CLINICAL STUDY PROTOCOL 52880

Study Title:	**A Phase 2, Open-Label, Cross-over Study to Assess the Safety and Efficacy of Avexitide in Acquired Hyperinsulinemic Hypoglycemia**
Investigational Product	Avexitide Injection
IND Number	[redacted]; [redacted] by cross-reference
Sponsor:	Stanford University School of Medicine
Principal Investigator	Marilyn Tan, MD
Date:	20 November, 2020
Amendment No.:	0001
Amendment submission date:	13 May, 2021

Sponsor:	Investigational Product:	Developmental Phase:
Stanford University School of Medicine	Avexitide Injection	Phase 2

Title of Study

A Phase 2, Open-Label, Cross-over Study to Assess the Safety and Efficacy of Avexitide in Acquired Hyperinsulinemic Hypoglycemia

Protocol Number: 52880

INTRODUCTION AND BACKGROUND

Hyperinsulinemic Hypoglycemia (HH) is a rare but growing disease state characterized by frequent episodes of severe symptomatic hyperinsulinemic hypoglycemia, with glucose concentrations low enough (<54 mg/dL) to cause seizures, altered mental status, loss of consciousness, cognitive dysfunction, disability, and possibly death. The predominant form of HH is post-bariatric hypoglycemia (PBH), which occurs in some 29-39% of patients undergoing Roux-en-Y gastric bypass (RYGB) and 10-23% of those undergoing vertical sleeve gastrectomy (VSG) (1-4). HH can also occur as a complication of other upper-gastrointestinal procedures, including esophagectomy (5), gastrectomy (6), and Nissen fundoplication (7). Currently, there are no effective medical therapies for patients with HH.

The mechanisms mediating PBH and other forms of HH that occur after gastrointestinal procedures have long been debated, though excessive postprandial secretion of the incretin gut hormone, glucagon-like peptide-1 (GLP-1), has been shown to play a critical role in mediating hyperinsulinism (5-6,8-10). Avexitide is a specific, competitive antagonist of the GLP-1 receptor formed by the terminal deletion of the 8 N-terminus amino acids from exenatide (commercial name Byetta), a GLP-1 agonist. Prior studies conducted by our laboratory and others involving either intravenous (7, 11-13) or subcutaneous (14-16) administration of avexitide have shown normalization of postprandial insulin concentrations with reduction in the occurrence and severity of hypoglycemia and associated symptoms.

The most recent study in which our laboratory participated, the PREVENT study (16), was a Phase 2, randomized, placebo-controlled crossover study evaluating two dosing regimens of avexitide (30 mg BID and 60 mg QD) in 18 patients with diet-refractory PBH. In this study, 18 participants received placebo injections for 14 days followed by avexitide 30 mg BID and avexitide 60 mg QD, each for 14 days in random order. The primary outcome was glucose nadir during mixed meal tolerance testing (MMTT) at the end of each 14-day treatment period. In addition, hypoglycemic events captured by SMBG, eDiary, and blinded continuous glucose monitoring (CGM) were captured. The primary and secondary endpoints were met by both avexitide regimens. Compared to placebo, avexitide 30 mg BID and 60 mg QD raised the plasma glucose nadir by 21% (p=0.001) and 26% (p=0.0002) and lowered the insulin peak by 23% (p=0.029) and 21% (p=0.042), corresponding to 50% and 75% fewer participants requiring rescue, respectively. Significant reductions in outpatient rates of Levels 1-3 hypoglycemia were observed, defined, respectively, as SMBG<70 mg/dL, SMBG<54 mg/dL, and a severe event characterized by altered mental and/or physical function requiring assistance. Blinded CGM demonstrated reductions in hypoglycemia without induction of clinically relevant hyperglycemia. Avexitide was well-tolerated, with no increase in adverse events.

Based on the safety and tolerability profile of avexitide and the dose-response relationship observed with higher daytime avexitide exposure in the PREVENT trial, we seek to evaluate whether higher dosing regimens of avexitide may confer greater yet protection against hypoglycemia. In addition, given that GLP-1 excursions are also known to occur in forms of HH other than PBH, we seek to evaluate for the first time whether subcutaneous injection of avexitide may provide protection against hypoglycemia in this expanded cohort of patients with HH. Thus, we seek to extend upon the the previously conducted studies by investigating the safety, tolerability and efficacy of avexitide administered as 45 mg BID and 90 mg QD dosing regimens in patients with HH occurring after RYGB, VSG, esophagectomy, gastrectomy, and Nissen fundoplication.

