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Rayaldee Phase 3 Trial Meets Primary Endpoints

- Top-line Data from Second Identical Pivotal Phase 3 Trial Expected in September 2014
- New Drug Application (NDA) Submission to the U.S. FDA on Track for End of 2014

MIAMI--(BUSINESS WIRE)-- OPKO Health, Inc. (NYSE: OPK), announced successful top-line results from the first pivotal phase 3 trial of Rayaldee™. This trial is one of two identical randomized, double-blind, placebo-controlled, multi-site studies intended to establish the safety and efficacy of Rayaldee as a new treatment for secondary hyperparathyroidism (SHPT) in patients with stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency. Both trials are the subject of a Special Protocol Assessment (SPA) established with the United States (U.S.) Food and Drug Administration (FDA) in August 2012.

“Top-line data from this study demonstrate that Rayaldee effectively controls secondary hyperparathyroidism in patients with stage 3 or 4 chronic kidney disease by correcting vitamin D insufficiency,” stated Joel Z. Melnick, MD, Vice President of Clinical Research and Development for OPKO’s Renal Division. “Rayaldee was equally effective in both disease stages, indicating that this new therapy is appropriate even for patients with minimal functioning kidney mass.”

This trial involved 213 adult patients recruited from 39 sites throughout the U.S. Patients were stratified by CKD stage and randomized in a 2:1 fashion to receive six months of treatment with either Rayaldee or placebo. On enrollment, all patients exhibited vitamin D insufficiency which was corrected in 96% of patients treated with Rayaldee.

The completed trial successfully met all primary efficacy and safety endpoints. The primary efficacy endpoint was a responder analysis in which “responder” was defined as any treated subject who demonstrated an average 30% decrease in plasma parathyroid hormone (PTH) from pre-treatment baseline during the last six weeks of the treatment period. A significantly higher response rate ($p<0.001$) was observed with Rayaldee which steadily increased with treatment duration. The response rate with Rayaldee was similar in CKD stages 3 and 4. Safety and tolerability data were comparable in both treatment groups.

“Rayaldee is designed to fill a void in the treatment armamentarium of nephrologists and endocrinologists who care for pre-dialysis chronic kidney disease patients,” commented Dr. Charles W. Bishop, CEO of OPKO’s Renal Division. “Controlled trials have shown that over-the-counter and prescription vitamin D supplements are ineffective in treating SHPT in these patients and are, at best, unreliable in correcting vitamin D insufficiency. On the other hand, vitamin D hormone drugs can effectively treat SHPT but, due to high potency, often oversuppress PTH, increasing the risk of adynamic bone disease and vascular calcification. These hormone drugs are entirely ineffective in treating vitamin D insufficiency, the underlying cause of SHPT in most pre-dialysis patients. Rayaldee addresses a long-standing unmet need to safely control SHPT by reliably correcting vitamin D insufficiency.”

“Physicians will embrace a product that does what we want, namely, treat vitamin D insufficiency and gradually correct elevated PTH, without safety concerns,” stated David A. Bushinsky, MD, Chief, Nephrology Division, University of Rochester Medical Center. “Data from this first pivotal trial indicate that Rayaldee may be such a product, and I look forward to confirmation from the second identical trial.”

Top-line data from the second, identical pivotal phase 3 trial are expected to be available in September 2014.

Patients completing the two pivotal trials are being treated, at their election, for an additional 6 months with Rayaldee during an ongoing open-label extension study. Enrollment in this extension study surpassed the targeted level of 270 patients by May 2014 and 141 patients have completed participation.

“Rayaldee is the lead candidate in a growing portfolio of products that OPKO is developing in its Renal Division for global commercialization,” explained Dr. Phillip Frost, Chairman and CEO of OPKO Health. “Rayaldee provides an excellent solution to the problem of secondary hyperparathyroidism associated with vitamin D insufficiency for more than 4 million CKD patients in the U.S. and many more elsewhere.”

A New Drug Application (NDA) submission to the U.S. FDA is on track for the end of 2014.

About Rayaldee™

Rayaldee is a first-in-class oral vitamin D prohormone treatment being developed for SHPT in patients with stage 3 or 4 CKD and vitamin D insufficiency. It has a proprietary modified-release formulation designed to gradually and reliably raise serum total 25-hydroxyvitamin D (prohormone) concentrations to targeted levels (at least 30 ng/mL) while avoiding upregulation of CYP24, a cytochrome P-450 enzyme that reduces the PTH-lowering potency of current vitamin D supplements. Activation of calcifediol, the active ingredient in Rayaldee, by the kidney is tightly regulated, preventing excessive elevation of serum calcium and related side effects which limit the value of current vitamin D hormone therapies by promoting vascular and renal calcification. Rayaldee is expected to address the approximately 4 million patients in the U.S., and many more elsewhere, with stage 3 or 4 CKD, SHPT and vitamin D insufficiency.

