Pooled Safety Analysis of Enobosarm from Phase 2 and Phase 3 Placebo-Controlled Clinical Trials

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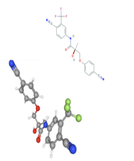
Conducted by GTx, Inc. and exclusive global license for enobosarm by Veru Inc.

Background

Enobosarm is a novel oral selective androgen receptor modulator shown to increase lean mass and decrease fat mass. Enobosarm may benefit patients on GLP-1 RA for weight loss by preserving muscle while augmenting fat loss.

veru | 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

Objective

A pooled analysis was conducted from randomized clinical trials (RCT) to evaluate the safety profile of enobosarm.

Methods and Material

The pooled safety analysis of enobosarm (3mg) included: Phase 2 study in older males (>60 yo) and postmenopausal women (n=48), two Phase 3 studies in patients with advanced lung cancer (n=651), and Phase 2 stress urinary incontinence in women study (n=328).

Results

Pooled analysis of 4 RCT consisted of 515 placebo and 512 enobosarm treated primarily non-obese subjects. TEAEs observed with enobosarm were comparable to the placebo group. Most common AEs for enobosarm were nausea (26.6% vs 26.0% in placebo), anemia (25.6% vs 23.9% in placebo), and vomiting (14.8% vs 14.6% in placebo), which were similar to the placebo groups. Notably, there was no increase in gastrointestinal side effects and no evidence of drug induced liver injury with enobosarm compared to placebo treatment. The incidence of deep vein thrombosis was higher (3.3%) in the placebo group compared to the enobosarm group (1.0%) (Table 1- TEAEs in at least 2% of the patients in either PBO or 3 mg enobosarm and at least 1% higher in one of the two groups).

	Placebo	Enobosarm 3 mg
	N=515	N=512
Anaemia	123 (23.9%)	131 (25.6%)
Neutropenia	86 (16.7%)	71 (13.9%)
Diarrhoea	49 (9.5%)	38 (7.4%)
Asthenia	47 (9.1%)	58 (11.3%)
Chest pain	24 (4.7%)	14 (2.7%)
Condition aggravated	12 (2.3%)	7 (1.4%)
Disease progression	63 (12.2%)	51 (10.0%)
Bronchitis	9 (1.7%)	15 (2.9%)
Pneumonia	27 (5.2%)	19 (3.7%)
Urinary tract infection	26 (5.0%)	33 (6.4%)
Alanine aminotransferase increased	7 (1.4%)	19 (3.7%)
Blood creatinine increased	20 (3.9%)	35 (6.8%)
Decreased appetite	56 (10.9%)	45 (8.8%)
Dehydration	22 (4.3%)	9 (1.8%)
Back pain	28 (5.4%)	15 (2.9%)
Hypokalaemia	18 (3.5%)	9 (1.8%)
Hypomagnesaemia	5 (1.0%)	10 (2.0%)
Hyponatraemia	5 (1.0%)	13 (2.5%)
Headache	33 (6.4%)	41 (8.0%)
Paraesthesia	17 (3.3%)	3 (0.6%)
Peripheral sensory neuropathy	13 (2.5%)	25 (4.9%)
Dyspnoea	23 (4.5%)	44 (8.6%)
Anxiety	5 (1.0%)	11 (2.1%)
Alopecia	69 (13.4%)	73 (14.3%)
Epistaxis	14 (2.7%)	5 (1.0%)
Haemoptysis	25 (4.9%)	13 (2.5%)
Hiccups	2 (0.4%)	10 (2.0%)
Rash	4 (0.8%)	12 (2.3%)
Deep vein thrombosis	17 (3.3%)	5 (1.0%)

Conclusion or Discussion

In a pooled analysis of 1027 older men, postmenopausal women, and older patients with advanced cancer, enobosarm was well tolerated with an AE profile comparable to the control patients. Notably, there was no increase in gastrointestinal side effects with enobosarm compared to placebo treatment. Despite a higher proportion of subjects having elevated ALT levels, these elevations were mild (grade 1/2) and transient with no evidence of drug induced liver injury by Hy's Law observed. CV adverse event rates were similar between the two groups (less than 2%). The incidence of deep vein thrombosis was higher (3.3%) in the placebo group compared to the enobosarm group (1.0%). A Phase 2b randomized trial is underway to evaluate enobosarm in older patients on a GLP-1 RA for weight loss.

References

1- Narayanan R et al. Mol Cell Endocrinol 2017|

2- Dalton JT et al. Curr Opin Support Palliat Care 7:345-351, 2013

3- Kamrakova M et al Calcif Tissue Int 106:147-157,2020

4- Hoffman DB et al. J Bone Metab 37:243-255, 2019

5- Kearbey JD et al Pharm Res 26:2471-2477, 2009

6- Dobs AS et al. Lancet Oncol 14:335-45, 2013

7- Dalton JT et al. J Cachexia Sarcopenia Muscle 2:153-161, 2011

8- Leciejewska N et al. J Phys and Pharma 70:525-533, 2019

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