Glucagon Receptor Antagonist: LGD-6972

Program Overview and Phase 1b Results

American Diabetes Association’s 75th Scientific Sessions
June 7, 2015
Boston
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Presentation Agenda

**Introduction**
John Higgins, CEO

**Glucagon Receptor Program and LGD-6972 Phase 1b Trial Results**
Eric Vajda, Ph.D., Head of Preclinical R&D
Douglas K. Logan, M.D., Sr. Medical Director – Medpace

**Diabetes Landscape & Program Next Steps**
John Higgins, CEO
Introduction

• Ligand has concluded 18 months of Phase 1 clinical work with its Glucagon Receptor (GCGR) program
  – Favorable safety and promising efficacy positions program competitively
  – LGD-6972 potentially best-in-class molecule in leading field of non-insulin diabetes research

• The diabetes commercial and regulatory landscape has positively shifted in past few years
  – Numerous clinical and regulatory successes
  – Growing market need for what is defined as a global epidemic

• Ligand is now advancing the program to conduct a Phase 2 trial
Introducing Eric Vajda, Ph.D.

• Head of Preclinical R&D at Ligand, joined in 2002
• Leadership roles in some of Ligand’s most successful discovery programs:
  — EPO, GCSF
  — SARM
  — IRAK-4
  — Glucagon Receptor Antagonist
• B.S. - Yale University
• Ph.D. in Bioengineering - University of Utah
• Author of more than 60 scientific publications and presentations
Diabetes

• Two main types of diabetes: type 1 and type 2

• Type 1 occurs when the immune system destroys the pancreatic cells that produce insulin
  – In the U.S., ~5% of cases are type 1

• Type 2 diabetes usually starts as insulin resistance, where cells cannot use insulin properly and eventually the pancreas loses its ability to make insulin
  – In the U.S., 90-95% of cases are type 2

Source: American Diabetes Association “Fast Facts” 2015
WHO Diabetes Fact Sheet; International Diabetes Federation Atlas, 2014 Update
Glucagon Antagonism

Leading Novel Non-Insulin Mechanism in Development

- DPP-IV inhibitors, GLP1 agonists and SGTL2 inhibitors are commercially available classes of anti-hyperglycemic drugs that have been effective, but are associated with issues
  - Glucose control remains a problem for many patients
  - Dosing and delivery improvements needed
  - Safety issues (gastrointestinal and renal limitations)
- The diabetes market is growing and is clearly underserved by existing medications
- Antagonism of the glucagon pathway is one of the most promising new therapeutic areas
  - Robust glucose reduction has been observed in both preclinical and clinical studies after glucagon receptor antagonism
  - Until recently, identification of drug-like molecules has been a major hurdle
Glucagon: History in Diabetes

• Glucagon is an essential regulator of glucose, recognized as an important pharmacological target for over 30 years
  — Glucagon increases glucose levels, opposing insulin
  — Glucagon antagonism reduces plasma glucose in diabetics

• Significant advancement of science during last 4 years

<table>
<thead>
<tr>
<th>1923</th>
<th>1953</th>
<th>1982</th>
<th>2001</th>
<th>2011-15</th>
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</thead>
<tbody>
<tr>
<td>Insulin discovered and hyperglycemic factor postulated</td>
<td>Glucagon purified and crystallized</td>
<td>Peptide GCGR antagonist reduces plasma glucose in diabetic rats</td>
<td>Small molecule GCGR antagonist first tested in humans</td>
<td></td>
</tr>
</tbody>
</table>

Demonstrated glucose and HbA1c reduction in human trials
Normal Pancreas Function

1. High blood glucose
2. Pancreas releases insulin
3. Insulin causes glucose to be used by tissue and stored in liver
4. Blood glucose decreased

1. Low blood glucose
2. Pancreas releases glucagon
3. Glucagon causes release of stored glucose from liver
4. Blood glucose increased

Insulin decreases blood glucose
Glucagon increases blood glucose
Diabetic Patients

Insulin Signalling is defective

1. High blood glucose
2. Insulin signalling compromised
3. Glucose not used or stored efficiently
4. Blood glucose remains high
Diabetic Patients

Glucagon
Signalling remains active

Glucagon causes release of stored glucose from liver

1. High blood glucose

2. Pancreas still releases glucagon

3. Blood glucose remains high

4. Glucagon
Diabetic Patients

LGD-6972 blocks glucagon action in liver, reducing glucose release.