OBJECTIVES

Primary Efficacy Objective

Evaluate the effect of avexitide injection on the number of diurnal Level 2 hypoglycemia events (ADA, <54 mg/dL) as measured by CGM in patients with severe HH

Secondary Efficacy Objectives

Evaluate the effect of avexitide injection on the:

- Rate of Level 2 hypoglycemia (ADA, <54 mg/dL) as measured by SMBG
- Rate of Level 3 hypoglycemia (ADA, severe hypoglycemia)
- Percent diurnal time <54 mg/dL as measured by CGM
- Postprandial glycemia during standardized mixed meal consumption

Exploratory Efficacy Objectives

Evaluate the effect of avexitide injection on:

- Quality of life (QoL)
- Rate of Level 1 hypoglycemia (ADA, <70 mg/dL) as measured by SMBG in patients with severe HH
- Percent time >250 mg/dL as measured by CGM
- Percent nocturnal time <54 mg/dL as measured by CGM
- Number of nocturnal Level 2 hypoglycemia events (ADA, <54 mg/dL) as measured by CGM
- Characterize the Pharmacokinetic/Pharmacodynamic (PK/PD) profile of avexitide 45 mg BID and 90 mg QD
- Evaluate development of anti-drug antibodies (ADA)

Primary Safety Objective

- Evaluate the safety and tolerability of avexitide

INVESTIGATIONAL PLAN

Study Design

Overview—This is a Phase 2b, single center, open-label, cross-over study of avexitide injection in patients with surgically-induced severe, diet-refractory HH. Eligible participants must have a confirmed diagnosis of surgically-induced HH and demonstrate severe, diet refractory HH, as documented by presence of at least two severe hypogycemia events from which at least one must be characterized by glucose <54 mg/dL as measured by CGM during the 14-day Run-in Period while adhering to medical nutritional therapy.

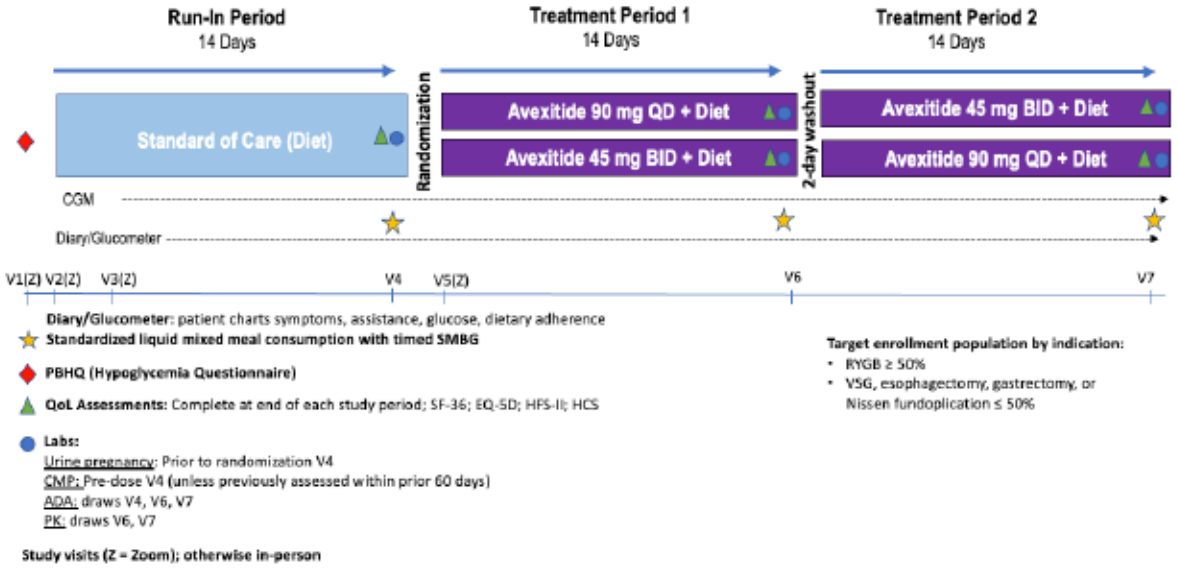
Eligible HH indications include hypoglycemia occurring after:

- Bariatric Surgery:
  -Roux-en-Y Gastric Bypass (RYGB) or Vertical Sleeve Gastrectomy (VSG)
- Upper-Gastrointestinal Surgery:
  -Gastrectomy, Esophagectomy, or Nissen Fundoplication

Provisionally eligible subjects will undergo a 14-day Run-In consisting of standard of care (SOC) treatment (medical nutrition therapy) with standardized mixed meal consumption and screening labs and collection of blood to test for anti-drug antibody (ADA) at the end of the 14-day SOC Run-In to confirm eligibility and establish a baseline within 90 days of randomization. Enrolled participants will be randomized to one of two 14-day avexitide dosing regimen orders (Figure 1). Doses are to be self-administered in the outpatient setting via subcutaneous (SC) injection. Throughout the study duration participants will continue to maintain SOC treatment following standard dietary guidelines for management of PBH and will be evaluated by blinded CGM, patient electronic diary (eDiary) and SMBG. At the end of Treatment Periods 1 and 2, participants will repeat baseline assessments with ADA and trough PK samples additionally drawn. At the end of Treatment Period 2, participants will return used and unused study drug vials during the safety follow-up visit.

Study Duration— Depending on when a patient completes the Run-In Period, the maximum anticipated time an individual patient will participate in the study will be ~120 days.

Figure 1 Diagram of Study Design



Number of Participants

Up to 20 participants will be enrolled in a 1:1 ratio to each of the two dosing regimen orders shown in Figure 1. Of the enrolled population, at least 50% will be post-RYGB; the remainder will be post-VSG, -gastrectomy, -esophagectomy, or -Nissen fundoplication. Randomization will be stratified by type of surgery RYGB vs Others (including VSG, gastrectomy, esophagectomy, or Nissen fundoplication).

Rationale for Dose and Dose Regimen Selection

The dose levels of avexitide and the dosing intervals selected for this study are based on results from the Phase 2 PREVENT study, a randomized, placebo-controlled crossover study evaluating two dosing regimens (30 mg BID and 60 mg QD) in 18 patients with diet-refractory PBH. On the basis of the strength and consistency of study results from the PREVENT trial and the safety and tolerability profile associated with avexitide exposure, we seek to conduct a preliminary analysis of use of a 90 mg total daily dose administered as 45 mg BID and 90 mg QD, as it is of our opinion that higher total daily exposure may be well-tolerated and has the potential to result in even more robust clinical outcomes.

STUDY POPULATION

Inclusion Criteria

Patients must meet all of the following inclusion criteria before study entry to be eligible for enrollment.

1. Able to understand the purpose and risks of the study; willing and able to adhere to scheduled visits, treatment plans, laboratory tests, procedures, and provide written informed consent
2. History of qualifying bariatric or upper-gastrointestinal surgery (RYGB, VSG, gastrectomy, esophagectomy, or Nissen fundoplication) at least 12 months prior to the start of Screening
3. Male or female, at least 18 years old (inclusive) at Visit 1 (Screening)
4. Body mass index (BMI) of up to 40 kg/m^2
5. Has stable body weight, i.e., not varying by >5% for at least 4 months prior to Visit 1 (Screening), as documented by the investigator
6. History of recurrent hypoglycemia refractory to bariatric dietary recommendations occurring after bariatric or upper-GI surgery, as documented in the medical record.
7. At least two severe hypogycemia events from which at least one must be characterized by glucose <54 mg/dL as measured by CGM during the 14-day Run-in Period while adhering to medical nutritional therapy.
8. If female, must meet the following criteria:
    a. Not breastfeeding or lactating
    b. Negative urine pregnancy test result at Visit 4 (Screening) (not applicable to hysterectomized females); urine pregnancy test at Screening must be confirmed negative prior to randomization and dosing.
    c. If of childbearing potential (including peri-menopausal women who have had a menstrual period within 1 year) must agree to use appropriate birth control (defined as a method which results in a low failure rate, i.e., less than 1% per year, when used consistently and correctly, such as implants, injectables, hormonal contraceptives, some intrauterine

contraceptive devices, sexual abstinence, tubal ligation or occlusion, or a vasectomized partner) during the entire duration of the study. Subjects must practice appropriate birth control as stated above for 4 weeks after the last dose of study drug.

- Nonchildbearing potential is defined as surgically sterile (documented hysterectomy, tubal ligation, or bilateral salpingo oophorectomy) or postmenopausal (defined as 12 months of spontaneous amenorrhea).

