Lobeglitazone,
A Novel PPAR-γ agonist with balanced efficacy and safety

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I have received lecture and consultation fees from Chong Kun Dang.
### Pros & Cons of PPAR-γ agonist

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Good glucose lowering</td>
<td>• Adverse effects (edema, weight gain, CHF, fracture or rare macular edema etc)</td>
</tr>
<tr>
<td>• Durability (ADOPT)</td>
<td>• Possible safety issues (risk of MI? – Rosi or bladder cancer? - Pio)</td>
</tr>
<tr>
<td>• Insulin sensitizing effects (especially in MS, NAFLD, PCOS etc)</td>
<td></td>
</tr>
<tr>
<td>• Prevention of new-onset diabetes (DREAM, ACT-NOW)</td>
<td></td>
</tr>
</tbody>
</table>

So, there is a need to develop PPAR-γ agonist with balanced efficacy and safety (PROactive)
Insulin Sensitizers: Several Issues

- Rosi, Peak sale ($3.3 billion)
- Dr. Nissen
- Rosi, lipid profiles
- DREAM
- ADOPT
- META analysis (5,8)
- Dr. Nissen
- RECORD
- FDA, Black box warning
- Tro out d/t hepatotoxicity
- PIO, bladder cancer
- FDA, All diabetes drug CV safety
- Rosi, CV safety = no evidence
- Rosi, - REMS in USA - Europe out
- PIO, bladder cancer

CKD 501
- Discovery & Preclinical study
- 2000.6-2004.6
- Phase I
- Phase II
- Phase III
- Lobeglitazone
- 2009.11-2011.04

- Dr. Nissen
- Rosi (5)
- Pio (7)
Discovery & Preclinical study

Phase I: 2000.06 - 2004.06
Phase II: 2004.11 - 2007.01
Phase III: 2007.03 - 2008.10
Phase III: 2009.11 - 2011.04

Efficacy
- PPAR activity
- In vitro & vivo efficacy
- Potent efficacy

ADME
- In vitro screening
- Metabolites
- CYP 450
- DDI

Safety
- Repeated dose toxicity
- Geno toxicity
- Reproductive toxicity
- Carcinogenic toxicity

Developmental Strategy
CV Safety / (Bladder) Cancer / Liver Toxicity / Bone loss
Lobeglitazone (Duvie)

1. Structure

![Chemical Structure of Lobeglitazone](image)

C_{24}H_{24}N_{4}O_{5}S \cdot H_{2}SO_{4} : MW = 578.62

2. Nomenclature

- Durable (for a long time) + Vie (a life), in French
- A better life or longer life

3. Features

- Insulin sensitizer
- Favorable lipid profiles & Improves Metabolic Syndrome
- Better safety (No bladder cancer in animal study)

4. MOA

- PPAR-γ agonism
DNA microarray analysis

Gene Expression

Glucose and lipid metabolism

Rosi
73
26
723
311
158
Lobe
68
28
In vitro study – PPARγ agonism

![Graph showing PPARγ agonism with different concentrations of DMSO, Pioglitazone, and Lobeglitazone.](image)
# In vivo study – ZDF rats

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg/kg/d)</th>
<th>B.W (g)</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (ng/ml)</th>
<th>TG (mg/dl)</th>
<th>NEFA (μEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>359.8 ± 4.8</td>
<td>402.1 ± 15.4</td>
<td>16.6 ± 1.4</td>
<td>625.0 ± 46.0</td>
<td>685.7 ± 80.9</td>
</tr>
<tr>
<td>Lobeglitazone</td>
<td>0.03</td>
<td>491.4 ± 10.2***</td>
<td>115.4 ± 8.1***</td>
<td>27.0 ± 5.7</td>
<td>526.8 ± 50.5</td>
<td>206.1 ± 44.1***</td>
</tr>
<tr>
<td>Lobeglitazone</td>
<td>0.1</td>
<td>530.9 ± 10.7***</td>
<td>108.1 ± 5.4***</td>
<td>10.2 ± 0.3*</td>
<td>282.0 ± 18.3***</td>
<td>50.1 ± 4.0***</td>
</tr>
<tr>
<td>Lobeglitazone</td>
<td>0.3</td>
<td>513.1 ± 11.2***</td>
<td>105.6 ± 4.4***</td>
<td>8.6 ± 1.1**</td>
<td>145.2 ± 9.8***</td>
<td>15.7 ± 3.1***</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>10</td>
<td>522.0 ± 8.6***</td>
<td>99.5 ± 1.7***</td>
<td>10.0 ± 1.0*</td>
<td>213.8 ± 22.0***</td>
<td>62.9 ± 12.6***</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>30</td>
<td>512.4 ± 11.7***</td>
<td>103.4 ± 2.6***</td>
<td>7.0 ± 0.6***</td>
<td>159.3 ± 10.5***</td>
<td>23.9 ± 3.3***</td>
</tr>
</tbody>
</table>

