with Lyo or Liq Ex 9-39

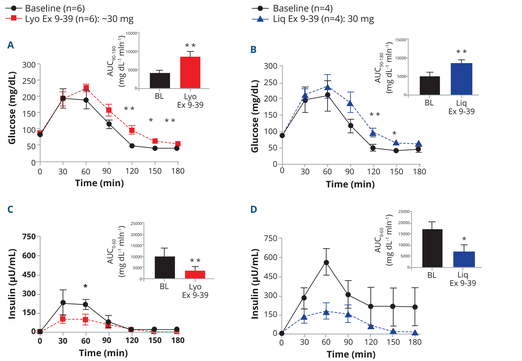


Figure 3: Mean metabolic responses to OGTT at baseline and final day of treatment with ~30 mg Lyo Ex 9-39 (A, C), n=6 or 30 mg Liq Ex 9-39 (B, D), n=4. Plasma concentrations (mean ± SEM) versus time and shown inset AUC levels (mean ± SEM) for (A, B) glucose, (C, D) insulin. Baseline (BL): solid black line, black bar. Lyo Ex 9-39: dashed red line, red bar. Liq Ex 9-39: dashed blue line, blue bar. *P*-values by paired two-tailed paired Student's *t* tests: * ≤ 0.05; ** ≤ 0.01.

All baseline studies were stopped at glucose ≤ 50 mg/dL and IV dextrose was administered. Baseline data shown beyond 120 minutes represents the last observation carried forward (LOCF), thereby underestimating the true difference between treatment and baseline results.

CONCLUSIONS

In patients with refractory PBH, repeat dosing of SC Ex 9-39 produced the following results during OGTT provocation:

- **Dose-dependent improvements in postprandial hyperinsulinemic hypoglycemia, and substantial reductions in the associated symptoms**
- **Prevention of neuroglycopenia, with no need for rescue at doses ≥ 18mg**
- **No drug related adverse events or tolerability concerns**

Liq Ex 9-39, a ready-to-use formulation, provided at least comparable protection against symptomatic postprandial hyperinsulinemic hypoglycemia and may confer greater pharmacokinetic exposure with longer duration of action. A robust evaluation of the PK profile of Liq Ex 9-39 including the potential for less frequent dosing is ongoing.

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