1. High blood glucose
2. Pancreas still releases glucagon
3. Blood glucose decreased
4.
Early Findings
From LGD-6972 Program
LGD-6972: Overview

• LGD-6972 is an orally available small molecule that potently binds to the glucagon receptor in vitro and competitively antagonizes the actions of glucagon.

• Glucose reduction has been demonstrated in animal models of both type 1 and type 2 diabetes.

• LGD-6972 has a clean safety profile in preclinical toxicology studies.

• The first-in-human trial demonstrated efficacy after a single dose of LGD-6972.
Earlier Studies

Significant Glucose Reduction in Diabetes Model in Mice

- The db/db mouse is an established model of advanced type 2 diabetes
- Daily oral doses of LGD-6972 for 28 days yielded significant glucose reductions
- Showed better reduction than sitagliptin
Earlier Studies

Glucose Reduction Shown in Type 1 Diabetes Model

• Streptozotocin injection in mice is a model of type 1 diabetes
• Once daily LGD-6972 significantly reduced blood glucose
• Glucagon antagonism was effective even in the absence of insulin

Vajda, et al., American Diabetes Association 73rd Scientific Sessions; Chicago, IL; June 21-25, 2013
Earlier Studies

Positive Phase 1a Clinical Data

- Double-blind, placebo-controlled, randomized single ascending oral dose evaluating safety, tolerability, PK, and PD in healthy individuals and type 2 diabetes subjects
- Dose-dependent decreases in fasting plasma glucose after a single dose
- Favorable safety profile

Vajda, et al., American Diabetes Association 74th Scientific Sessions; San Francisco; June 13-17, 2014
LGD-6972: Phase 1b Trial
Introducing Dr. Douglas Logan

- Clinical Lead, Principal Investigator, Sr. Medical Director - Medpace
- B.A. – Stanford University
- M.D. – University of Cincinnati
- Areas of medical focus:
  - Internal medicine - primary care and hospital settings
  - Cardiovascular and metabolic early clinical development
- Key investigator in development of novel lipid lowering agents
Phase 1b Study Design

• Phase 1b multiple ascending dose trial in normal healthy volunteers (NHV) and type 2 diabetes mellitus (T2DM) subjects

• T2DM subjects were on a stable dose of metformin throughout the study

• 14-day dosing period, evaluated in 4 cohorts:
  — 15 mg per day in NHV
  — 5, 10, and 15 mg per day in T2DM subjects

• 48 subjects
  — $n = 12$ per cohort (9 active + 3 placebo); 3 clinical sites

• LGD-6972 dosed as ready-to-use pharmacy-compounded solution, in a water/Captisol® mixture

• **Primary Endpoints:** Safety and tolerability of LGD-6972

• **Secondary Endpoints:** Pharmacokinetics and plasma glucose influence
### Subject Demographics

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<tr>
<th>Volunteers</th>
<th>Healthy</th>
<th></th>
<th>Diabetics</th>
<th></th>
<th></th>
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</thead>
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<tr>
<td></td>
<td>Placebo</td>
<td>15 mg</td>
<td>Placebo</td>
<td>5 mg</td>
<td>10 mg</td>
<td>15 mg</td>
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<td>Number of subjects</td>
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<td>9</td>
<td>9</td>
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<tr>
<td>Age (years) (%)</td>
<td>47.3 (8.7)</td>
<td>42.3 (10.8)</td>
<td>52.2 (6.2)</td>
<td>55.1 (6.0)</td>
<td>58.9 (6.7)</td>
<td>53.6 (8.7)</td>
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<td></td>
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<td>Race (n)</td>
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<td>4</td>
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<td>7</td>
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<tr>
<td></td>
<td>African American</td>
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<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m^2) (%)</td>
<td>27.4 (1.7)</td>
<td>24.4 (2.9)</td>
<td>31.0 (4.7)</td>
<td>33.6 (4.2)</td>
<td>32.0 (4.9)</td>
<td>31.3 (5.1)</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>Not taken</td>
<td>Not taken</td>
<td>8.5 (0.9)</td>
<td>8.2 (0.7)</td>
<td>8.2 (1.1)</td>
<td>8.5 (0.9)</td>
</tr>
</tbody>
</table>