p.o., 28 days / Mean± SD. *<0.05, **<0.01, ***<0.001
TG : triglyceride. NEFA : non-esterified fatty acid.
Safety – Toxicology data

1. Insulin Sensitizers and CV safety
2. Insulin Sensitizers and (Bladder) cancer
3. Insulin Sensitizers and Liver toxicity
4. Insulin Sensitizers and Bone loss
# Effect of Lobeglitazone on Plasma volume

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>B.W. (g)</th>
<th>Heart Wt.</th>
<th>Plasma Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>g/kg</td>
<td>ml/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inc.%</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>-</td>
<td>299 ± 26</td>
<td>2.91 ± 0.07</td>
<td>50.0 ± 3.5</td>
</tr>
<tr>
<td>Lobeglitazone</td>
<td>1</td>
<td>294 ± 13</td>
<td>2.91 ± 0.11</td>
<td>54.4 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>292 ± 16</td>
<td>2.93 ± 0.14</td>
<td>58.0 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>308 ± 26</td>
<td>2.95 ± 0.11</td>
<td>63.3 ± 3.8*</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>10</td>
<td>301 ± 11</td>
<td>2.86 ± 0.20</td>
<td>56.5 ± 3.0*</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>311 ± 26</td>
<td>2.90 ± 0.17</td>
<td>57.5 ± 3.4*</td>
</tr>
</tbody>
</table>

p.o., qdx5/week, 4 weeks SD rat
Insulin Sensitizers & (Bladder) Cancer

1. Carcinogenic studies
   Rodents [Mice & Rats]

2. Bladder tumor studies
   Rodents [Rats]
## Carcinogenicity in Mice

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Dose (mg/kg)</th>
<th>LOAEL (mg/kg)</th>
<th>Neoplastic lesions</th>
<th>AUC (㎍.h/ml)</th>
<th>Exposure ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobeglitazone</td>
<td>0.2, 1.0, 6.0</td>
<td>&gt; 6.0</td>
<td>-</td>
<td>&gt; 18</td>
<td>&gt; 26</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>0.4, 1.5, 6.0</td>
<td>&gt; 6.0</td>
<td>-</td>
<td>&gt; 26</td>
<td>&gt; 8.7</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>3, 10, 30, 100</td>
<td>30</td>
<td>Pheochromocytoma, Leiomyosarcoma</td>
<td>180</td>
<td>14</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>50, 400, 800</td>
<td>400</td>
<td>Hemagiosarcoma, Hepatocellular carcinoma</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Muraglitazar</td>
<td>1, 5, 20</td>
<td>20</td>
<td>Adenoma</td>
<td>304</td>
<td>62</td>
</tr>
</tbody>
</table>
**Insulin Sensitizers & (Bladder) Cancer – (2)**

**Uninary bladder tumors with pioglitazone [Male rats]**

<table>
<thead>
<tr>
<th>Urinary Bladder Lesion</th>
<th>Incidence by dose (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>Carcinoma, transitional cell</td>
<td>0</td>
</tr>
<tr>
<td>Transitional tumor, benign</td>
<td>0</td>
</tr>
<tr>
<td>Transitional hyperplasia</td>
<td>4</td>
</tr>
</tbody>
</table>

