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Ligand Announces Top-Line Results from Phase 2 Study of LGD-6972 in Patients with Type 2 Diabetes

Findings show robust, statistically significant, dose-dependent reductions from baseline in hemoglobin A1c after 12 weeks of treatment

LGD-6972 was safe and well tolerated

SAN DIEGO--(BUSINESS WIRE)-- **Ligand Pharmaceuticals Incorporated (NASDAQ: LGND)** today announced positive top-line results from a Phase 2 clinical study evaluating the efficacy and safety of LGD-6972, as an adjunct to diet and exercise, in subjects with type 2 diabetes mellitus (T2DM) inadequately controlled on metformin monotherapy. LGD-6972 is Ligand's novel, oral, small molecule, glucagon receptor antagonist (GRA). The study achieved statistical significance ($p < 0.0001$) in the primary endpoint of change from baseline in hemoglobin A1c (HbA1c) after 12 weeks of treatment at all doses tested, demonstrating a robust, dose-dependent reduction in HbA1c of 0.90%, 0.92% and 1.20% with 5 mg, 10 mg and 15 mg of LGD-6972, respectively, compared to a 0.15% reduction with placebo.

LGD-6972 was safe and well tolerated, with no drug-related serious adverse events and no dose dependent changes in lipids (including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), body weight or blood pressure after 12 weeks of treatment.

Additional details from the Phase 2 study will be submitted for presentation at future scientific conferences and for publication.

"Diabetes is a growing and global medical epidemic and despite many approved therapies, there is need for new mechanisms to treat the disease," said John Higgins, Chief Executive Officer. "Based on these trial results and previous data, we believe LGD-6972 has best-in-class type properties given its potency and effectiveness in patients with type 2 diabetes and given its potential applicability to type 1 diabetes as well. We look forward to presenting the full data set at an upcoming conference and to exploring potential partnership opportunities for this program."

"A safe and effective small molecule glucagon receptor antagonist would be a major advancement in the treatment of type 2 diabetes, providing a novel and unique mechanism to manage the disease and potentially a way to influence the natural progression of the disease", said Robert Henry, M.D., Professor of Medicine, Division of Endocrinology and Metabolism, University of California, San Diego School of Medicine; Chief, Section of Endocrinology and Metabolism and Director, Center for Metabolic Research, VA; and Past-President Medicine and Science, American Diabetes Association. "The clinical data set, lack of adverse events, and strong and clinically-relevant reduction of HbA1c shows promise for

patients with type 2 diabetes and clearly warrants further clinical evaluation and advancement."

"Inhibition of glucagon action is a novel approach to improve glycemic control in both type 1 and type 2 diabetes mellitus," said Jeremy Pettus, M.D., Assistant Professor of Medicine Division of Endocrinology, University of California, San Diego and a Principal Investigator on the study. "In Type 1 diabetes, a safe and effective glucagon receptor antagonist may provide a means to reduce daily insulin requirements and improve glucose control throughout the day. LGD-6972 may provide these benefits along with the convenience of oral administration."

About the Phase 2 Study

In this Phase 2 study, subjects with T2DM on a stable dose of metformin were treated with one of three doses of LGD-6972 (5 mg, 10 mg, or 15 mg) or placebo once daily for 12 weeks. The primary endpoint was change from baseline in hemoglobin A1c (HbA1c) after 12 weeks of treatment compared to placebo. Secondary endpoints included change from baseline compared to placebo in fasting plasma glucose, insulin, glucagon and GLP-1, as well as changes in lipids, blood pressure and body weight. In a subset of subjects, an oral glucose tolerance test was conducted at baseline and at the end of treatment. A total of 166 subjects were randomized to drug treatment among 29 clinical sites. Ligand plans to present detailed study results, including data from the secondary efficacy and safety endpoints, at upcoming medical meetings and in a peer-reviewed publication.

About Ligand's Glucagon Receptor Antagonist Program

Glucagon is a hormone produced by the pancreas that stimulates the liver to produce glucose (sugar). Overproduction of glucose by the liver is an important cause of high glucose levels in patients with type 2 diabetes and is believed to be due in part to inappropriately elevated levels of glucagon. GRAs are designed to lower glucose levels by reducing the production of glucose by the liver. Other small molecule GRAs have demonstrated a reduction of glucose and hemoglobin A1c (HbA1c) in mid-stage clinical trials, but also produced dose-dependent or significant side effects, such as increases in LDL cholesterol, body weight and blood pressure, that have impeded further clinical development.

LGD-6972 is Ligand's potent, small molecule Glucagon Receptor Antagonist. Based in part on unique elements of the chemical structure of LGD-6972 as compared to other small molecules that have been tested clinically, Ligand believes LGD-6972 to potentially be a best-in-class molecule. Details of the chemical structure of LGD-6972 will be submitted for presentation at a future scientific meeting.