9. Has no clinically significant abnormal complete metabolic panel (CMP) as judged by the investigator. Note: CMP collected at Visit 4 unless assessed within 6 months prior to randomization.
10. Has no clinically significant medical condition, as judged by the investigator, at Screening

Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study.

General Exclusions

1. Use of an investigational drug within 5 half-lives of the study drug before Screening.
2. Donation or loss of >500 mL of blood or blood product within 56 days before the first dose of study drug.
3. Clinically significant active infection within 14 days before the first dose of study drug.
4. Any clinically relevant acute or chronic psychiatric, renal, hepatic, pancreatic, cardiovascular, neurological, hematological, or gastrointestinal abnormality (eg, inflammatory bowel disease) or active malignancy.
5. Major surgery within 6 months before randomization.
6. History of or current insulinoma or other cause of endogenous hyperinsulinism other than HH (e.g., insulin autoimmune hypoglycemia). Such causes must be ruled out if clinically suspected by the Investigator.

Exclusions Based on Laboratory Values

7. Abnormal laboratory values of clinical significance as assessed by the Investigator. Note:

Exclusions Based on Recent or Concomitant Medication or Drug Use

8. Use of agents that may interfere with glucose metabolism within 5 half-lives, as follows:
    a. Anti-hyperglycemic agents (eg, insulin, sulfonylureas, meglitinides, metformin, thiazolidinediones [TZDs], dipeptidyl-peptidase [DPP-4] inhibitors, sodium-glucose-linked transporter 2 [SGLT2] inhibitors, GLP-1 agonists).
    b. Alcohol (eg, beer, wine, drinks containing distilled spirits)
    c. Fluoroquinolone antibiotics (eg, ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin)
    d. Tramadol (chronic use of other opioids is permitted as long as dose remains stable throughout study)
    e. Current use of acarbose, verapamil, diazoxide and or somatostatin analogs (eg. octreotide, pasirotide, lanreotide)

f. Systemic or inhaled glucocorticoids (eg, prednisone, prednisolone, methylprednisolone, beclomethasone, betamethasone, dexamethasone, hydrocortisone, triamcinolone) with exception of topically or nasally administered steroids

Subject Restrictions

Participants must report any new prescription medications or over-the-counter preparations or any changes to concomitant medications to study staff for the duration of study participation

INVESTIGATIONAL PRODUCT, DOSAGE AND ADMINISTRATION

Avexitide injection is a sterile, clear, colorless solution and is supplied in single-use 3 mL vials containing 0.5 mL solution. The drug product composition consists of 90 mg/mL avexitide injection (active ingredient). The avexitide investigation product should be stored refrigerated between 2°C to 8°C (35.6°F to 46.4°F), inclusive.

Dispensing and Administration of Study Drug

Three kits of study drug (two containing 28 x 3mL vials and one containing 6 x 3mL vials of 90 mg/ml solution) will be dispensed by the Investigator on V4. Participants will be given written and oral instructions on how to store, draw up and safely administered study drug. The study drug will be administered as subcutaneous injections either once daily in the morning (90 mg QD), or twice daily (45 mg BID): once in the morning and the second daily dose approximately 12 hours later. During once daily dosing, the morning dosing will occur at least 60 minutes prior to the first morning meal. During twice daily dosing, the morning dosing will not be relative to the timing of the first meal of the day.

Missed Doses

If patients miss a dose or a dose is delayed, the dose should be taken as soon as the missed or delayed dose is noted. In the event a dose is missed and it is time for the next dose to be taken, the missed dose should be taken along with the scheduled dose. However no more than 3 doses should be administered within any given 24-hour period.

Drug Accountability

Drug accountability will be maintained by the principal investigator, who will ensure that a current record of investigational product disposition is maintained and that the investigational product is used only in accordance with the approved protocol.

Patients will be instructed to return all used and unused vials of study drug when they come to the clinic for the final study visit. Adherence with the prescribed regimen for each study drug will be estimated by counting the number of used and unused vials.