From pioglitazone NDA files

…… increased incidence of urinary bladder tumor ≥ 4 mg/kg/day (40 mg/human).
Uninary bladder hyperplasia with Lobeglitazone

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg/day)</td>
<td>Vehicle 0.03 0.12 1.0/0.24</td>
<td>Vehicle 0.03 0.06 0.12</td>
</tr>
<tr>
<td>Carcinoma, Transitional cell</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
<tr>
<td>Transitional tumor, benign</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
<tr>
<td>Urinary Bladder Transitional cell hyperplasia</td>
<td>0 1 3 1 0 1 2 7</td>
<td></td>
</tr>
</tbody>
</table>

A 2-year carcinogenicity study in Rats
Scheme of 1° metabolic pathways involved in TGZ metabolism

<table>
<thead>
<tr>
<th></th>
<th>Lobeglitazone</th>
<th>Rosiglitazone</th>
<th>Troglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical dose (mg)</td>
<td>0.5</td>
<td>8</td>
<td>600</td>
</tr>
<tr>
<td>Liver : plasma ratio (rat)</td>
<td>0.85</td>
<td>0.5</td>
<td>15</td>
</tr>
<tr>
<td>Biliary recirculation</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Quinone metabolites</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>In vitro liver toxicity (IC₅₀)</td>
<td>57.6 uM</td>
<td>190 uM</td>
<td>37.5 uM</td>
</tr>
<tr>
<td>Half-life in humans (h)</td>
<td>9.5 (M), 15 (F)</td>
<td>4</td>
<td>16-34</td>
</tr>
<tr>
<td>Cmax (liver)</td>
<td>0.085 μM</td>
<td>0.85 μM</td>
<td>95 μM</td>
</tr>
<tr>
<td>In vitro liver toxicity : Cmax</td>
<td>676</td>
<td>223</td>
<td>0.39</td>
</tr>
</tbody>
</table>
Insulin Sensitizers & Bone Loss

Oil red O staining

Rosiglitazone

Pioglitazone

Lobeglitazone

MSC, male wistar rat (6 wks)

ALP activity

Relative Increase

con 5nM 50nM 500nM 5uM 50uM

Rosiglitazone
Pioglitazone
Lobeglitazone
Lobeglitazone

A 52-week oral capsule toxicity study in monkeys
- No increased toxicity compared to pioglitazone
Phase III clinical trial

Monotherapy

An Evaluation of Glycemic Effects of Lobeglitazone Monotherapy in Patients With Type 2 Diabetes Mellitus
Objective: To assess the efficacy and safety of Lobeglitazone 0.5mg in T2DM

Patients: 173 patient (Type 2 DM for a duration of at least 3 months)

Dose: Lobeglitazone 0.5mg vs matching placebo (a 2:1 ratio)

Treatment period: 24 weeks (extension to 52 weeks)

Primary endpoint: HbA$_{1c}$ change from baseline

Study sites: 5 sites in Korea
A significant reduction in HbA1c was observed with lobeglitazone versus placebo.
The HbA1c target of <7% was achieved significantly more often in the lobeglitazone group compared to the placebo group.

![Graph showing A1c target achievement rate (%) <7.0 %](image-url)
### Effects on various gluco-metabolic and lipid parameters of lobeglitazone