- No study discontinuations
- No adverse events requiring stoppage of dosing
## Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Healthy</th>
<th>15 mg</th>
<th>Diabetics</th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>3</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Any TEAE (%)</td>
<td>1 (33.3)</td>
<td>4 (44.4)</td>
<td>4 (44.4)</td>
<td>2 (22.2)</td>
<td>6 (66.7)</td>
<td>4 (44.4)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Any study drug related TEAE (%)</td>
<td>-</td>
<td>2 (22.2)</td>
<td>1 (11.1)</td>
<td>1 (11.1)</td>
<td>5 (55.6)</td>
<td>2 (22.2)</td>
<td></td>
</tr>
</tbody>
</table>

### Detail of study drug related TEAE

| Gastrointestinal disorders (%) | - | - | 1 (11.1) | 1 (11.1) | 1 (11.1) | 1 (11.1) |
| Investigations (%) | - | - | - | 1 (11.1)* | - | - |
| ALT increased | - | - | - | 1 (11.1)* | - | - |
| AST increased | - | - | - | 1 (11.1)* | - | - |
| Blood urine present | - | - | - | 1 (11.1)* | - | - |
| GGT increased | - | - | - | 1 (11.1)* | - | - |
| Neutrophil increased | - | - | - | 1 (11.1)* | - | - |
| WBC increased | - | - | - | 1 (11.1)* | - | - |
| Nervous system disorders | Headache (%) | - | 2 (22.2) | - | - | 3 (33.3) | 1 (11.1) |
| Respiratory disorder (%) | Oropharyngeal pain | - | - | - | - | 1 (11.1) | - |

*occurred in a single subject on day 28, 14 days after dosing had ended
Favorable Pharmacokinetics of LGD-6972

- Well absorbed after oral administration with dose-dependent exposure, suitable for once-daily administration
- Comparable exposure in normal and T2DM subjects
Phase 1b Trial: Pharmacodynamic Data

Eric Vajda, Ph.D.
LGD-6972 reduces fasting plasma glucose after a single dose and the effect persisted throughout 14-day dosing period.
LGD-6972 Reduces Fasting Plasma Glucose

**Type 2 Diabetics**

- LGD-6972 shows a dose-dependent reduction in fasting plasma glucose, with a maximal decrease of 60 mg/dL
Glucose is Reduced Throughout the Day

**Type 2 Diabetics**

- 7 point glucose measurements performed on Day 1 and Day 14
- LGD-6972 decreased glucose in both fasting and post-prandial states (approximate decrease in weighted mean glucose > 50 mg/dL)
LGD-6972 Increases in Plasma Glucagon

**Type 2 Diabetics**

- LGD-6972 increased plasma glucagon on Day 2 and Day 14
Conclusions

• LGD-6972 is a promising agent for the potential treatment of type 2 diabetes
  – Safe and well tolerated in a multi-dose study
  – Robust reduction in glucose in both fasting and post-prandial states

• Efficacy and safety profiles are highly encouraging; potentially a best-in-class molecule

• Glucose reduction observed with glucagon receptor antagonists is highly competitive with other approved therapeutic classes

• Glucagon receptor antagonists have the potential for use as monotherapy or in combination with other oral anti-hyperglycemic medications
Diabetes Landscape & Next Steps

John Higgins
Diabetes: Serious and Growing Epidemic

- Diabetes is the 7th leading cause of death in the U.S., and significantly increases risks of other serious health problems
  - Heart disease, stroke, kidney failure, neuropathy, lower-limb amputations and blindness

