A Phase 2 Trial to Evaluate the Effect on Body Composition and Safety of Enobosarm in Patients Treated with Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists for Chronic Weight Management

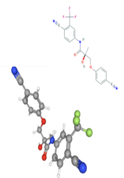
G. BARNETTE[1], D. RODRIGUEZ[1], G. BIRD[1], I. SHALEV[1], H. FISCH[1], M. STEINER[1]
1- Department of Research and Development, Veru Inc., Miami, Florida, USA

INTRODUCTION

There is a need for a drug when combined with a GLP-1 receptor agonist (RA) that can prevent muscle loss, while preferentially reducing fat resulting in high quality weight loss. Older sarcopenic obese patients receiving a GLP-1 RA are at the highest risk for muscle atrophy and muscle weakness leading to frailty. Enobosarm, a novel oral selective androgen receptor modulator, has been studied in 5 clinical muscle studies involving 968 older men, postmenopausal women, and older patients who have muscle loss due to advanced cancer. The totality of the clinical data demonstrates that enobosarm therapy results in dose-dependent reductions in fat mass and increases in muscle mass with improvement in physical function.

Enobosarm is a novel oral selective androgen receptor modulator (SARM) designed to reduce fat mass and increase lean mass (muscle and bone)

- Enobosarm (Ostarine, MK2866, GTx-024) is a nonsteroidal, selective androgen receptor modulator[1,2]
- Data from clinical trials and preclinical studies support enobosarm's potential:
  - Once-a-day oral dosing
  - Activates the androgen receptor, a well-established mechanism
  - Tissue selective
    - Improves muscle mass and physical function[2,6]
    - Stimulates lipolysis, inhibits lipogenesis, and decreases fat mass[7,8]
    - Builds and heals bone-potential to treat bone loss/osteoporosis[3-5]
  - Safety
    - Lack of masculinizing effects
    - Not converted to estrogen or dihydrotestosterone
    - No liver toxicity



Chemical structure of enobosarm

OBJECTIVES

The primary objective of this study is to assess the effect of enobosarm on total lean mass as measured by DEXA in patients maintained on GLP-1 receptor agonists.

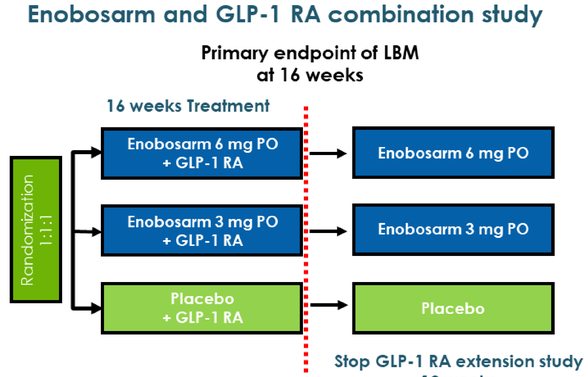
The secondary objectives of this study are to assess the following:
- The effect of enobosarm on total fat mass.
- The effect of enobosarm on total body weight.
- The effect of enobosarm on physical function.

STUDY ENDPOINTS

The primary endpoint for the study is the percent change from baseline in total lean body mass at 112 days.
The key secondary endpoints of this study are:
1. Percent change from baseline in total body fat to Day 112
2. Percent change from baseline in stair climb to Day 112
3. Percent change from baseline in total body weight to Day 112
4. Percent change from Day 112 in total body weight to Day 196
5. Percent change from Day 112 in total body fat to Day 196

STUDY DESIGN

Enobosarm and GLP-1 RA combination study



ELIGIBILITY CRITERIA

Inclusion Criteria:
1. Aged ≥60 years
2. Documented evidence of obesity (BMI ≥30 or ≥27 with the presence of at least one weight-related comorbid condition (e.g., hypertension or dyslipidemia). NOTE – monogenic or syndrome obesity, and endocrine causes of obesity (such as untreated hypothyroidism or Cushing's syndrome, and obesity caused by medications that cause weight gain are excluded from the study)
3. The patient is able to complete the physical function (stair climb) assessment
4. Complete a valid OSA assessment

Exclusion Criteria:
1. Known hypersensitivity or allergy to enobosarm or a GLP-1 receptor agonist
2. Creatinine clearance < 30 milliliter mL/min per minute/1.73 m2 as measured using the measured using the chronic kidney disease-epidemiology collaboration (CKD-EPI) calculation formula (patients with mild and moderate renal failure are not excluded from participation in this study)
3. Testosterone, methyltestosterone, oxandrolone (Oxandrin®), oxymetholone, danazol, fluoxymesterone (Halotestin®), testosterone-like agents, myostatin inhibitors, apelin receptor agonists, or antiandrogens. Previous therapy with testosterone and testosterone-like agents is acceptable with a 30-day washout or any other androgenic agent.
4. Pre-existing liver disease
5. Baseline ALT or AST >3x upper limit of normal
6. Baseline total bilirubin levels >upper limit of normal
7. History of acute pancreatitis within one year of screening or history of chronic pancreatitis
8. Severe gastrointestinal disease, including gastroparesis
9. Major depressive disorder within 2 years prior to screening, history of other severe psychiatric disorder, including schizophrenia and bipolar disorder, any lifetime history of suicide attempt, or with suicidal ideation or behavior within 1 month prior to screening.
10. Diagnosis of diabetes requiring current use of any antidiabetic drug or HbA1c ≥ 6.5% Note: Metabolic syndrome is not an exclusion, even if managed with an anti-diabetic drug such as metformin or an SGLT2 inhibitor. A diagnosis of prediabetes or impaired glucose tolerance managed exclusively with non-pharmacologic approaches (e.g., diet and exercise) is not an exclusion.
11. Creatine kinase >ULN
12. Male subjects with a lifetime history of malignant prostate disease, such as prostate cancer.
13. Male subjects with a PSA ≥4 ng/mL

ASSESSMENTS & STATS

Lean mass changes will be assessed by DXA.
Physical function will be assessed by stair climb test.

Semaglutide treatment for obesity[9]
6.92 kg of lean body mass lost by 68 weeks (40% of total weight loss)
49% of total weight loss at 68 weeks occurred by 16 weeks

Study Power Assumptions:
α=0.05 (two-sided), power = 80%
1.6 kg loss in lean mass at 16 weeks in placebo group with 100% coefficient of variability
Expect between 1.6 and 3.4 kg lean mass loss
0.3 kg loss in lean mass at 16 weeks in enobosarm groups
Expect between 0.3 kg loss and 0.4 kg gain in lean mass

STUDY UPDATE

Patient enrollment has begun in April 2024.

Study is conducted across 15 clinical sites in the US.

Top Line data readout for primary endpoint is expected by the end of the year.

Study is sponsored by Veru Inc.

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