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


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
- Star climbing power and speed

Trend analyses of change from baseline up to day 28 was computed using a mixed-model analysis of repeat measures. Plasma 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.

<table>
<thead>
<tr>
<th>Preferred Term*, n (%)</th>
<th>PBO 0.1 mg</th>
<th>0.3 mg</th>
<th>1 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6 (21)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Rashes</td>
<td>1 (7)</td>
<td>2 (14)</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Low density lipoprotein increased</td>
<td>0</td>
<td>0</td>
<td>2 (14)</td>
</tr>
<tr>
<td>Insulin resistance increased</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Transaminase increased</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>0</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Total (5%)</td>
<td>7%</td>
<td>7%</td>
<td>8%</td>
</tr>
</tbody>
</table>

PHARMACOKINETICS

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

PHARMACODYNAMICS

- 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

- 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.