May 31, 2012

New Data Showed LIVALO® (pitavastatin) Met Primary Endpoint of LDL-C Reduction When Compared with Pravastatin

PREVAIL U.S. primary and secondary lipid endpoints and lipoprotein particle analysis presented at the National Lipid Association Scientific Sessions

SCOTTSDALE, Ariz., May 31, 2012 /PRNewswire/ -- Kowa Pharmaceuticals America, Inc. and Eli Lilly and Company (NYSE:LLY) today announced results of the PREVAIL U.S. study (Pitavastatin compaREd with praVAstatin In Lowering LDL-C in the U.S.) which evaluated the efficacy of LIVALO® (pitavastatin) 4 mg compared with pravastatin 40 mg in reducing low-density lipoprotein cholesterol (LDL-C), the primary endpoint, as well as effects on other lipid parameters and lipoprotein particles in adult patients with primary hyperlipidemia or mixed dyslipidemia.[1] Study results were presented during two poster sessions at the National Lipid Association's (NLA) Scientific Sessions in Scottsdale, Arizona.

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PREVAIL U.S. was designed as a superiority trial for the primary endpoint, LDL-C reduction, and evaluated the adult population age 18-80 with primary hyperlipidemia or mixed dyslipidemia. LIVALO 4 mg showed superior LDL-C reduction compared with pravastatin 40 mg after 12 weeks of therapy. The study did not compare LIVALO 4 mg with pravastatin 80 mg.[1]

Data for secondary endpoints showed LIVALO 4 mg reduced apolipoprotein B (Apo-B), non-HDL-C, and total cholesterol compared with pravastatin 40 mg and improved high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG).[1] In addition, the effect of LIVALO and pravastatin on individual lipoprotein particles was evaluated as a pre-specified exploratory analysis using nuclear magnetic resonance (NMR) spectroscopy. LIVALO showed significantly greater reductions in total LDL particle (LDL-P) concentration and increases in HDL particle (HDL-P) concentration and size.[2]

"We are very pleased with the results of PREVAIL U.S., which are consistent with previous trials evaluating LIVALO's effect on LDL-C reduction," said Dr. Craig Sponseller, Vice President of Medical Affairs at Kowa Pharmaceuticals America, Inc. "Although the clinical relevance of these data require further study, these data are important as they represent the first of such particle analysis with LIVALO."

PREVAIL U.S. study investigator, Dr. Kari Uusinarkaus, Fellow of the National Lipid Association, and Associate Medical Director, Adult Primary Care and Disease Management Departments, Colorado Springs Health Partners, explains, "We continue to research and pursue a greater understanding on the effect of lipid-modifying agents, particularly statins, on lipoprotein particles and the use of direct measures of particle number and size in advancing our clinical assessment of dyslipidemia and its treatment."

About the Study

In the 12-week, Phase 4, multicenter, randomized, double-blind study, 328 adults meeting the established profile for inclusion were randomly assigned to receive once-daily morning doses of LIVALO 4 mg or pravastatin 40 mg.[1] Full lipid panels and lipoprotein particle assessments using nuclear magnetic resonance (NMR) were performed on blood samples drawn on Day 1 and following the final dose at 12 weeks.[2]

The data were presented in two posters at the NLA meeting. In the first poster, "Pitavastatin 4 mg is Superior to Pravastatin 40 mg in LDL-C Reduction: Results from PREVAIL U.S. Trial in Primary Hyperlipidemia or Mixed Dyslipidemia," subjects treated with LIVALO 4 mg experienced a median percent reduction in LDL-C of 38.1% over the treatment period compared to a 26.4% median percent reduction in patients randomized to pravastatin 40 mg. LIVALO reduced total cholesterol by 25.8%, with pravastatin showing a total cholesterol reduction of 18.3%. LIVALO treated patients experienced a significant 26.9% reduction in Apo B compared with a 17.7% reduction associated with pravastatin.[1]

In the second poster, "Pitavastatin 4 mg Significantly Reduces LDL-P and Increases HDL Size Compared with Pravastatin 40 mg: Results from PREVAIL U.S.," the pre-specified, exploratory objective was to evaluate LIVALO 4 mg vs. pravastatin 40 mg on lipoprotein particle concentrations and size. LIVALO 4 mg significantly reduced the concentration of LDL-P by 517.0

nanomoles per liter (nmol/L) compared with 396.0 nmol/L for pravastatin 40 mg ($p < 0.001$). Both LIVALO and pravastatin increased HDL-P with a mean percent change in HDL-P of 9.59% versus 7.03%, respectively ($p=0.045$). Significant increases in HDL size, and small HDL, as well as significant decreases in VLDL-P and IDL-P were also noted for LIVALO compared with pravastatin over the 12-week study period. Improvement was observed in Apo A1, medium and large HDL for both agents, but were not statistically different between treatment arms. Additional studies are needed to better understand the clinical impact. [2]

No clinically important differences in the safety profiles were observed between LIVALO and pravastatin in PREVAIL U.S. The overall incidence of treatment-emergent adverse events (TEAEs) was similar between treatment groups (47.6% for LIVALO and 44.5% for pravastatin), and most events were mild or moderate in severity. The most frequently reported drug-related TEAEs were muscle spasms and myalgia (each of which occurred at an incidence of 1.8% for LIVALO and 1.2% for pravastatin).[1]

About LIVALO

LIVALO is a HMG-CoA reductase inhibitor indicated for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C).