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lobeglitazone (n=110)</th>
<th>Placebo (n=58)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOMA-IR</td>
<td>3.51 ± 1.86</td>
<td>2.80 ± 1.58&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.30 ± 3.82</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>44.42 ± 23.02</td>
<td>54.93 ± 34.16&lt;sup&gt;c&lt;/sup&gt;</td>
<td>44.48 ± 26.65</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>178.70 ± 32.08</td>
<td>184.70 ± 34.48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>188.26 ± 37.66</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>137.51 ± 74.72</td>
<td>118.45 ± 56.24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>177.14 ± 119.34</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48.69 ± 12.78</td>
<td>52.99 ± 13.62&lt;sup&gt;c&lt;/sup&gt;</td>
<td>46.33 ± 13.56</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>109.00 ± 32.25</td>
<td>109.95 ± 32.89</td>
<td>114.76 ± 34.01</td>
</tr>
<tr>
<td>Small dense LDL (%)</td>
<td>8.10 ± 6.70</td>
<td>6.40 ± 6.55&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.51 ± 6.81</td>
</tr>
<tr>
<td>Free Fatty acid (uEq/L)</td>
<td>622.28 ± 214.18</td>
<td>561.89 ± 236.24&lt;sup&gt;a&lt;/sup&gt;</td>
<td>699.57 ± 262.28</td>
</tr>
<tr>
<td>Apolipoprotein B (mg/dL)</td>
<td>80.15 ± 19.64</td>
<td>76.01 ± 18.73&lt;sup&gt;b&lt;/sup&gt;</td>
<td>85.93 ± 21.85</td>
</tr>
</tbody>
</table>
Lobeglitazone 0.5 mg significantly lowered the proportion of subjects with metabolic syndrome.
Hypoglycemia & Weight (Monotherapy)

- Hypoglycemia was not observed in both treated groups
- More weight gain was observed in the lobeglitazone group than in the placebo group, about 1kg over 24 weeks
Summary of AE (Monotherapy)

<table>
<thead>
<tr>
<th>Adverse events summary</th>
<th>Placebo N (%)</th>
<th>Lobeglitazone 0.5 mg N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>58</td>
<td>112</td>
<td>-</td>
</tr>
<tr>
<td>Number of patients experienced an AE</td>
<td>30 (51.72)</td>
<td>55 (49.11)</td>
<td>0.7463</td>
</tr>
<tr>
<td>Number of patients experienced an ADR</td>
<td>3 (5.17)</td>
<td>10 (8.93)</td>
<td>0.5461</td>
</tr>
<tr>
<td>Number of patients experienced a SAE</td>
<td>-</td>
<td>4 (3.57)</td>
<td>0.3005</td>
</tr>
</tbody>
</table>

- Serious AEs in the lobeglitazone 0.5 mg group included lung cancer, traumatic cerebral hemorrhage, cerebrovascular accident (underlying atrial fibrillation), and right scrotal laceration and hemorrhoidectomy. These serious AEs were not considered by the investigators to be related to the study medication.
- In addition, heart failure, ischemic heart disease, renal insufficiency, or bone fracture was not observed in either group.
Summary (Monotherapy)

- **Lobeglitazone 0.5 mg**
  - Effectively controlled blood glucose
    (Significantly reduced HbA1c)
  - Increased target HbA1C achievement rates
  - Improved insulin resistance and beta-cell function
  - Improved lipid profile
    (Significantly reduced triglyceride, small dense LDL-C and increased HDL-C)
  - Lowered the proportion of subjects with metabolic syndrome

- The safety profile was comparable between the two groups and lobeglitazone was well tolerated
Phase III clinical trial 2 Combination therapy

Efficacy and Safety of Lobeglitazone Versus Pioglitazone When Added to Metformin
Objective: To assess the efficacy and safety of Lobeglitazone 0.5 mg compared with Pioglitazone 15 mg as an add-on therapy in patients with T2DM

Patients: 253 patients (Inadequate glycemic control while taking metformin alone (HbA1c 7~10%))

Dose: Lobeglitazone 0.5mg vs Pioglitazone 15 mg

Treatment period: 24 weeks (extension to 52 weeks)

Primary endpoint: HbA1c change from baseline

Study sites: 18 sites in Korea
Lobeglitazone 0.5mg showed non-inferiority in HbA1c reduction compared to pioglitazone 15mg.
Proportion of patients achieving HbA1c < 7 % in the lobeglitazone group was comparable to the pioglitazone group.
Both pioglitazone 15mg and lobeglitazone 0.5mg significantly improved insulin resistance and β cell function.