STUDY CONDUCT AND ASSESSMENTS

Screening Procedures

Patients providing written informed consent will be evaluated to determine eligibility to participate in the study. An initial eligibility review will be conducted, including:

- review of medical history and concomitant medications
- review of Level 2 and Level 3 hypoglycemia event rate (<54 mg/dL by CGM or Level 3 hypoglycemia) during Run-In
- review of clinical lab results

- pregnancy testing (as applicable)

The preliminary eligibility assessments may be performed up to 90 days prior to randomization, consisting of a 14-day Baseline Run-in period during which the following items will be supplied concurrent with training:

- eDiary
- dietary guidelines (describes SOC medical nutrition therapy)
- glucometer, lancets and test strips
- Dexcom G6PRO

Study Schedule

The screening period comprises:

- Visit 1 (Zoom): Informed Consent, review of medical history, hypoglycemia questionnaire, concomitant medications, assessment of preliminary eligibility
- Visit 2 (Zoom): training on patient eDiary, glucometer use, and Dexcom G6PRO application and activation. Participants begin 14-day Run-In Period
- Visit 3 (Zoom): Check in with patient.
- On day 10 of the Run-In Period, participants place a new Dexcom G6PRO sensor.
- Visit 4 (SHC): On day 14 of the Run-In Period, participants go to SHC for a urine pregnancy test, an ADA draw, and CMP as applicable then consume a standardized liquid mixed meal over 10 minutes, with fingerstick glucose checks every 30 minutes for a total of 180 minutes. Eligible participants are then enrolled, randomized and dispensed study drug.

  Enrolled participants will be randomized 1:1 to one of 2 avexitide dosing regimen orders, and will be trained on study medication injection procedures. Avexitide should be injected subcutaneously either once daily in the morning, or twice daily; once in the morning and the second daily dose approximately 12 hours later. During once daily administration (avexitide 90 mg QD), morning dosing will occur at least 60 minutes prior to the first morning meal. During twice daily administration (avexitide 45 mg BID) morning dosing will not be relative to the timing of the first meal of the day. Throughout, patients will follow currently accepted dietary guidelines for treatment of PBH.
- Visit 5 (Zoom): Participants are trained on study drug injection; initiate Treatment Period 1. Place new Dexcom G6PRO device.
- Day 10 of Treatment Period 1: Participants place a new Dexcom G6PRO device.
- Visit 6 (SHC): On day 14 of Treatment Period 1 participants have a PK and an ADA draw, have their final Treatment Period 1 study drug injection and 90 minutes later consume a standardized mixed meal over 10 minutes, with fingerstick glucose checks every 30 minutes for 180 minutes. Participants are dispensed new study drug and initiate a 2-day washout period.
- Day 4 of Treatment Period 2: Participants place a new Dexcom G6PRO device.
- Visit 7 (SHC): On day 14 of Treatment Period 2 participants have a PK and an ADA draw, have their final Treatment Period 2 study drug injection and 90 minutes later participants consume a standardized mixed meal over 10 minutes, with fingerstick glucose checks every 30 minutes for a total of 180 minutes. Participants then remove their Dexcom sensor/transmitter and return their used/unused study drug vials.

Study Procedures

eDiary and Glucometer

Patients will be trained on the use of an eDiary on Visit 2 in which they will record all hypoglycemia signs, symptoms, and outcomes, any corrective actions taken for hypoglycemia, any assistance received related to an episode, and dietary intake. Patients will also receive a glucometer prior to Visit 2 and be instructed to check fingerstick glucose concentrations whenever they experience hypoglycemic symptoms. Patients will also enter into the eDiary all SMBG glucose values obtained during consumption of the 3 standardized liquid meals. Study personnel will train participants on the use of the eDiary and glucometer.

Blinded Continuous Glucose Monitoring (CGM)

During the Run-In phase, a Dexcom Mobile G6 Pro Continuous Glucose Monitoring System in blinded mode (i.e., the CGM device) will be issued to potential study participants. Each participant will be trained on its use in accordance with the manufacturer's instructions. Written instructions for CGM use and maintenance will be provided. The instructions will, if necessary, be repeated at site visits. The data from CGM will be downloaded after Run-In and at the end of each 14-day period for enrolled subjects. Each device will be blinded for use during the study. The Dexcom Mobile G6 Pro CGM System must be removed before magnetic resonance imaging (MRI), computed tomography (CT) scan, or high-frequency electrical heat (diathermy) treatment.