- According to the ADA, $245 billion in annual costs are attributable to diabetes
  - $176 billion in direct costs and $69 billion in indirect costs (e.g., disability, work loss, premature death)

- Currently affects over 387 million people worldwide, including over 29 million in the U.S. (9.3% of the total population)
  - 1.7 million Americans are diagnosed every year

Source: American Diabetes Association “Fast Facts” 2015
WHO Diabetes Fact Sheet; International Diabetes Federation Atlas, 2014 Update
By 2050, 1 in 3 adults in U.S. will have diabetes if trend continues

Major Global Market for Diabetes Drugs

- One of the largest drug categories
- Global market projected to grow to $68 billion by 2022, over 75% increase in 10 years
- Significant opportunity for novel treatment mechanisms
- Over the past 5 years there have been 32 licensing deals (pre-clinical to Phase 3) in diabetes with disclosed deal payments of >$11 billion
- Combination therapy highly prevalent and necessary to optimize management of the disease

Sources: EvaluatePharma June 2014; Global Data: Type 2 Diabetes-Global Drug Forecast & Market Analysis to 2022 Thomson Reuters Cortellis
Top Selling Non-Insulin Anti-Diabetic Drugs

*Significant growth associated with new class launches*

- Non-insulin category essentially did not exist in 2005
- Now over $12 billion in 2014 sales and seven major new brands

*Source: Thomson Reuters Cortellis*
## Top 10 Non-Insulin Diabetes Drugs

### Current Top 10 - 2014 Sales

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Company</th>
<th>2014 Sales ($ million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-IV</td>
<td>Januvia</td>
<td>Merck</td>
<td>3,900</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Victoza</td>
<td>Novo</td>
<td>2,400</td>
</tr>
<tr>
<td>DPP-IV</td>
<td>Janumet</td>
<td>Merck</td>
<td>2,100</td>
</tr>
<tr>
<td>DPP-IV</td>
<td>Galvus</td>
<td>Novartis</td>
<td>1,200</td>
</tr>
<tr>
<td>DPP-IV</td>
<td>Onglyza</td>
<td>Astra</td>
<td>820</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Byetta/Bydureon</td>
<td>Astra</td>
<td>767</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>Invokana</td>
<td>J&amp;J</td>
<td>552</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>Forxiga</td>
<td>Astra</td>
<td>138</td>
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<tr>
<td>SGLT-2</td>
<td>Jardiance</td>
<td>Eli Lilly/BI</td>
<td>15</td>
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<tr>
<td>GLP-1</td>
<td>Trulicity</td>
<td>Eli Lilly</td>
<td>10</td>
</tr>
</tbody>
</table>

**TOTAL 2014 SALES** | **$12 B**

### Top 10 - Estimated 2020 Sales

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug</th>
<th>Company</th>
<th>Est. 2020 Sales ($ million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-IV</td>
<td>Januvia</td>
<td>Merck</td>
<td>4,190</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Victoza</td>
<td>Novo</td>
<td>3,445</td>
</tr>
<tr>
<td>SGLT-2</td>
<td>Invokana</td>
<td>J&amp;J</td>
<td>3,300</td>
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<tr>
<td>DPP-IV</td>
<td>Janumet</td>
<td>Merck</td>
<td>2,800</td>
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<tr>
<td>DPP-IV</td>
<td>Galvus</td>
<td>Novartis</td>
<td>1,425</td>
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<td>SGLT-2</td>
<td>Forxiga</td>
<td>Astra</td>
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<td>GLP-1</td>
<td>Trulicity</td>
<td>Eli Lilly</td>
<td>1,100</td>
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<tr>
<td>DPP-IV</td>
<td>Onglyza</td>
<td>Astra</td>
<td>851</td>
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<td>GLP-1</td>
<td>Byetta/Bydureon</td>
<td>Astra</td>
<td>810</td>
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<tr>
<td>SGLT-2</td>
<td>Jardiance</td>
<td>Eli Lilly/BI</td>
<td>620</td>
</tr>
</tbody>
</table>