About Chronic Kidney Disease

CKD is a condition characterized by a progressive decline in kidney function. The kidney is normally responsible for excreting waste and excess water from the body, and for regulating various hormones. CKD is classified in five different stages — mild (stage 1) to severe (stage 5) disease — as measured by the kidney's glomerular filtration rate. According to the National Kidney Foundation, CKD afflicts over 26 million people in the U.S., including more than eight million patients with moderate (stages 3 or 4) and severe (stage 5) forms of CKD. In stage 5 CKD, kidney function is minimal to absent and patients require regular dialysis or a kidney transplant for survival.

About Vitamin D Insufficiency

Vitamin D insufficiency is a condition in which the body has low vitamin D stores,

characterized by inadequate blood levels of vitamin D prohormone, known as 25-hydroxyvitamin D. An estimated 70-90% of CKD patients have vitamin D insufficiency, which can lead to SHPT and resultant debilitating bone diseases. Vitamin D insufficiency has been associated with increased mortality in CKD.

About Secondary Hyperparathyroidism (SHPT)

SHPT is a condition commonly associated with CKD in which the parathyroid glands secrete excessive amounts of PTH. SHPT arises as a result of vitamin D insufficiency or impaired kidney function that prevents sufficient production of vitamin D hormone to properly regulate calcium and phosphorus metabolism, and PTH secretion. Prolonged elevation of blood PTH causes excessive calcium and phosphorus to be released from bone, leading to elevated serum calcium and phosphorus, softening of the bones (osteomalacia) and calcification of vascular and renal tissues. SHPT affects 40-60% of patients with moderate CKD and approximately 90% of patients with severe CKD. Vitamin D therapy for SHPT is associated with reduced mortality in CKD patients.

About Special Protocol Assessment

The Special Protocol Assessment (SPA) provided a mechanism for the FDA and OPKO to reach agreement on the design, size, execution and analysis of the two pivotal phase 3 trials with Rayaldee. The FDA agreed that the design and planned analysis of these studies adequately addressed the objectives necessary to support an NDA submission.

About OPKO

OPKO is a multinational biopharmaceutical and diagnostics company that seeks to establish industry leading positions in large, rapidly growing markets by leveraging its discovery, development and commercialization expertise and novel and proprietary technologies.

This press release contains "forward-looking statements," as that term is defined under the Private Securities Litigation Reform Act of 1995 (PSLRA), regarding product development efforts and other non-historical facts about our expectations, beliefs or intentions regarding our business, technologies and products, financial condition, strategies or prospects, including statements regarding our ability to successfully launch and commercialize proprietary renal disease products, expectations about Rayaldee™, its market potential, that it will address the approximately 4 million CKD stage 3 and 4 patients in the U.S. and many more elsewhere, with SHPT and vitamin D insufficiency, that Rayaldee™ will treat vitamin D insufficiency and gradually correct elevated PTH, without safety concerns, and that we will be able to successfully develop, obtain approval for and launch sales of Rayaldee™. Many factors could cause our actual activities or results to differ materially from the activities and results anticipated in forward-looking statements. These factors include those described in our filings with the Securities and Exchange Commission, as well as risks inherent in funding, developing and obtaining regulatory approvals of new, commercially-viable and competitive products and treatments, including the risks that the phase 3 clinical trials for Rayaldee™ may not be successful or achieve the expected results or effectiveness, and may not generate data that would support the approval or marketing of this product for the indications being studied, that others may develop products which are superior to Rayaldee™, and that Rayaldee™ may not have advantages or prove to be superior over presently marketed products, including the currently used high monthly doses of prescription

vitamin D_2, activated vitamin D hormone and over-the-counter vitamin D supplements . In addition, forward-looking statements may also be adversely affected by general market factors, competitive product development, product availability, federal and state regulations and legislation, the regulatory process for new products and indications, manufacturing issues that may arise, patent positions and litigation, among other factors. The forward-looking statements contained in this press release speak only as of the date the statements were made and we do not undertake any obligation to update forward-looking statements. We intend that all forward-looking statements be subject to the safe-harbor provisions of the PSLRA.

OPKO Health, Inc.
Investor Relations:
FTI Consulting
Barbara Ryan, 212-850-5679
Managing Director
Barbara.Ryan@fticonsulting.com
or
Media Relations:
Kimberly Ha, 212-850-5612
Senior Director
Kimberly.Ha@fticonsulting.com

Source: OPKO Health, Inc.