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OPKO Submits IND for Rayaldee™ as Adjunctive Cancer Therapy

MIAMI--(BUSINESS WIRE)-- OPKO Health, Inc. (NYSE: OPK), announced the submission of an Investigational New Drug (IND) Application to the United States (U.S.) Food and Drug Administration (FDA) under which *Rayaldee*™ will begin clinical evaluation as an adjunctive therapy for the prevention of skeletal-related events (SREs) in patients with bone metastases undergoing anti-resorptive therapy.

The initial investigation described in this IND is a phase 1 dose titration study designed to evaluate the safety and tolerability of *Rayaldee* in patients with breast or prostate cancer that has metastasized to bone who are receiving treatment with zoledronic acid (a bisphosphonate) or denosumab (a RANKL inhibitor). Approximately 24 subjects (12 with each cancer type) will receive *Rayaldee* at a starting daily dose of 30 µg (1 capsule) for 4 weeks. The dose will escalate in 30 µg increments at 4-week intervals until predetermined biochemical endpoints are reached, at which time the subjects will enter a 12-week maintenance phase. Safety parameters and various markers of bone metabolism, immune function and tumor burden will be monitored at regular intervals.

This study is expected to commence later this year and to take approximately 18 months to complete. Following evaluation of this initial study, OPKO plans to conduct subsequent studies investigating the effects of *Rayaldee* on SREs and other parameters deemed to indicate potential clinical benefits in the targeted population.

About *Rayaldee*™

Rayaldee is a first-in-class oral vitamin D prohormone treatment in late-stage clinical development for secondary hyperparathyroidism (SHPT) in patients with stage 3 or 4 chronic kidney disease (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 and cancer patients have vitamin D insufficiency, which can lead to SHPT, hypocalcemia (low serum calcium) and resultant debilitating bone diseases. Vitamin D insufficiency has been associated with increased mortality in CKD and various cancers.

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, use of anti-resorptive therapies, 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.

About Anti-Resorptive Therapy for Metastatic Bone Cancer

Anti-resorptive therapy effectively reduces bone loss caused by cancer progression, thereby preventing or delaying SREs. This therapy causes SHPT and increases the risk of serious hypocalcemia which can be fatal. Risk of SHPT and hypocalcemia is elevated in patients who are receiving anti-resorptive therapy due to the high prevalence of vitamin D insufficiency, which reduces intestinal absorption of dietary calcium.

About Skeletal-Related Events (SREs)

Bone metastases are a common in advanced breast and prostate cancer, and represent a major cause of morbidity and mortality. In the absence of anti-resorptive therapy, they produce hypercalcemia, pathological fractures and spinal cord compression, collectively known as skeletal-related events (SREs). Current approaches to management of SREs include suppressing osteolytic activity with zoledronic acid (a bisphosphonate) or denosumab (an antibody targeting RANK ligand). These anti-resorptive agents are highly effective but increase the risk of fatal hypocalcemia.

Anti-resorptive agents reduce the efficiency of PTH-stimulated release of calcium from bone, promoting SHPT and forcing reliance on intestinal calcium absorption for calcium homeostasis. Since cancer patients frequently have poor dietary intake (due to cachexia) and vitamin D insufficiency, intestinal calcium absorption can be inadequate. In a recent study, 39% of patients treated with zoledronic acid developed hypocalcemia, and numerous other studies have reported reduced serum calcium with denosumab treatment. Labeling for both

agents requires correction of hypocalcemia before dosing and ongoing supplementation with calcium and vitamin D during therapy.

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 US and many more elsewhere, with SHPT and vitamin D insufficiency, whether it will be an effective adjunctive therapy for the prevention of SREs in patients with bone metastases, expectations about the timing to commence and complete clinical studies for Rayaldee, 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 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 D2, 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.

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