Evaluation of Safety and Physiologic Changes Following 13 Weeks of Exposure to the Selective Androgen Receptor Modulator VK5211 (LGD-4033) in Primates

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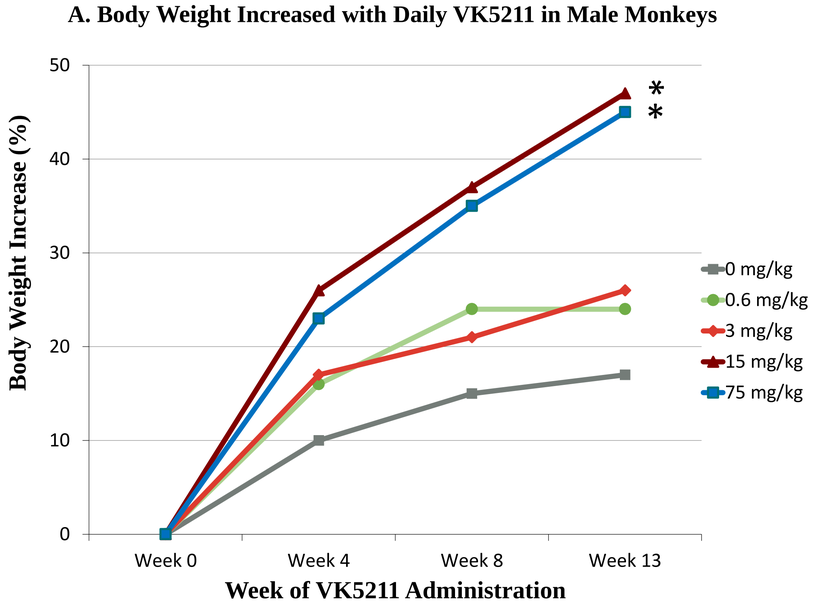
INTRODUCTION

- VK5211 is a highly selective androgen receptor modulator (SARM) that has demonstrated potent anabolic effects on bone and muscle with reduced activity and cross-reactivity to other steroid hormone receptors.
- VK5211 is being developed to treat muscle loss associated with injuries such as hip fracture, as well as age-related muscle loss, cancer cachexia, and chronic illness.
- A 13-week daily oral dosing study was conducted in cynomolgus monkeys. Monkeys received daily oral doses of VK5211 at 0, 0.6, 3, 15, or 75mg/kg/day.
  - Increases in body weight were progressive through the duration of the treatment window. Treated animals experienced body weight gains of 20% to 47% from baseline (Figure 1A and 1B).
  - Significant weight gains were observed at week 13 (Figure 2).
  - 70% of the increased weight was retained after a 4-week recovery period.
- In a rat model of male hypogonadism, increased anabolic activity in muscles was observed with high selectivity for muscle versus prostate tissue. Restoration of muscle was observed at doses of ~1mg/kg/day (Figure 3).
- Anti-resorptive and anabolic activity in bones was demonstrated in an ovariectomized rat model of post-menopausal osteoporosis (Figure 4).
- Safety data from the 13-week study in cynomolgus monkeys included:
  - Signs of toxicity that were primarily manifestations of exaggerated pharmacology (Table 1).
  - Histopathology observed at ~30x the free concentrations relative to observed concentrations in clinical studies (Table 1).
- In humans, VK5211 has demonstrated encouraging safety and improvements in lean body mass, without changes in fat mass, when dosed for 21 days (Figure 5).
- A Phase 2 study with 12 weeks of treatment is on-going to evaluate VK5211 in elderly patients recovering from hip fracture surgery.