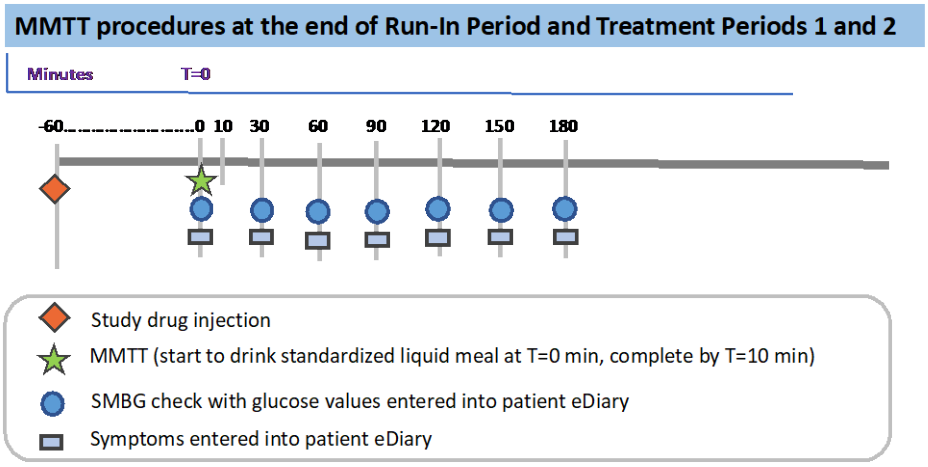
Dietary Treatment

All patients will be expected to follow accepted dietary treatment guidelines for PBH throughout the study including during the Run-In period. Guidelines provided include limiting dietary carbohydrates to no more than 30 g per meal or 15 g per snack, avoiding simple, high glycemic index carbohydrates, maintaining adequate protein intake, abstaining from consumption of alcohol, and maintaining post-bariatric vitamin and mineral supplementation. A written description of guidelines will be provided to each participant for at-home reference. The site personnel will be responsible for reviewing the guidelines with patients at each study visit. Patients will report dietary adherence in their eDiary on a daily basis.

Mixed Meal Tolerance Test

At the end of each study period (Run-In, Treatment Periods 1 and 2), participants will consume a standardized liquid meal (e.g., Boost Nutritional Drink) over 10 minutes, with fingerstick glucose checks every 30 minutes for a total of 180 minutes. Participants will record glucose values in the eDiary.

Figure 2



Quality of Life Assessments

The Short-Form (36) Health Survey (SF-36v2), EQ-5D, Hypoglycemia Fear Survey-II (HSF-II), and Hypoglycemia Confidence Scale (HSC) are patient-reported outcomes measures that enrolled patients will complete via RedCap survey at the end of the Run-In period and at the end of each of study period.

Clinical Laboratory Tests

A urine pregnancy test as applicable, a complete metabolic panel (unless assessed within the 6 months prior), and blood samples for ADA will be obtained. Any out of range laboratory results should be assessed for clinical significance with study entry eligibility at the discretion of the PI.

Safety Assessments

Safety assessments will consist of monitoring and recording adverse events (AEs) and serious adverse events (SAEs). The investigator will carefully monitor each subject throughout the study for possible AEs. Patients enrolled into this study have hypoglycemia and severe hypoglycemic events due to their disease state. Thus, hypoglycemia and severe hypoglycemic events are expected and captured as endpoints. Hypoglycemia will therefore not be captured as an AE, whereas consequences of hypoglycemia, such as loss of consciousness or seizure, may be reported as an AE.

Stopping Parameters

Participant Stopping Parameters: If a study participant experiences an SAE that is determined by the study investigator and medical monitor to be likely related to study drug, study drug may be discontinued for that participant.

Study Stopping Parameters: If 2 subjects experience an SAE determined by the study investigator and medical monitor to be likely related to study drug, the study may be stopped.

Pharmacokinetic Assessments

Blood samples will be collected to determine the plasma concentration of avexitide at predose on Day 14 of Treatment Periods 1 and 2. Trough PK samples will be obtained 12 hours after the last 45 mg BID dose and 24 hours after the last 90 mg QD dose. Additional PK samples may be collected.