Limitations of Use:

- Doses of LIVALO greater than 4 mg once daily were associated with an increased risk for severe myopathy in premarketing clinical studies. Do not exceed 4 mg once daily dosing of LIVALO.
- The effect of LIVALO on cardiovascular morbidity and mortality has not been determined.
- LIVALO has not been studied in Fredrickson Type I, III, and V dyslipidemias.

In addition to being launched in the U.S. in June 2010, LIVALO is also approved in Japan (2003), South Korea (2005), Thailand (2007), China (2008), European Union (2010), Taiwan (2011), Mexico (2009) and Australia (2010).

About Primary Hyperlipidemia and Mixed Dyslipidemia

Primary Hyperlipidemia is defined as an elevation of cholesterol, particularly "bad" cholesterol (LDL-C), triglycerides (TG), or both. Mixed dyslipidemia is usually characterized by an elevation of LDL-C, TG, and a decrease in the "good" cholesterol (HDL-C) in the blood.

Important Safety Information for LIVALO® (pitavastatin) Tablets

CONTRAINDICATIONS

LIVALO is contraindicated in patients with a known hypersensitivity to product components, in patients with active liver disease (which may include unexplained persistent elevations in hepatic transaminase levels), in women who are pregnant or may become pregnant, in nursing mothers, or in coadministration with cyclosporine.

WARNINGS AND PRECAUTIONS

Skeletal Muscle Effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including LIVALO.

- The risk of skeletal muscle effects (e.g., myopathy and rhabdomyolysis) increases in a dose-dependent manner with advanced age (> 65 years), renal impairment, inadequately treated hypothyroidism, and in combination use with fibrates or lipid-modifying doses of niacin (> /= 1 g/day).
- Concomitant administration of LIVALO with gemfibrozil should be avoided.
- LIVALO therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. LIVALO therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis; hypotension; dehydration; major surgery; trauma; severe metabolic, endocrine, and electrolyte disorders; or uncontrolled seizures).
- Advise patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, and to discontinue LIVALO if these signs or symptoms appear.

Liver Enzyme Abnormalities

Increases in serum transaminases have been reported with HMG-CoA reductase inhibitors, including LIVALO.

- It is recommended that liver enzyme tests be performed before the initiation of LIVALO and if signs or symptoms of liver injury occur.
- There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including pitavastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with LIVALO, promptly interrupt therapy. If an alternate etiology is not found do not restart LIVALO.
- Advise patients to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice.
- LIVALO should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of chronic liver disease.

Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including LIVALO.

ADVERSE REACTIONS

In short-term controlled studies, the most frequent adverse reactions reported by > /=2% of patients treated with LIVALO 1 mg, 2 mg, and 4 mg, respectively, and at a rate > /= placebo were back pain (3.9%, 1.8%, 1.4% vs 2.9%), constipation (3.6%, 1.5%, 2.2% vs 1.9%), diarrhea (2.6%, 1.5%, 1.9% vs 1.9%), myalgia (1.9%, 2.8%, 3.1% vs 1.4%), and pain in extremity (2.3%, 0.6%, 0.9% vs 1.9%). This is not a complete listing of all reported adverse events.

For additional information please visit **http://www.kowapharma.com/documents/LIVALO_PI_CURRENT.pdf**

About Kowa Company, Ltd. and Kowa Pharmaceuticals America, Inc.

Kowa Company, Ltd. (KCL) is a privately held multinational company headquartered in Nagoya, Japan. Established in 1894, KCL is actively engaged in various manufacturing and commercial activities in the fields of pharmaceutical, life science, information technology, textiles, machinery and various consumer products. KCL's pharmaceutical division is focused on cardiovascular therapeutics, with sales of the company's flagship product LIVALO, totaling $530 million (14.6% market share) in Japan in the 2010 fiscal year, and was launched in the United States in June 2010.

Kowa Pharmaceuticals America, Inc. (KPA) is a pharmaceutical company specializing primarily in the area of cardiometabolic diseases. The company, started in 2001 as ProEthic Pharmaceuticals, Inc., was acquired by KCL in September of 2008. A privately held company, KPA directs its efforts towards the acquisition, licensing and marketing of pharmaceutical products.

exchange rate used $1=85JPY

About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers — through medicines and information — for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

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[1] Data on File: Morgan R, Campbell S, et al, "Pitavastatin 4 mg is Superior to Pravastatin 40 mg in LDL-C Reduction: Results from PREVAIL US Trial in Primary Hyperlipidemia or Mixes Dyslipidemia," Poster presented at the National Lipid Association Annual Scientific Sessions 2012, May 31-June 3, 2012; Scottsdale, AZ.

[2] Data on File: Sponseller C, Morgan R, et al, "Pitavastatin 4 mg Significantly Reduces LDL-P and Increases HDL Size Compared with Pravastatin 40 mg: Results from PREVAIL US," Poster presented at the National Lipid Association Annual Scientific Sessions 2012, May 31-June 3, 2012; Scottsdale, AZ.

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