A. Body Weight Increased with Daily VK5211 in Male Monkeys



B. Body Weight Increased with Daily VK5211 in Female Monkeys

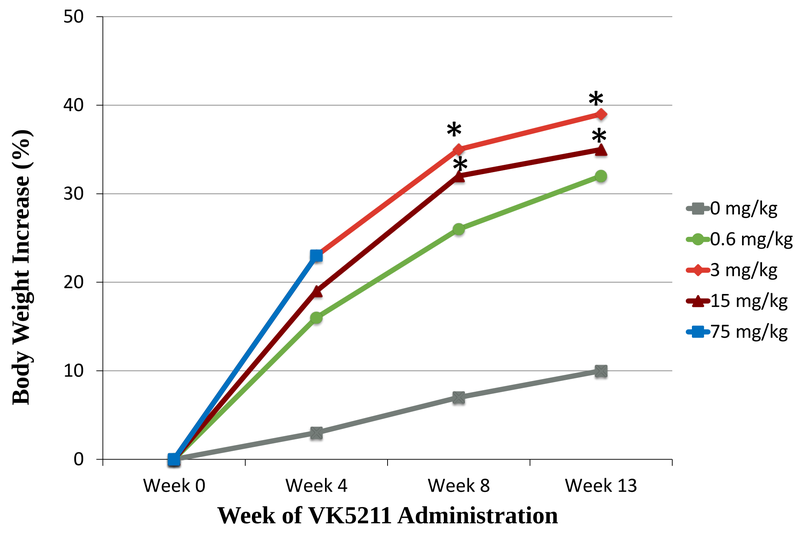


Figure 1A&B. Cynomolgus monkeys were orally dosed with VK5211 for 13 weeks in an attempt to elicit toxicity. Body weights were measured weekly (N=4-6/sex/group). Toxicity was observed in female monkeys at 75 mg/kg and dosing was discontinued on Day 48. * p< 0.05

Body Weight Gain was Significant after 13 Weeks Treatment with VK5211 in Cynomolgus Monkeys

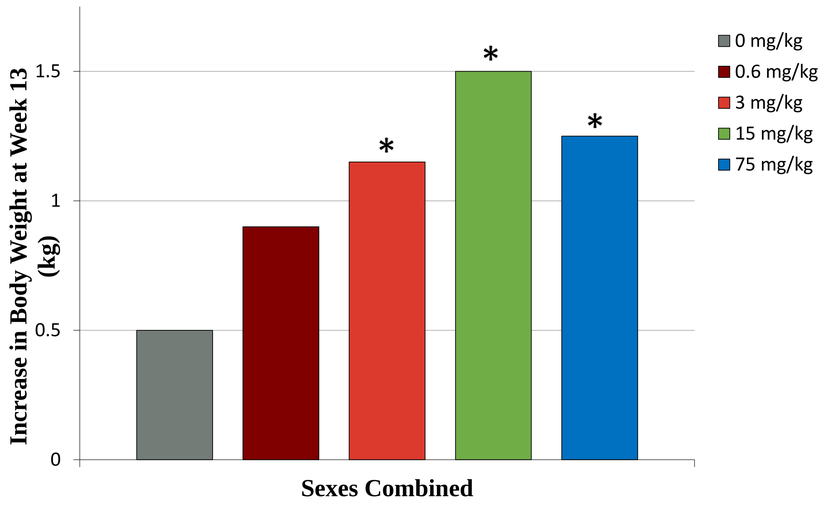


Figure 2. Increases in mean body weight following 13 weeks of dosing with VK5211. Initial mean body weights ranged from 3.4 kg to 3.7 kg. Dosing in females at 75 mg/kg was discontinued at Day 48 due to signs of toxicity. * p< 0.05

Atrophied Levator Ani Muscle Restored in Castrated Rats

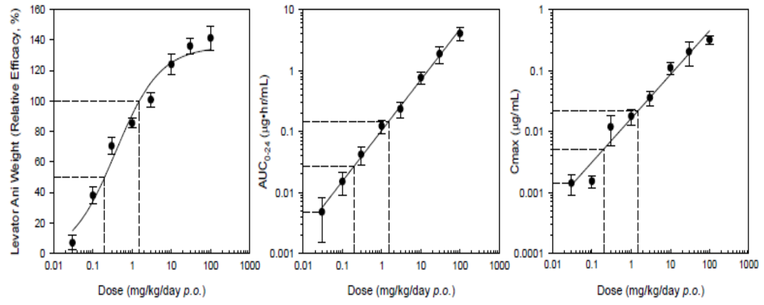


Figure 3. Two-month-old male Sprague Dawley rats were castrated and left untreated for 14 days. After 14 days, animals were treated with various doses of VK5211 (0.03 to 100 mg/kg/day PO) for 14 days. Restoration of levitor ani muscle was observed at low doses.