**TOTAL Est. PEAK SALES** | **~$20 B**

- Market projected to grow over 65% to ~$20 billion in 2020
- 7 products in category projected to have sales greater than $1 billion

*Source: Thomson Reuters Cortellis - 2020 sales based on analyst consensus projections, 2015*
## Significant Opportunity for GCGR Antagonists

- Branded treatments have multibillion-dollar sales potential
- By 2020, existing classes will all have four or more competing agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Estimated Peak Sales Potential</th>
<th>Potential Drugs in 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-IV Inhibitors</td>
<td>$12 Billion</td>
<td>5</td>
</tr>
<tr>
<td>GLP-1 Agonists</td>
<td>$7 Billion</td>
<td>5</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
<td>$2 Billion</td>
<td>4</td>
</tr>
<tr>
<td>GCGR Antagonists</td>
<td>++++</td>
<td>3</td>
</tr>
</tbody>
</table>

Source: Thompson Reuters, Annual Reports

- **GCGR antagonist class:** Only three companies currently (Ligand, Eli Lilly and Pfizer), could potentially share a multibillion-dollar opportunity
Advantages of Potent GCGR Antagonist

Product profile and recent clinical data suggest significant market advantages for a safe, highly potent, oral GCGR antagonist.

<table>
<thead>
<tr>
<th>Existing Class</th>
<th>Product Profile</th>
<th>GCGR Advantage</th>
<th>GCGR Competitive with Class</th>
<th>Potential GCGR Combo with Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-IV</strong></td>
<td>Modest reduction of plasma glucose</td>
<td>Expected higher glucose reduction</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>GLP-1</strong></td>
<td>Only available as injectables</td>
<td>Oral</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>SGLT-2</strong></td>
<td>Contraindicated for renally impaired patients, safety considerations</td>
<td>Potentially effective in renally impaired</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
GCGR Antagonist Role in Type 2 Diabetes

*Diversity of use settings also creates significant opportunity*

- The safety and drug pharmacology suggests LGD-6972 could be effective across a broad population of diabetes
  - Lean & Obese - Elevated hepatic glucose production determinant in early and late disease
  - Renally Impaired
  - Advanced Disease

- Combination therapy
  - Potential to be prescribed in combination with other diabetes drugs, including the newer classes of treatments
Global Diabetes “Dance Card”

$ Ranked by non-insulin based therapies

- GCGR antagonism is the leading non-insulin diabetes mechanism in development
- Two major diabetes players now pursuing GCGR, Ligand is the only other company with published data

<table>
<thead>
<tr>
<th>Class</th>
<th>Company</th>
<th>Source: Thomson Reuters Recap IQ; Commercial or later-stage clinical assets, single region molecules not shown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Merck</td>
<td>Novo</td>
</tr>
<tr>
<td>DPP-IV</td>
<td>$7.3B\textsuperscript{1}</td>
<td>$0.9B</td>
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<td>$3.3B</td>
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<tr>
<td>GCGR</td>
<td></td>
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<tr>
<td>Total</td>
<td>$8.2B</td>
<td>$3.7B</td>
</tr>
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</table>

1 - Includes Januvia and Janumet
2 - Co-promotion between Lilly and BI
3 - Co-promotion agreement between Merck and Pfizer
Planned LGD-6972 Phase 2 Clinical Program

- Ligand advancing program to initiate a Phase 2 trial for LGD-6972 in 2016
- Phase 2 trial: multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with T2DM
- 12-week treatment with a 4-week follow-up
  - Estimate 3 doses tested
  - Randomize ~100 subjects (20 - 25 per group)
- Key inclusion criteria
  - Patients treated with diet and exercise in combination with stable dose of metformin for at least 3 months prior to screening, HbA1c 7% - 10%; BMI 25-35 kg/m²
- ~$10 million estimated costs for this Phase 2 trial, target completion in 2017
- Goal to maximize value to Ligand, securing a partner for late-stage clinical development and commercialization to come at a later date