A Phase 2, Multicenter, Randomized, Single-Blind, Placebo-Controlled Cross-Over Study to Assess the Efficacy and Safety of Exendin 9-30 in Patients with Postbariatric Hypoglycemia

NCT03373435

Document date: March 31, 2021

Protocol:

Study Objective

PREVENT is a multicenter, randomized placebo controlled Phase 2 trial to evaluate the efficacy of a pharmacologic agent: Avexitide for patients with postbariatric hypoglycemia (PBH) in the outpatient setting.

Study design

The PREVENT trial was a randomized, placebo-controlled, crossover study conducted at five U.S. academic centers. The study design, consisting of three 14-day treatment periods. After a run-in period during which eligibility was confirmed, 18 participants with severe, diet-refractory PBH were randomized 1:1 to one of two arms, each differing in the order of dosing regimen. For both groups, Treatment Period 1 consisted of subcutaneous placebo injections. During Treatment Periods 2 and 3, avexitide was administered 30 mg twice daily (BID) and 60 mg once daily (QD) in crossover design and random order. At the end of each treatment period, participants underwent standardized mixed-meal tolerance testing (MMTT) in the clinical research unit (CRU) with hormonal, metabolic, and symptomatic assessments. Throughout, participants were required to adhere to PBH dietary recommendations and document all hypoglycemic events in the outpatient setting using electronic diaries (eDiaries), self-monitoring of blood glucose (SMBG), and blinded continuous glucose monitors (CGM).

Participants

Eligible participants were men or women ages 18-65 years old who had undergone RYGB surgery at least 12 months before screening and had a documented history of PBH defined as Whipple's triad, with inappropriately elevated insulin (⩾3 μU/mL) or C-peptide (>0.6 ng/mL) at the time of hypoglycemia (⩽54 mg/dL glucose).17 Eligible participants were further required to exhibit at least 2 episodes of hypoglycemic symptoms confirmed by SMBG⩽54 mg/dL while following dietary guidelines during the run-in period.

Patients who had any of the following criteria were excluded from study participation:

- history of hypoglycemia predating RYGB surgery;
- history of insulinoma or other cause ofendogenous hyperinsulinism;
- clinically significant acute medical conditions;
- pregnancy, lactation, and/or women of childbearing potential not using effective contraceptive methods;
- and use of any agents known to interfere with glucose metabolism within 5 half lives at screening.

Pregnancy status for individuals of childbearing potential was confirmed by documentation of negative plasma pregnancy test at screening and a negative urine

pregnancy test on the first day of dosing. Nonchildbearing potential was defined as surgical sterility (documented hysterectomy, tubal ligation, or bilateral salpingo-oophorectomy) or postmenopausal status (defined as 12 months of spontaneous amenorrhea)

Randomization and masking

Participants were informed that one treatment period would involve placebo injections and were blinded to treatment sequence and study drug composition. Participants received two subcutaneous injections daily throughout all three study periods to fulfill blinded conditions, with injections comprised of the appropriate combination of placebo and/or active avexitide 30 mg dose(s). Investigators and site staff were blinded to avexitide sequence during Treatment Periods 2 and 3 and to laboratory results. For safety reasons, investigators, but not participants, had access to point-of-care glucose results during the MMTTs to determine whether glycemic rescue was indicated.

Procedures

In-clinic MMTT procedures: At the end of each treatment period, subjects were admitted to the CRU after an overnight fast for a 180-minute MMTT. After a baseline blood draw, subjects consumed two Ensure® Compact Drinks containing 64g of carbohydrate over 10 minutes, with labs drawn every 15 minutes (for plasma glucose, insulin, c-peptide, GLP-1 and glucagon) and bedside assessment of neuroglycopenic symptoms and point-of-care glucose via the HemoCue® Glucose 201 System every 30 minutes. If rescue parameters were met (the earlier of point-of-care glucose $\leqslant$50 mg/dL with documented neuroglycopenic symptoms or $\leqslant$40 mg/dL irrespective of symptoms), final blood samples were drawn and participants were rescued by intravenous dextrose. The primary outcome of plasma glucose nadir was based on plasma samples assayed per standard methods.

Pharmacokinetic assessments: Blood samples for the determination of plasma avexitide concentrations were collected at the end of each 14-day avexitide treatment period at -90, 0, 60, 180 and 330 min relative to the timing of study drug injection.

At home procedures: Throughout all treatment periods subjects used an eDiary (internetconnected web application), a CONTOUR®Next One glucometer, and blinded Dexcom Mobile G4® CGM for recording of hypoglycemic events occurring in the ambulatory setting.

For each episode, patients recorded hypoglycemia symptoms/signs, the lowest SMBG reading during the episode, actions taken to treat or prevent the episode, requirement for assistance, and whether the episode was postprandial. Study drug injections were also recorded, and adherence was additionally monitored via accounting of returned study drug vials.

Outcomes Measurement

Primary and secondary endpoints were based on participant responses to MMTT in the CRU, while exploratory endpoints were based on events captured via eDiary, SMBG, and blinded CGM in the outpatient setting. The primary outcome was postprandial plasma glucose nadir during MMTT and the main secondary outcome was postprandial insulin peak during MMTT. Exploratory outcomes captured by SMBG and eDiary were pre-specified with definitions updated post-hoc according to current international consensus guidelines on the reporting of hypoglycemia in clinical trials, as follows: Level 1 hypoglycemia: SMBG<70 mg/dL; Level 2 hypoglycemia: SMBG<54 mg/dL; Level 3 hypoglycemia: a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery.

Exploratory outcomes captured by CGM were prespecified with definitions revised post-hoc in accordance with current guidance36 and included percent time above or below extreme glycemic thresholds (<54 mg/dL; >250 mg/dL) and number of events <54 mg/dL. Percent time <54 mg/dL and number of events <54 mg/dL were also defined temporally by fasting (12am-8am) vs. prandial/post-prandial (8am-12am) periods; the latter more broadly representing the hours during which meal-induced hypoglycemia may occur and accounting for the mean 1-2-hour delay from mealtime to glucose nadir observed in patients with PBH. The pharmacokinetic profile for each dosing regimen was evaluated on an exploratory basis. Safety assessments included adverse events, clinical laboratory results, and physical examination findings.

Statistical Analysis Plan

A sample size of 12 completed patients was selected to provide more than 90% power to detect an increase in glucose nadir of at least 15.0 mg/dL assuming a standard deviation of 14.0 mg/dL at a significance level (α) of 0.05 using a two-sided paired t-test. The primary efficacy endpoint was calculated and examined in a mixed-effect model, including treatment, treatment sequence, and treatment period as fixed effect, and subject-within sequence as random effect. The Least Squares (LS) mean, standard error (SE), 95% confidence interval (CI), and p-value were derived from the mixed-effect model for each active treatment. No multiplicity adjustment was planned, and the primary endpoint was evaluated through the nominal p-values. Placebo-corrected secondary and exploratory endpoint data were analyzed in the same manner as the primary endpoint, with the exception of pharmacokinetic data, which were summarized descriptively.