A Phase 2a Multi-Ascending Dose Trial to assess the efficacy, tolerability and pharmacokinetic profile of BID Exendin (9-39) in patients with post-bariatric hyperinsulinemic hypoglycemia

Background and Study Rationale.

Post-Bariatric Hyperinsulinemic Hypoglycemia (PBHH) is a rare, but increasingly reported complication of bariatric surgery, characterized by severe hypoglycemic episodes with neuroglycopenic symptoms. At the moment, no medical therapies have been developed for this disorder, but the clinical need is great. While the underlying cause is not known, the major contributory factor is thought to be an exaggerated postprandial secretion of glucagon-like peptide-1 (GLP-1) due to altered nutrient transit after bariatric surgery. GLP-1 is an incretin hormone secreted primarily by the distal ileum that contributes to postprandial glucose regulation. Exendin (9-39) (Ex9) is a specific GLP-1 receptor antagonist, that when given via continuous IV infusion, effectively prevents postprandial hypoglycemia in patients with PBHH (1). A single dose of subcutaneous (SC) Ex9 has been shown to effectively reverse postprandial hypoglycemia and substantially reduce symptoms in patients with hyperinsulinemic hypoglycemia (2). Based upon the results of this single ascending dose study designed to examine the pharmacokinetics, pharmacodynamics, and local tolerability of SC Ex9, relatively low doses of Ex9, up to only 37,500 pmol/kg have been shown to effectively prevent hypoglycemia and reduce associated symptoms. Building upon the success of these results, the proposed 3-day MAD study is a critical next step that will elucidate the pharmacokinetic and pharmacodynamic dose-response of BID SC Ex9.

Study objectives and endpoints.

Objective	**Endpoint**
Primary:	
• To evaluate the treatment effect on plasma glucose of SC BID Ex9	Response rate in plasma glucose nadir, defined as proportion of patients in each dose arm with no plasma glucose ≤50 mg/dL at any timepoint from 0-180 minutes during OGTT on Day 3 of treatment vs. on Day 0.
Secondary:	
• To evaluate the treatment effect on symptoms of hypoglycemia of SC BID Ex9	Improvement in composite symptom score as compared to baseline during OGTT on Day 3 of treatment vs. on Day 0.
• To assess the pharmacokinetics of SC BID Ex9 at each dose level	Plasma PK parameters include $AUC_{0\text{-}12h}$, C_{max}, T_{max}, $T_{1/2}$, and C_{trough}, after SC injection.
• To assess the safety and tolerability of SC BID Ex9 at each dose level	AEs, laboratory parameters, vital signs; NMR score, VAS score.

Study Design.

Overview: This is a single-blinded, dose-randomized, cross-over design study that will be conducted at the Stanford University School of Medicine. All subject visits will take place in the Clinical and Translational Research Unit (CTRU). Sixteen eligible subjects will be assigned to 1 of 4 dose levels to receive BID Ex9 over 3 days. After a baseline Oral Glucose Tolerance Test (OGTT) is conducted on Day 0 wherein metabolic and symptomatic analyses will occur, subjects will return to the research clinic on Day 1 to initiate a BID dosing schedule for 3 days. During this time, subjects will return daily for fasting labs in the morning, a morning dose, PK sampling, and an evening trough sample, followed immediately by the second daily dose at T+720 min. Safety, tolerability, and pharmacokinetic parameters will be measured on a daily basis for the full 3 day duration of the study, after which a repeat OGTT is performed on the morning of Day 3 after the morning dose to evaluate for efficacy (no hypoglycemia and reduction in composite symptom score). Day 4 will consist solely of clinical safety monitoring with a plasma trough drawn 1440 minutes after the last Day 3 injection. This study if properly conducted is expected to demonstrate that BID dosing can result in meaningful therapeutic activity in each dosing arm.

Randomization/Blinding: Computer-generated block randomization will be employed for the first 8 subjects, such that 2 subjects are randomized to each of 4-dose levels. If no clinical efficacy is seen at a given level after 2 subjects have been tested at that level, that dose level will be removed and remaining subjects will be randomized to one of the remaining doses. Otherwise, a total of 4 subjects will be evaluated in each of 4 dose levels. All subjects will remain blinded throughout. With the exception of the PI and sub-investigator who will remain un-blinded for safety purposes, all site personnel including nurses and study coordinators, who conduct patient symptom surveys, will remain masked to treatment assignment.

