Phase 2 Randomized Single Ascending Dose Study in Post-Bariatric Hypoglycemia Subjects to Determine the Effect of Mizagliflozin Formulations on Postprandial Glucose and Insulin Levels

Protocol : VGX-001-011

NCT05541939

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Protocol:

Study Objective

To evaluate the safety, tolerability, and pharmacodynamics of two formulations of mizagliflozin with respect to postprandial plasma glucose levels in participants with Post-Bariatric Hypoglycemia (PBH).

Study Design

This was a Phase 2 randomized, sequential crossover single ascending dose study in participants with PBH to determine the effect of two mizagliflozin formulations on safety, tolerability, and postprandial glucose and insulin levels. This study examined single doses of mizagliflozin (2.5, 5.0, and 10.0 mg) in either a liquid (2.5 mg) or encapsulated (2.5, 5.0, and 10.0 mg) formulation. Participants were randomly assigned to one of two treatment arms (A: 2.5 mg encapsulated/washout/5 mg encapsulated, or B: 2.5 mg solution/washout/10 mg encapsulated).

Baseline: A Baseline mixed meal tolerance test (MMTT) was performed once all screening assessments had been performed. Pharmacodynamic samples for glucose and insulin were obtained.

Treatment Period: Following the Baseline MMTT assessment, subjects were randomized into Treatment Arm A or Treatment Arm B. Subjects were administered the assigned dose/formulation followed by an MMTT. Pharmacodynamic samples for glucose and insulin were obtained.

Participants

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.

History of reactive hypoglycemia with Whipple's triad: the occurrence of hypoglycemic symptoms associated with blood glucose of ≤50 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).

Inclusion Criteria:

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 ≤50 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. Subjects (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: abstinence from penile-vaginal intercourse; 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 subject's screening visit, and this male is the sole partner for that subject (the information on the male partner's sterility can come from the site personnel's review of the subject's medical records or interview with the subject 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:

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. History of current dumping syndrome.
4. History of current fasting hypoglycemia.
5. Subjects 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 before consent or subjects suspected of having a structural disease of the large intestine
6. Active infection or significant acute illness within 2 weeks prior to dosing
7. Subjects with mental development disorder.
8. Subjects who received the following drug therapies within 1 week before the start of the observation period (Week −2).
    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
9. Subjects with a medical history of severe drug hypersensitivity
10. Chronic kidney disease stage 4 or 5

11. 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 total bilirubin >2.0 upper limit of normal at screening.
12. Congestive heart failure, New York Heart Association class II, III or IV
13. History of myocardial infarction, unstable angina or revascularization within the past 6 months
14. History of a cerebrovascular accident within 6 months of screening.
15. Active treatment with any diabetes medications, except metformin.
16. Active malignancy, except basal cell or squamous cell skin cancers
17. Major surgical operation within 30 days prior to screening
18. Blood donation (1 pint of whole blood) within the past 2 months
19. Active alcohol abuse or substance abuse
20. Current administration of oral or parenteral corticosteroids
21. 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.
22. Other subjects considered inappropriate by the Investigator

Randomization and blinding

After performing Baseline assessments and meeting randomization criteria, Subjects were randomized into one of two treatment arms in a 1:1 fashion. The Treatment Arms are defined as follows:

Treatment Arm	
A	In Period 1, subjects will receive an encapsulated formulation of 2.5 mg mizagliflozin. Following at least a 7 day washout period, in Period 2, subjects will return to the clinic to receive an encapsulated formulation of 5.0 mg mizagliflozin.
B	In Period 1, subjects will receive a liquid dose formulation of 2.5 mg mizagliflozin. If after consultation with the medical monitor and PI that there are no concerns regarding any treatment-related AEs, subjects will return to the clinic for a 10 mg encapsulated dose (Period 2) and MMTT after at least a 7 day washout period.

As this is an open-label study, the subject, Investigator, site personnel and sponsor were not blinded to study drug.

Procedures

At in-clinic visits on visit days for MMTTs, patients reported to the clinic in the morning after a minimum 8 hour fast. A blood sample was obtained (Pre-MMTT). In addition, a clinical lab serum sample was collected. Shortly thereafter (within 30 min), subjects were administered a water dose (Baseline), or the assigned dose of mizagliflozin with water, and at 20 (±5) min, an MMTT was administered. The MMTT was started by consumption of a liquid meal (350 kcal distributed as 57% carbohydrate, 15% protein, and 28% fat). Pharmacodynamic blood samples to measure plasma glucose and insulin were collected at (hr:min) 0:05, 0:10, 0:20, 0:40, 1:00, 1:20, 1:40, 2:00, 2:30, 3:00, 4:00, and 6:00 after MMTT initiation.

Outcome Measurements

Primary Endpoints

- Safety endpoints were as follows:
  - Adverse Events
  - Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
  - Laboratory analyses (to include chemistries and hematology)
  - 12-lead ECGs
- MMTT glucose nadir after mizagliflozin dosing [Time Frame: 0-3 hours].

Secondary Endpoints

- MMTT plasma glucose and insulin peak concentration after mizagliflozin dosing [Time Frame: 0-3 hours].
- MMTT plasma glucose 1, 2, and 3 hour area under the curve (AUC_{0-1}, AUC_{0-2}, and AUC_{0-3}) after mizagliflozin dosing
- MMTT insulin concentration 1, 2, 3, 4, and 6 hour area under the curve (AUC_{0-1}, AUC_{0-2}, AUC_{0-3}, $AUC_{0-4,}$ and AUC_{0-6}) after mizagliflozin dosing
- MMTT time to peak plasma glucose concentration after mizagliflozin dosing [Time Frame: 0-3 hours]
- MMTT time to peak insulin concentration after mizagliflozin dosing [Time Frame: 0-3 hours]

Statistical Analysis Plan

No formal hypothesis testing was planned. This study was sized for feasibility, study design optimization, and to investigate a difference in the nadir plasma glucose concentration during an MMTT. As such for descriptive purposes, in an inequality test on data from a three-period, single-sequence cross-over design, a sample size of 6 achieves approximately 80% power at a 2-sided 5.0% significance level when the absolute difference between the two treatment means is 15, the between-subject standard deviation is 14.6 and the correlation between any two measurements on the same subject is 0.6.