**HOMA-IR**
- Pioglitazone 15 mg (N=103): -1.34, 34.18% ▼
- Lobeglitazone 0.5 mg (N=97): -1.49, 36.43% ▼

**HOMA-β**
- Pioglitazone 15 mg (N=103): 6.82, 15.21% ▲
- Lobeglitazone 0.5 mg (N=97): 7.70, 16.67% ▲

**QUICKI**
- Pioglitazone 15 mg (N=103): 0.015
- Lobeglitazone 0.5 mg (N=97): 0.013

*: P < 0.05 vs Baseline
Both pioglitazone 15mg and lobeglitazone 0.5mg significantly improved triglyceride and free fatty acid levels

- Pioglitazone 15 mg (N=103)
- Lobeglitazone 0.5 mg (N=97)

* : P < 0.05 vs Baseline
Lipid profile-HDL-C, small dense LDL-C (Combination therapy)

- Both Pioglitazone 15mg and Lobeglitazone 0.5mg significantly improved HDL-C and small dense LDL-C levels.

![Graph showing mean change from baseline for HDL-C and small dense LDL-C](image-url)

- HDL-C: Pioglitazone 15 mg (N=103) vs Lobeglitazone 0.5 mg (N=97)
  - Mean change from baseline: Pioglitazone 6.38 mg/dL, Lobeglitazone 4.98 mg/dL
  - Differences: Pioglitazone 13.15% ▲, Lobeglitazone 16.38% ▼
  - Significance: P < 0.05 vs Baseline

- Small dense LDL-C: Pioglitazone 15 mg (N=103) vs Lobeglitazone 0.5 mg (N=97)
  - Mean change from baseline: Pioglitazone -0.78 mg/dL, Lobeglitazone -1.25 mg/dL
  - Differences: Pioglitazone -10.07% ▲, Lobeglitazone 29.48% ▼
  - Significance: P < 0.05 vs Baseline
Subgroup Analysis – BMI (Combination Therapy)

- HbA1c (%) change from baseline
  - Lobeglitazone 0.5 mg (N=97)
  - Pioglitazone 15 mg (N=103)

< BMI 25 kg/m²
- Lobeglitazone: -0.61
- Pioglitazone: -0.54

≥ BMI 25 kg/m²
- Lobeglitazone: -0.85
- Pioglitazone: -0.93

NS

*: P < 0.05 vs Baseline
Subgroup Analysis – Waist Circumference (Combination Therapy)

- HbA1c (%) change from baseline

- Lobeglitazone 0.5 mg (N=97)
- Pioglitazone 15 mg (N=103)

- Male ≤ 90 or Female ≤ 80: NS
- Male > 90 or Female > 80: NS

- Male ≤ 90 or Female ≤ 80: -0.60
- Male > 90 or Female > 80: -1.02

- Male > 90 or Female > 80: -0.88

* : P < 0.05 vs Baseline
The incidence of hypoglycemia and weight gain were not different between the two groups.
### Summary of AE (Combination therapy)

<table>
<thead>
<tr>
<th>Adverse events summary</th>
<th>Lobeglitazone 0.5 mg N (%)</th>
<th>Pioglitazone 15 mg N (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>128</td>
<td>125</td>
<td>-</td>
</tr>
<tr>
<td>Number of patients experiencing an AE</td>
<td>66 (51.56)</td>
<td>64 (51.20)</td>
<td>0.9540</td>
</tr>
<tr>
<td>Number of patients experiencing an ADR</td>
<td>8 (6.25)</td>
<td>6 (4.80)</td>
<td>0.6140</td>
</tr>
<tr>
<td>Number of patients experiencing an SAE</td>
<td>7 (5.47)</td>
<td>6 (4.80)</td>
<td>0.8096</td>
</tr>
</tbody>
</table>
Summary (Combination therapy)

- Lobeglitazone 0.5mg was not inferior to pioglitazone 15mg regarding:
  - A1c reduction
  - Achievement rate in HbA1c goal
  - Improvement in insulin resistance, β cell function, and lipid profiles
- The safety profile was comparable between the two groups and lobeglitazone was well tolerated
Lobeglitazone 0.5 mg showed improvements in glucose and lipids endpoints with a favorable safety profile. The results support lobeglitazone as a promising option for treating type 2 diabetes, especially in patients with metabolic syndrome.
Thank you for

Your Attention!