[redacted]

Study drug preparation and dispensation: All doses will be prepared by the Stanford Investigational Drug Services, and dispensed at the Stanford Clinical and Translational Research Unit by qualified staff, as previously described [redacted]

Oral Glucose Tolerance Test (OGTT): The OGTT will consist of administration of one 75 gram glucola drink with 1 gram of crushed acetaminophen to be consumed over 20 minutes.

Assays: Metabolic: glucose, c-peptide, insulin, GLP-1, GIP, glucagon; PK: $AUC_{0\text{-}720}$, C_{max}, T_{max}, $T_{1/2}$, C_{trough}

[redacted]

Overview of Visits.

Day 0: Baseline OGTT with Metabolic analysis

Timepoints: Plasma samples obtained at: T-10, T+30, 60, 90, 120, 150, 180.

Metabolic Assays: Glucose, c-peptide, insulin, GLP-1, GIP, glucagon

Days 1-3: SC injections at T=0 min and T=720 min, PK plasma samples with PK analysis

Timepoints: Plasma samples at T-1, T+60, 120, 180, 210, 240, 300, 360, 480, 720

Assays: $AUC_{0\text{-}720}$, C_{max}, T_{max}, $T_{1/2}$, C_{trough}

Day 3: Repeat OGTT after 5 SC injections with metabolic and PK analyses

Timepoints: Plasma samples at T-1, +150, 180, 210, 240, 270, 300, 330, 480, 720

Assays: Metabolic: Glucose, c-peptide, insulin, GLP-1, GIP, glucagon; PK: $AUC_{0\text{-}720}$, C_{max}, T_{max}, $T_{1/2}$, C_{trough}

Day 4: Safety monitoring, PK trough draw

Timepoints: Plasma samples at T-1, T+60, 120, 180, 210, 240, 300, 360, 480, 720

A schedule of all laboratory and clinical assessments by visits are outlined in detail on **Table 4** below.

Table 4. Visit evaluation schedule

	Day 0	Day 1	Day 2	Day 3	Day 4
Screening/Enrollment					
Obtain Informed consent	X				
Patient history	X				
Demography	X				
Inclusion/exclusion criteria	X				
Prior/concomitant medications	X				
Physical exam	X			X	
Height	X				
Weight	X	X	X	X	X
Pulse rate	X	X	X	X	X
Blood pressure	X	X	X	X	X
Oral Glucose Tolerance Test	X			X	
Hypoglycemic symptom assessment	X			X	
Metabolic assays: Glucose, c-peptide, insulin, GLP-1, GIP, glucagon	X			X	
Ex9 injection		X (AM), X (PM)	X (AM), X (PM)	X (AM), X (PM)	
Tolerability assessment		X (AM), X (PM)	X (AM), X (PM)	X (AM), X (PM)	
PK plasma samples		X	X	X	X
Assessment for AEs	Ongoing				
Laboratory assessments:					
Urine pregnancy test	X				
CBC	X				X
Comprehensive Chemistry	X				X

Subjects.

N=16 subjects

Inclusion criteria.

1. Male or female patients 18-70 years of age
2. Post-bariatric surgery more than 6 months prior to signing the informed consent
3. Documented history of hyperinsulinemic hypoglycemia
4. Hypoglycemia during the baseline/screening OGTT on Visit Day 0, as defined by the presence of Whipple's triad: the occurrence of hypoglycemic symptoms associated with a plasma glucose of ≤55 mg/dL, and resolution with glucose or carbohydrate administration.

Exclusion criteria.

1. Patients currently using sulfonylureas or other medications that may interfere with glucose metabolism within 5 half-lives of drug.
2. Participation in any clinical investigation involving an experimental drug within 4 weeks prior to dosing
3. History of or current insulinoma
4. Active infection or significant acute illness within 2 weeks prior to dosing
5. Female patients who are pregnant or lactating
6. Women of childbearing potential and not utilizing effective contraceptive methods
7. Inadequate end organ function as defined by:
    a. Serum creatinine >2.0 mg/dL
    b. ALT and AST > 3 x ULN

[redacted]

[redacted]

Strategy proposed for interim data analysis.

[redacted]

Dose cohort modification.

No efficacy: In instances wherein no clinical efficacy is observed in the first two subjects at a given dose level (plasma glucose on Day 3 repeat OGTT reaches 50 mg/dL or less), no further subjects will be assigned to that dose level. Remaining subjects will be randomized to 1 of the remaining dose levels, as depicted in **Figure 4** below.

[redacted]