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Ligand Presents Positive Results from Phase 1 Clinical Trial of Captisol-enabled Iohexol

Presentation at the American Society of Nephrology (ASN) Kidney Week 2019

SAN DIEGO--(BUSINESS WIRE)-- **Ligand Pharmaceuticals Incorporated (NASDAQ: LGND)** presented positive results today from a Phase 1 clinical trial of its Captisol-enabled (CE) Iohexol program at ASN Kidney Week 2019 in Washington, D.C. The CE-Iohexol program was established in January 2018 to develop a Captisol-enabled, next-generation contrast agent for diagnostic imaging with a reduced risk of renal toxicity. The trial achieved the primary endpoint demonstrating pharmacokinetic bioequivalence between CE-Iohexol injection and a reference Iohexol injection (OMNIPAQUE™) after intravenous (IV) administration in healthy adults. CE-Iohexol injection was safe and well tolerated, and adverse events were in line with the known safety profile of OMNIPAQUE.

Contrast agents are used to enhance diagnostic imaging. Despite their benefits and widespread use, contrast agents may place patients at an increased risk for acute kidney injury (AKI), especially those with certain risk factors undergoing cardiac interventional procedures utilizing intravascular iodinated contrast.[1] CE-Iohexol is designed to reduce the risk of AKI during imaging procedures where iodinated contrast agents are administered. In preclinical studies using an animal model of AKI, CE-Iohexol administered at a dose similar to the clinical usage of iohexol in humans significantly reduced renal injury compared to iohexol alone and increased survival from 50% to 88%.[2]

The goal of the Phase 1 trial was to establish pharmacokinetic bioequivalence to support subsequent clinical trials that could support the submission of a 505(b)(2) new drug application (NDA) to the U.S. Food and Drug Administration (FDA). The trial design consisted of a single-center, randomized, double-blind, two-period crossover study to determine relative bioavailability of CE-Iohexol and a reference Iohexol injection (OMNIPAQUE) after IV administration in a population of 24 healthy adults (NCT03869983).

Highlights of the data presented today include:

- In two treatment periods, subjects received each treatment as a single IV dose of 80 milliliters (mL) infused over approximately 20 seconds by a power injector: CE-Iohexol, 755 mg/mL iohexol (350 mg I/mL)/50 mg CAPTISOL®/mL; OMNIPAQUE, 755 mg/mL iohexol (350 mg I/mL).

- Bioequivalence between CE-Iohexol and OMNIPAQUE was demonstrated for the key pharmacokinetic (PK) parameters of area under the concentration-time curve (AUC) and maximum concentration (C_{max}).

- Geometric mean ratio of AUCs for CE-Iohexol and OMNIPAQUE was 1.0 with 94% confidence interval of 0.98-1.02. Geometric mean ratio of C_{max} for CE-Iohexol and OMNIPAQUE was 1.0 with 94% confidence interval of 0.95-1.06.
- The means of AUC, C_{max}, as well as half-life and elimination constant, were similar between treatments; the mean elimination constant was 0.3/hour for both treatments.
- Based on these results, it can be concluded that CE-Iohexol is bioequivalent to the reference OMNIPAQUE following IV injection in healthy adults.
- No subject had a serious adverse event or discontinued from the study due to an adverse event. All adverse events were mild to moderate in severity and the incidence of subjects with adverse events was similar in both treatment groups.
- The most common adverse event was a sensation of warmth, which is an adverse event known to occur during IV administration of iodinated contrast agents such as OMNIPAQUE.[3]
- There were no clinically significant abnormal physical examination findings, and there were no clinically meaningful changes in vital signs, laboratory parameters., hematology, urinalysis or ECG results.
- Overall, administration of the Captisol-containing CE-Iohexol following IV injection was safe and well tolerated in normal healthy subjects.

“This trial represents a promising milestone in the pursuit of a safer agent for patients who receive intravenous contrast for their radiology and cardiology tests and procedures,” said Peter A. McCullough, MD, MPH, Vice Chief of Medicine, Baylor University Medical Center, Dallas TX, and President, Cardiorenal Society of America. “The results showed that this unique product candidate incorporating a patented formulation ingredient had the expected pharmacokinetic profile compared to the reference standard agent, yet it offers potential for less kidney injury when given to patients with baseline kidney disease, diabetes, and multiple associated risk factors.”

