Phase 2 Crossover, Randomized, Placebo-Controlled, Single-Blind, Repeat Dose Study in Patients with Post-Bariatric Hypoglycemia to Determine the Effect of Mizagliflozin on Adverse Events and Postprandial Glucose Excursions

Protocol: VGX-001-012

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Study Objective

The primary objectives of this study are to evaluate the tolerability of different repeat dose treatment regimens of mizagliflozin in addition to the effects on postprandial glucose nadir in response to a mixed meal tolerance test (MMTT) in patients with post-bariatric hypoglycemia (PBH).

Study Design

This is a phase 2 crossover, randomized, placebo-controlled, single-blind, repeat dose study in patients with PBH to determine the effect of mizagliflozin on adverse events and postprandial glucose excursions. As a single-blind study, the patient, investigator, and site personnel, except the pharmacist, will be blinded. The Sponsor will not be blinded. This study will examine repeat doses of mizagliflozin (0.5, 1, 2.5, 5, and 10 mg) and placebo while also evaluating once daily (QD), twice daily (BID) or three times a day (TID) dosing. Up to 15 patients (males and non pregnant females) are expected to complete the study. Patients will be randomly assigned to a treatment arm within a cohort (up to 5 cohorts, 3 patients per cohort). Each patient should receive placebo and 2 active dose regimens in a crossover fashion. Results from completed cohorts will inform decisions on mizagliflozin dose regimens in the next cohort.

Patients will be screened for initial inclusion/exclusion criteria for study participation from Days -14 to -1 (Study Visit 1). At Study Visit 2 (Day 1), patients will be randomized to one of 15 sequences so that each patient receives placebo and 2 dosing regimens of mizagliflozin as described in Table 7. Patients will be administered the dosages as per Table 7 over a 7-day period. Food diaries, Bristol Stool Form Scale (BSFS) diaries and PRO questionnaires will be administered during this period. After a minimum 8 hour fast, patients will return to the clinic for Study Visit 3. A blood sample (Pre Dose) will be obtained and then patients will receive a single dose of mizagliflozin or placebo as per assigned dosing sequence. After 20 (±5) minutes, patients will receive an MMTT. Pharmacodynamic blood samples to measure plasma glucose, insulin and incretins will be collected at (hr:min) 0:05, 0:10, 0:20, 0:40, 1:00, 1:20, 1:40, 2:00, 2:30, 3:00, and 3:30 after MMTT initiation. Patients will be allowed to leave the clinic after the final timepoint, unless additional time is required based on the patient's status at the discretion of investigator.

After a wash-out period of at least 7 days, patients will begin a new dosage and will then repeat the procedures as described for Day 1 of Period 1 for each subsequent Period.

Participants

Inclusion Criteria:

Patients must meet all of the following inclusion criteria to be eligible to enroll in the clinical study:

1. Males and nonpregnant females, ages 18 to 75 years old, having had Roux-en-Y bariatric surgery more than 6 months prior to signing the ICF.

2. History of reactive hypoglycemia with Whipple's triad: the occurrence of hypoglycemic symptoms associated with blood glucose of ≤54 mg/dL, and resolution with glucose or carbohydrate administration. Symptoms associated with reactive hypoglycemia include neuroglycopenic symptoms (e.g., behavioral changes, confusion or impaired cognitive function, seizure, loss of consciousness).

3. Willing and able to give informed consent and follow all study procedures and requirements.

4. Patients (male and female) must agree to use an adequate method of contraception from signed consent through 2 weeks after last dose of investigational product (IP).

Adequate contraception is defined as a contraceptive method with a failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, for example: oral contraceptives, either combined or progestogen alone; injectable progestogen; implants of etonogestrel or levonorgestrel; estrogenic vaginal ring; percutaneous contraceptive patches; intrauterine device or intrauterine system; male partner sterilization at least 6 months prior to the female patient's Screening, and this male is the sole partner for that patient (the information on the male partner's sterility can come from the site personnel's review of the patient's medical records or interview with the patient on her medical history); male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository); male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository).

Exclusion Criteria:

The presence of any of the following exclusion criteria excludes a patient from study enrollment:

1. History of current medical conditions (other than PBH) which may result in hypoglycemia such as insulinoma, adrenal insufficiency, insulin autoimmune hypoglycemia, congenital hyperinsulinemia.

2. Current use of insulin or insulin secretagogues

3. Current use of GLP-1 agonists or GLP-1/GIP dual agonists.

4. History of current fasting hypoglycemia.

5. Patients in whom a structural disease of the large intestine (including occlusion, stenosis, cancer, and inflammatory bowel disease) was observed by colonoscopy or contrast enema performed within 3 years of Screening or patients suspected of having a structural disease of the large intestine.