LGD-6972 has been studied in previously-published preclinical and clinical studies. Presentations from preclinical studies have shown that LGD-6972 is highly potent and selective and inhibits glucagon-induced hyperglycemia in both rats and monkeys, and that it also significantly lowers glucose in a mouse model of type 2 diabetes. Additionally, LGD-6972 significantly lowered fasting and non-fasting glucose levels in a mouse model of type 1 diabetes and also reduced HbA1c, ketone bodies and free fatty acids. LGD-6972 also has been shown to have additive effects when used in combination with insulin therapy and may also be useful in an insulin-sparing regimen.

In the single- and multiple-dose Phase 1 studies, LGD-6972 demonstrated favorable safety, tolerability and pharmacokinetics in normal healthy volunteers and in subjects with T2DM, and demonstrated a robust, dose-dependent reduction of fasting plasma glucose[1]. Baseline adjusted glucose values showed dose-dependent effects of LGD-6972 on subjects with T2DM with a maximal decrease of 57 mg/dL after 14 days of treatment. The robust glycemic responses were not associated with dose-related or clinically meaningful changes in hematology, clinical chemistry, including liver enzymes and lipids, urinalysis, electrocardiography or vital signs, and no subject experienced a hypoglycemic event during the 14-day treatment or follow-up periods.

About Diabetes

Diabetes is a growing global epidemic that as of 2015 affected over 400 million adults worldwide[2]. According to a new report by the Centers for Disease Control and Prevention (CDC)[3], approximately 30 million people in the United States have diabetes, or roughly 9% of the total population. Another 84 million have prediabetes, a condition that may lead to diabetes if not treated. If current trends continue, by 2050 fully 33% of the U.S. population will be affected[4]. People with type 2 diabetes either are resistant to the effects of insulin or do not produce enough insulin to maintain a normal glucose level. Sustained high glucose levels can cause diabetic complications such as heart disease, stroke, kidney failure, neuropathy, lower-limb amputations and blindness. Although type 2 diabetes is more common in adults, it increasingly affects children as rates of childhood obesity increase. An estimated 95% of Americans with diabetes have type 2 diabetes[3].

The global market for diabetes drugs is expected to nearly double to $68 billion by 2022[5] as treatment paradigms shift toward combination therapies and novel non-insulin drugs. Global sales of the top 10 non-insulin diabetes drugs exceeded $15 billion in 2016 and are expected to increase to $20 billion by 2020[6].

About Ligand Pharmaceuticals

Ligand is a biopharmaceutical company with a business model focused on developing or acquiring royalty generating assets and coupling them with a lean corporate cost structure. Ligand's goal is to produce a bottom line that supports a sustainably profitable business. By diversifying the portfolio of assets across numerous technology types, therapeutic areas, drug targets and industry partners, we offer investors an opportunity to invest in the increasingly complicated and unpredictable pharmaceutical industry. In comparison to its peers, we believe Ligand has assembled one of the largest and most diversified asset portfolios in the industry with the potential to generate revenue in the future. These therapies seek to address the unmet medical needs of patients for a broad spectrum of diseases including diabetes, hepatitis, muscle wasting, Alzheimer's disease, dyslipidemia, anemia, asthma and osteoporosis. Ligand's Captisol® platform technology is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Ligand has established multiple alliances with the world's leading pharmaceutical companies including; Novartis, Amgen, Merck, Pfizer, Baxter International and Eli Lilly.

Forward-Looking Statements

This news release contains forward-looking statements by Ligand that involve risks and uncertainties and reflect Ligand's judgment as of the date of this release. These forward-looking statements include comments regarding the timing of reporting additional results from the Phase 2 study at future conferences or in publications; the potential for LGD-6972 to have best-in-class properties to treat patients with T2DM; whether the Phase 2 study results warrants further clinical evaluation and advancement; and the need for new mechanisms to treat diabetes. Actual results may differ from such forward-looking statements due to risks and uncertainties which may be beyond Ligand's control, including the timing of reporting additional details from the Phase 2 study which may be delayed, costs and timing of future clinical trials, the ability of Ligand to enroll patients in a new clinical trial, if any, the expectation that the results from completed clinical trials predict the results of future clinical trials, the ability of Ligand's cash flow from operations to cover the costs of any future clinical trials, the impact of clinical trials on Ligand's financial guidance, as well as the growth of the population with diabetes and the trends in the market to treat diabetes. The failure to meet expectations with respect to any of the foregoing matters may reduce Ligand's stock price. Additional information concerning these and other important risk factors affecting Ligand can be found in Ligand's prior press releases available at www.ligand.com as well as in Ligand's public periodic filings with the Securities and Exchange Commission, available at www.sec.gov. Ligand disclaims any intent or obligation to update these forward-looking statements beyond the date of this press release, except as required by law. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

References

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