Criteria for Evaluation

Primary Efficacy Endpoint

- The primary endpoint is the baseline-adjusted number of diurnal Level 2 hypoglycemia events (ADA, <54 mg/dL) as measured by CGM and defined as the number of events captured by CGM with glucose measures <54 mg/dL during diurnal hours (8am-10pm) within each treatment period divided by number of days for a given treatment period, then normalized to duration of 14 days. The baseline-adjusted number of diurnal Level 2 hypoglycemia events during 14 days of avexitide treatment (Treatment Periods 1 and 2) and 14 days of standard of care treatment (Run-In Period) will be calculated and examined in a mixed-effect model, including treatment, treatment sequence, treatment period, and surgery type stratum (RYGB vs. Others) as fixed effect, and subject-within-sequence as random effect. The least squares (LS) mean, the standard error (SE), the 2-sided 95% confidence interval (CI), and the p-value will be derived from the mixed-effect model for each active treatment. No multiplicity adjustment is planned, and the primary endpoint will be evaluated through the nominal p-values. $P<0.05$ is considered statistically significant.

Secondary Endpoints

The secondary endpoints include the following:

- Rate of Level 2 hypoglycemia, defined as number of distinct episodes of Level 2 hypoglycemia **(**SMBG glucose <54 mg/dL), divided by number of days for a given treatment period, then normalized to duration of 14 days.
- Rate of Level 3 hypoglycemia (severe hypoglycemia), defined as the number of severe events during each treatment period characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, divided by number of days for a given treatment period, then normalized to duration of 14 days. This applies regardless of whether a patient actually receives external assistance. Since the categorization of a severe hypoglycemia event can be subjective, particularly in cases where severe neuroglycopenic symptoms/signs occurred and external assistance was needed but was not received, all potential qualifying severe hypoglycemia events will be adjudicated by the principal investigator.
- Percent diurnal time <54 mg/dL, defined as the percentage of CGM values <54 mg/dL during daytime hours (8am-10pm) within each treatment period, normalized to 14 days.
- The magnitude of postprandial hypoglycemia, defined as the glucose nadir as measured by fingerstick glucose occurring within 3 hours of standardized liquid meal consumption. The plasma glucose nadir obtained during avexitide plus standard of care (Treatment Periods 1 and 2) will be compared to during standard of care (Run-In). Particularly, the baseline-adjusted plasma glucose nadir will be calculated for each patient and evaluated.

Secondary endpoints will be analyzed in the same manner as the primary efficacy endpoint.

Exploratory Endpoints

- QoL as measured by SF 36 v2, EQ-5D, HSF-II, and HCS.
- Rate of hypoglycemia, defined as the number of distinct episodes of SMBG glucose <70 mg/dL divided by number of days for a given treatment period, then normalized to duration of 14 days.

- Percent time >250 mg/dL, defined as the percentage of CGM values >250 mg/dL during each treatment period, normalized to 14 days
- Percent nocturnal time <54 mg/dL as measured by CGM, defined as as the percentage of CGM values <54 mg/dL during nocturnal hours (12am-6am) within each treatment period, normalized to 14 days.
- Number of nocturnal Level 2 hypoglycemia events (ADA, <54 mg/dL) as measured by CGM and defined as the number of events captured by CGM with glucose measures <54 mg/dL during nocturnal hours (12am-6am) within each treatment period divided by number of days for a given treatment period, then normalized to duration of 14 days.

Safety Endpoints

Safety endpoints include evaluation of adverse events

References

1. Lee CJ, Brown TT, Schweitzer M, Magnuson T, Clark JM. The incidence and risk factors associated with developing symptoms of hypoglycemia after bariatric surgery. Surg Obes Relat Dis 2018;14:797-802.
2. Lee CJ, Clark JM, Schweitzer M, et al. Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy. Obesity (Silver Spring). 2015;23:1079-84.
3. Kefurt R, Langer FB, Schindler K, Shakeri-Leidenmühler S, Ludvik B, Prager G. Hypoglycemia after Roux-En-Y gastric bypass: detection rates of continuous glucose monitoring (CGM) versus mixed meal test. Surg Obes Relat Dis 2015;11:564-9.
4. Brix JM, Kopp HP, Höllerl F, Schernthaner GH, Ludvik B, Schernthaner G. Frequency of Hypoglycaemia after Different Bariatric Surgical Procedures. Obes Facts 2019;12:397-406.
5. Elliott JA, Docherty NG, Murphy CF, et al. Changes in gut hormones, glycaemic response and symptoms after oesophagectomy. Br J Surg 2019;106:735-46.
6. Larraufie P, Roberts GP, McGavigan AK, et al. Important role of the GLP-1 axis for glucose homeostasis after bariatric surgery. Cell Rep 2019;26:1399-1408.
8. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide-1 stimulated postprandial insulin secretion in humans. Diabetes 2011;60:2308-14.
9. Korner J, Bessler M, Inabnet W, Taveras C, Holst JJ. Exaggerated glucagon-like peptide-1 and blunted glucose dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis 2007;3:597–601.
10. Goldfine A, Mun E, Devine E, et al. Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. J Clin Endocrinol Metab 2007;92:4678-85.
11. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide-1 stimulated postprandial insulin secretion in humans. Diabetes 2011;60:2308-14.
12. Craig CM, Liu LF, Deacon CF, Holst JJ, McLaughlin TL. Critical role for GLP-1 in symptomatic post bariatric hypoglycemia. Diabetologia 2017;60:531-40.

