Safety and Tolerability of LGD-4033, a Novel Non-Steroidal Oral Selective Androgen Receptor Modulator (SARM), in Healthy Men

Shehzad Basaria[1], Lauren Collins[1], Melinda Sheffield-Moore[2], Edgar L. Dillon[2], Katie Orwoll[1], Kishore M. Lakshman[1], Renee Miciek[1], Thomas Storer[1], Jagadish Ulloor[1], Anqi Zhang[1], Heather Zientek[3], Keith Marschke[3], Joanna Peterkin[4], Shalender Bhasin[1]

[1]Boston University School of Medicine, [2]University of Texas Medical Branch, [3]Ligand Pharmaceuticals, Inc., [4]JJ Peterkin Consulting

Abstract P3-207

BACKGROUND

- Testosterone administration increases muscle mass and strength, but concerns regarding potential adverse effects on the prostate have restrained enthusiasm for its use as anabolic therapy.
- SARMs are a new class of androgen receptor (AR) ligands that are tissue-selective and being developed to treat muscle wasting associated with cancer, acute and chronic illness and age-related muscle loss.
- LGD-4033 is a novel non-steroidal, oral SARM that binds to AR with high affinity (Ki of ~1 nM) and selectivity.
- In animal models, LGD-4033 demonstrated anabolic activity in muscles, anti-resorptive and anabolic activity in bones, and robust selectivity for muscle versus prostate.
- A previous Phase I single ascending dose study established safety and tolerability of LGD-4033 up to doses of 22 mg.
- In this randomized, double-blind, placebo-controlled Phase I study, the safety and tolerability of LGD-4033 was evaluated.

STUDY DESIGN AND METHODS

Study Design

In this double-blind, placebo-controlled, single center, multiple ascending dose study, healthy men age 21-50 years were randomized to receive 0.1, 0.3 or 1 mg LGD-4033 or placebo once-daily over 21 days. Liver function tests (LFTs), fasting lipids, hematocrit, PSA, ECGs and serum sex hormones were monitored throughout the treatment period and the subsequent 5-week observation period.

Primary Objectives

To assess the safety and tolerability of escalating doses of LGD-4033.

Secondary Objectives

To assess pharmacokinetics and pharmacodynamics of LGD-4033.

Exploratory Objectives

To assess the effects of treatment with LGD-4033 on:

- Lean body mass (LBM) measured by (DEXA) scan
- Maximal voluntary leg press strength measured by 1-RM method
- Stair climbing power and speed

Trend analysis of change from baseline up to day 28 was computed using a mixed-model analysis of repeat measures. Placebo subjects from the 3 cohorts were pooled for analysis. Sample size: PBO (placebo) N=29; 0.1 mg N=17; 0.3 mg N=10; 1.0 mg N=11

SAFETY RESULTS

- LGD-4033 was safe and well tolerated at all doses
- Adverse Event Profile:
  - No drug-related severe or serious AEs occurred
  - All adverse events were mild or moderate
  - No event led to study discontinuation
- No clinically significant changes in LFTs, hematocrit or PSA were seen at any dose
- No clinically significant changes in ECG were seen at any dose

Table 1: Related treatment-emergent adverse events.

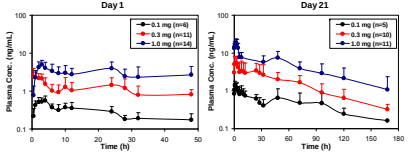
Preferred Term*, n (%)	PBO (N=33)	0.1 mg (N=18)	0.3 mg (N=11)	1 mg (N=14)
Total Subjects with AE	***4 (12.1)***	***0***	***3 (27.3)***	***5 (35.7)***
Dry mouth	3 (9.1)	0	1 (9.1)	0
Acne	0	0	1 (9.1)	1 (7.1)
Low density lipoprotein increased	0	0	0	2 (14.3)
Aspartate aminotransferase increased	0	0	1 (9.1)	0
Erectile dysfunction	0	0	0	1 (7.1)
Gynaecomastia	0	0	0	1 (7.1)
Rash	0	0	1 (9.1)	0
Somnolence	1 (3.0)	0	0	0

*MedDRA dictionary V12

PHARMACOKINETICS

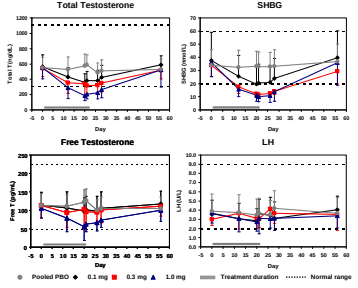
- LGD-4033 displayed a prolonged elimination half-life (24–36 hours), linear pharmacokinetics, and predictable accumulation with multiple dosing.

Figure 1: Dose proportional increase in systemic exposure on days 1 and 21.



PHARMACODYNAMICS

Figure 2: Dose dependent decrease in testosterone (T), free T and SHBG. Significant reversible changes at all doses. Consistent with AR-mediated activity. No significant change in LH or FSH.



- Changes in lipid profile are as follows:
  - No significant changes in total and LDL cholesterol
  - Decrease in triglyceride levels across all doses
  - Reversible dose-dependent decrease in HDL cholesterol was seen at doses ≥ 0.3 mg; overall, changes are not considered clinically relevant to target indications

EXPLORATORY MEASURES

Figure 3: Dose-dependent increase in total lean body mass with ~1.2 kg increase at 1 mg dose. Fat mass appeared to decrease with LGD-4033 treatment. LS-Mean (SE) change from baseline up to day 28 (kg).

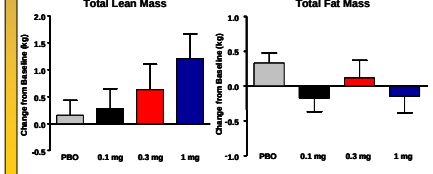


Figure 4: Positive trend towards an increase in maximal voluntary leg press strength with LGD-4033 treatment. LS-Mean (SE) change from baseline up to day 28.

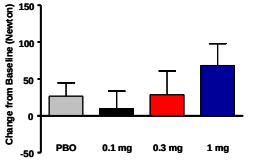
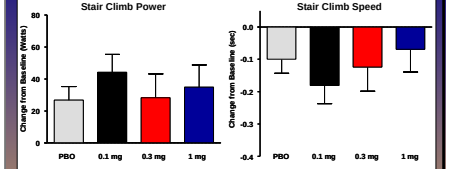


Figure 5: Trend toward an increase in physical performance measures (stair climb power and speed) over the short treatment period. LS-Mean (SE) change from baseline up to day 28.



CONCLUSIONS

In young healthy men:

- LGD-4033 was safe and well tolerated at all doses following daily oral administration for 3 weeks.
- No clinically significant changes in LFTs, PSA, hematocrit or ECG were seen.
- Positive trends in lean body mass and functional measures were seen, consistent with anabolic activity.

FUTURE DIRECTION

- Phase II studies with 12 weeks of treatment are planned to evaluate LGD-4033 in conditions such as muscle wasting associated with cancer, rehabilitation and acute illness.