6. Patients with rectal prolapse or pelvic floor dysfunction or a medical history of the disorders.

7. Patients who received the following drug therapies within 2 weeks of Screening

a. Cathartics (bulk cathartic, osmotic laxative, stimulant laxative)

b. Drugs that improve gastrointestinal function

c. Herbal medicines indicated for constipation

d. Drugs that inhibit intestinal motility

e. Drugs for the treatment of irritable bowel syndrome

f. Drugs for the treatment of chronic constipation

g. Macrolides

h. Supplements intended for improvement of constipation

8. Patients allergic to mizagliflozin

9. Chronic kidney disease stage 4 or 5 within 6 months of Screening

10. Hepatic disease, including serum alanine aminotransferase or aspartate aminotransferase greater than or equal to 3 times the upper limit of normal; hepatic synthetic insufficiency as defined as serum albumin < 3.0 g/dL; or serum bilirubin > 2.0 upper limit of normal at Screening.

11. Congestive heart failure, New York Heart Association class II, III or IV within 6 months of Screening

12. History of myocardial infarction, unstable angina or revascularization within 6 months of Screening

13. History of a cerebrovascular accident within 6 months of Screening

14. Active treatment with any diabetes medications

15. Active malignancy, except basal cell or squamous cell skin cancers

16. Major surgical operation within 30 days of Screening

17. Blood donation (1 pint of whole blood) within 2 months of Screening

18. Active alcohol or substance abuse

19. Current administration of oral or parenteral corticosteroids

20. Pregnancy and/or lactation: For women of childbearing potential: there is a requirement for a negative urine pregnancy test and for agreement to use contraception during the study and for at least 2 weeks after participating in the study.

21. Other patients considered by the investigator to be inappropriate.

Randomization and Blinding

Upon meeting eligibility criteria, enrolled patients will be randomized into one of 3 sequences by Cohort.

Approximately 15 patients may be enrolled with up to 15 patients required to complete. The treatment sequences are presented in the table below.

Patients who do not complete the study or have an associated major protocol deviation may be replaced at the discretion of the Sponsor.

Study Drug Treatment Sequences

Cohort	Sequence #	Period 1	Period 2	Period 3
1	1	P	A	B
	2	A	B	P
	3	B	P	A
2	4	C	P	D
	5	P	D	C
	6	D	C	P
3	7	F	E	P
	8	E	P	F
	9	P	F	E
4	10	P	G	H
	11	G	H	P
	12	H	P	G
5	13	I	P	J
	14	P	J	I
	15	J	I	P

P=Placebo; A=0.5 mg BID; B=1 mg QD; C=0.5 mg TID; D=1 mg BID. Other treatment regimens (e.g., E, F, G, H, I, J) for Cohorts 3 to 5 are TBD.

The patient, investigator, and site personnel, except for the pharmacist, will be blinded to study drug. The Sponsor will not be blinded.

The investigator or treating physician may unblind a patient's treatment assignment only in the case of an emergency when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the patient. Whenever possible, the investigator must first discuss options with the Vogenx Medical Monitor or appropriate Vogenx study personnel before unblinding the patient's treatment assignment. If this is impractical, the investigator must notify Vogenx as soon as possible, unless that information is important for the safety of patients currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

Vogenx's staff may unblind the treatment assignment for any patient with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the patient's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or Vogenx policy.

Procedures

Patients are provided with study drug for each 7 day treatment period. At the end of each treatment period patients report to the clinic for an MMTT. At in-clinic visits patients will report to the clinic on the morning of the Study Visit after a minimum 8 hour fast. A blood sample (Pre-Dose) will be obtained and then patients will receive a single dose of mizagliflozin or placebo. Shortly thereafter (20 min±5), patients will be administered an MMTT. The MMTT will start by consumption of a 237 mL liquid test meal (350 kcal distributed as 57% carbohydrate, 15% protein, and 28% fat). Pharmacodynamic blood samples to measure plasma glucose, insulin and incretins will be collected at (hr:min) 0:05, 0:10, 0:20, 0:40, 1:00, 1:20, 1:40, 2:00, 2:30, 3:00, and 3:30 after MMTT initiation. There is a 7 day washout period between each treatment period.

Outcome measurements

Primary endpoints

- Adverse Events
- Vital signs
- Safety laboratory Assessments
- MMTT glucose nadir after mizagliflozin dosing [Time Frame: 0-3 hours]

Secondary Endpoints

- MMTT plasma glucose and insulin peak concentration after mizagliflozin dosing
- MMTT time to peak plasma glucose concentration after mizagliflozin dosing [Time Frame: 0 3 hours].
- MMTT plasma glucose 1, 2, and 3 hour area under the curve (AUC0-1, AUC0-2, and AUC0 3) after mizagliflozin dosing
- MMTT time to peak insulin concentration after mizagliflozin dosing [Time Frame: 0 3 hours].
- MMTT insulin concentration 1, 2, and 3 hour area under the curve (AUC0-1, AUC0-2, and AUC0-3) after mizagliflozin dosing

Statistical Analysis

This study was sized for feasibility, study design optimization, and to evaluate nadir plasma glucose concentration, hence precision estimation is appropriate for this study design. Using a minimum sample size of 6 per treatment regimen, a sample size of 6 produces a two-sided 95% confidence interval with a distance from the mean paired difference to the limits that is equal to 12 when the estimated standard deviation of the paired differences is 11.3.