13. Calabria AC, Charles L, Givler S, De Leon DD. Postprandial hypoglycemia in children after gastric surgery: clinical characterization and pathophysiology. Horm Res Paediatr 2016;85:140-6.
14. Craig CM, Liu L, Nguyen T, Price C, Bingham J, McLaughlin T. Efficacy and pharmacokinetics of subcutaneous exendin (9-39) in patients with post-bariatric hypoglycaemia. Diabetes Obes Metab 2018;20:352-61.
15. Tan M, Lamendola C, Luong R, McLaughlin T, Craig CM. Safety, efficacy and pharmacokinetics of repeat subcutaneous dosing of avexitide (exendin 9-39) for treatment of post-bariatric hypoglycaemia. Diabetes Obes Metab 2020;22(8):1406-16
16. Craig CM, Lawler HL, Lee CJE et al. PREVENT: A Randomized, Placebo-Controlled Crossover Trial of Avexitide for Treatment of Post-Bariatric Hypoglycemia. J Clin Endocrinol Metab. 2021 Feb 22:dgab103. doi: 10.1210/clinem/dgab103. Epub ahead of print.

APPENDIX A **SCHEDULE OF EVENTS**

	DAY-0 ZOOM VISIT 1	RUN-IN PERIOD (DAY-1) ZOOM VISIT 2	RUN-IN PERIOD (DAY-4) ZOOM VISIT 3	RUN-IN PERIOD (DAY-10) NO VISIT	RUN-IN PERIOD (DAY-14) STANFORD VISIT 4	TREATMENT PERIOD 1 (DAY-1) ZOOM VISIT 5	TREATMENT PERIOD 1 (DAY-10) NO VISIT	TREATMENT PERIOD 1 (DAY-14) STANFORD VISIT 6	TREATMENT PERIOD 2 (DAY-1) NO VISIT	TREATMENT PERIOD 2 (DAY-4) NO VISIT	TREATMENT PERIOD 2 (DAY-14) STANFORD VISIT 7
Informed Consent	**X**										
Medical History	**X**										
Hypoglycemia Questionnaire	**X**										
Quality of Life Assessments**					**X**			**X***			**X***
Physical Exam	**X**				**X***						**X***
Preliminary Eligibility Determination	**X**										
eDiary Training		**X**									
Glucose Meter Training		**X**									
Check-In with Patients			**X**								
Review Dietary Guidelines and SOC Adherence	**X**	**X**	**X**		**X**	**X***		**X***			**X***
Initiate eDiary and glucometer Use		**X**									
CGM Training		**X**									
CGM Placement/Activation		**X**		**X**		**X***	**X***			**X***	
Mixed Meal Tolerance Test					**X**			**X***			**X***
CGM Removal				**X**			**X***			**X***	**X***

Trough PK Draw								**X***			**X***
Blood Draw (CMP)***					**X**						**X***
ADA Draw					**X**			**X***			**X***
Urine Pregnancy Test as applicable					**X**						
Final Eligibility Determination					**X**						
Randomization					**X***						
Dispensing of Study Drug					**X***						
Study Drug Injection Training						**X***					
14-Day Treatment Period 1 Starts						**X***					
2-Day Washout Period Starts								**X***			
14-Day Treatment Period 2 Starts									**X***		
Concomitant Medications	**X**	**X**	**X**		**X**	**X***		**X***			**X***
Adverse Events			**X**		**X**	**X***		**X***			**X***
Return of Used and Unused Study Drug Vials											**X***
Study Drug Accountability											**X***

* Procedures and activities are only applicable to enrolled participants (determined on Visit 4 at Stanford Health Clinic).
** QoL assesements **are not** completed during the visit.
*** CMP drawn at Visit 4 unless assessed within the prior 6 months.