About Captisol-enabled Iohexol

More than 30 million imaging procedures are performed each year in the United States. Iodinated contrast agents represent more than 60% of all X-ray imaging agents sold with an annual U.S. market of approximately $1.5 billion.[4] Iohexol (marketed as OMNIPAQUE™ by GE Healthcare), the most widely-used injectable diagnostic contrast agent for imaging procedures, has global sales exceeding $500 million and no generic competition in the United States.

Contrast-induced acute kidney injury (CI-AKI) is the acute impairment of renal function following intravascular administration of an iodinated contrast agent, and occurs most frequently following coronary angiography, percutaneous coronary intervention and contrast-enhanced computed tomography, especially among patients at risk of renal injury such as those with advanced age, diabetes or heart failure. CI-AKI is an issue with broad medical visibility as more than 50% of cardiovascular imaging procedures are performed in patients age 65 or older.[5]

Currently no products are approved to prevent or treat CI-AKI in this setting, and therefore Ligand believes a significant opportunity exists for a safer formulation of contrast agents. The goal is for CE-Iohexol to establish a new safety standard that enables a future partner to gain meaningful market share.

About Captisol®

Captisol is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. Captisol was invented and initially developed by scientists in the laboratories of Dr. Valentino Stella, University Distinguished Professor at the University of Kansas' Higuchi Biosciences Center for specific use in drug development and formulation. This unique technology has enabled several FDA-approved products, including Amgen's KYPROLIS®, Baxter International's NEXTERONE®, Acrotech Biopharma L.L.C.'s and CASI Pharmaceuticals' EVOMELA® and Melinta Therapeutics' BAXDELA™ and Sage Therapeutics' ZULRESSO™. There are many Captisol-enabled products currently in various stages of development.

About Ligand Pharmaceuticals

Ligand is a biopharmaceutical company focused on developing or acquiring technologies that help pharmaceutical companies discover and develop medicines. Ligand's business model creates value for stockholders by providing a diversified portfolio of biotech and pharmaceutical product revenue streams that are supported by an efficient and low corporate cost structure. Ligand's goal is to offer investors an opportunity to participate in the promise of the biotech industry in a profitable, diversified and lower-risk business than a typical biotech company. Ligand's business model is based on doing what we do best: drug discovery, early-stage drug development, product reformulation and partnering. Ligand partners with other pharmaceutical companies to leverage what they do best (late-stage development, regulatory management and commercialization) to ultimately generate our revenue. Ligand's Captisol® platform technology is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility and stability of drugs. OmniAb® is a patent-protected transgenic animal platform used in the discovery of fully human mono-and bispecific therapeutic antibodies. Ligand has established multiple alliances, licenses and other business relationships with the world's leading pharmaceutical companies including Amgen, Merck, Pfizer, Bristol-Myers Squibb, Gilead, Janssen, Baxter International and Eli Lilly.

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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 include statements regarding: the potential that Ligand's CE-Iohexol program to increase the safety of widely-used commercial contrast agents; Ligand's expectations that the top-line Phase 1 clinical trial results can support further clinical development or a new drug application to the FDA in the future; the potential to partner or out-licensing the CE-Iohexol program; the market size of contrast agent procedures and the addressable market of CE-Iohexol; the potential that CE-Iohexol could reduce renal toxicity and deliver a safer radiocontrast agent;

Ligand's expectations that it will partner the program or obtain a higher royalty rate or milestone payments due to Ligand's development activities; and Ligand's view of that there is a significant unmet need for safer radiocontrast agents. Actual events or results may differ from our expectations. For example the FDA may not agree with Ligand's interpretation of the data Ligand has reported; future clinical trials may demonstrate unexpected adverse side effects or inadequate therapeutic efficacy of CE-Iohexol may limit regulatory approval and/or commercialization, or may result in recalls or product liability claims; Ligand may choose to abandon the program for any reason or no reason; the anticipated benefits of CE-Iohexol, including the possible improvements in kidney safety, may not materialize; and Ligand may be unable to secure licensing partners or buyers for products developed from the contrast agent program. 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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