Femur Bone Mineral Content (BMC) and Femur Strength Increased in Ovariectomized Rats

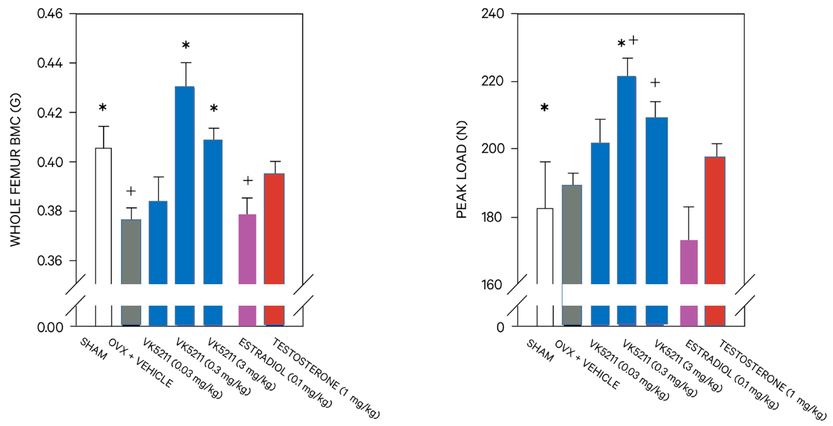


Figure 4. Female Sprague-Dawley rats were ovariectomized (OVX) and allowed to develop osteopenia for 8 weeks. Treatment began 8 weeks post-OVX and lasted for 12 weeks. Bone density was assessed by DXA. Mechanical testing and histomorphometry were performed on bones harvested at necropsy. * p< 0.05

Summary of Safety Findings at all Doses after 13 Weeks of Treatment in Monkeys

Male Reproductive	Effect	Thymus	Effect
Atrophy	-	Weight	D
Organ Weights	-	Atrophy	I
Maturation	Mismatch		
Testosterone	d	**Cardio**	
LH	-	Cardiomyopathy	-
FSH	-	Polycythemia	-
Mammary Secretion/Dialation	I	Monocytos	I
Mammary Hypertrophy	I	Prothrombin	I
Female Reproductive		**Liver**	
Estrodiol	D	Hypertrophy	-
FSH	-	Clinical Chemistry	I
Uterus Weight	D	Weight	-
Uterus hypertrophy	Mismatch	Cholesterol	D
Ovary Weight	d		
Mammary Hypertrophy	-	**Adrenal Gland**	
Vaginal Cornification	I	Weight	
		Cortisol	I
Pancreas		Aldosterone	-
Hypertrophy	I	Vacuolation	D
Insulin	-	Zona reticularis loss	-
Glucagon	I		
Renal		**Body Weight**	
Intratubular protein	-	Males	i
Basophilic staining	-	Females	I

Table 1. Safety parameters in cynomolgus monkeys after 13 weeks of oral dosing with VK5211. Sexes combined unless noted.
Key: - = no effect, I=increase, i=slight increase, D=decrease, d= slight decrease

Increased Lean Mass and Leg Press Force in Healthy Males Dosed for 3 Weeks with VK5211

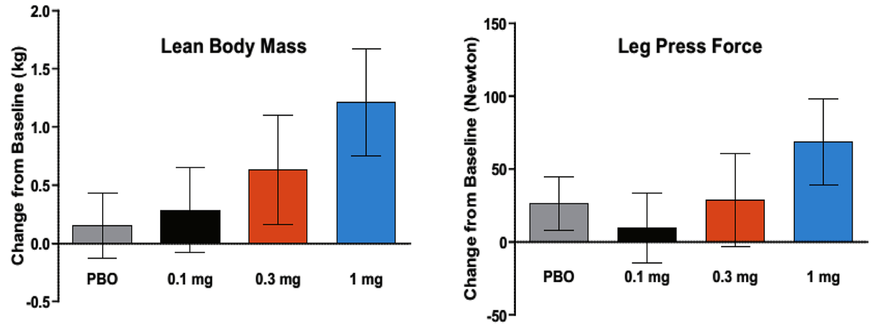


Figure 5. Increased lean body mass (measured by DXA) and leg press force (measured using a one-repetition maximum technique) observed after 3 weeks dosing in healthy male subjects (Clinical Study VK5211-02). PBO = placebo. * p < 0.05

SUMMARY

VK5211 resulted in:

- Significant body weight gain in male and female monkeys during 13 weeks of dosing
- Progressive weight gain throughout the dosing window
- Retention of body weight gain after 4-weeks without treatment
- Restoration of atrophied muscle mass in castrated rats
- Improved bone density and femur strength in an ovariectomized rat model of osteoporosis
- Safety signals in monkey, primarily known exaggerated pharmacology, which largely resolved after 4-weeks without treatment
- Increased lean body mass and leg press force, without an increase in fat mass, in human volunteers after 3-weeks of dosing of up to 1 mg VK5211

Conclusion: These data support the potential use of VK5211 in humans with hip fracture, as well as age-related muscle loss and other wasting diseases such as cancer cachexia, and chronic illness.