Exelixis' Phase 3 CELESTIAL Trial of Cabozantinib Meets Primary Endpoint of Overall Survival in Patients with Advanced Hepatocellular Carcinoma

October 16, 2017

– Exelixis to submit a supplemental New Drug Application to the U.S. Food and Drug Administration (FDA) in the first quarter of 2018; cabozantinib previously granted orphan drug designation by FDA –

– Data to be submitted for presentation at an upcoming medical meeting –

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Oct. 16, 2017-- Exelixis, Inc. (NASDAQ:EXEL) today announced that its global phase 3 CELESTIAL trial met its primary endpoint of overall survival (OS), with cabozantinib providing a statistically significant and clinically meaningful improvement in median OS compared to placebo in patients with advanced hepatocellular carcinoma (HCC). The independent data monitoring committee for the study recommended that the trial should be stopped for efficacy following review of the second planned interim analysis. CELESTIAL is a randomized, global phase 3 trial of cabozantinib versus placebo in patients with advanced HCC who have been previously treated with sorafenib. The safety data in the study were consistent with the established profile of cabozantinib. Based on these results, Exelixis plans to submit a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) in the first quarter of 2018. Detailed results from CELESTIAL will be submitted for presentation at a future medical conference.

This press release features multimedia. View the full release here: http://www.businesswire.com/news/home/20171016005409/en/

"We are excited that these positive results from the phase 3 CELESTIAL trial bring us one step closer to the potential of offering previously treated patients with this aggressive form of advanced liver cancer a much-needed new treatment option," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "This is an important milestone for the cabozantinib development program; we are committed to studying cabozantinib in a range of tumor types as part of our mission to deliver medicines that improve treatment outcomes and give patients hope for the future."

Exelixis will discuss the trial results with regulatory authorities and determine next steps for the trial, including offering patients currently receiving placebo the opportunity to cross over to cabozantinib.

In March 2017, the FDA granted orphan drug designation to cabozantinib for the treatment of advanced HCC. Orphan drug designation is granted to treatments for diseases that affect fewer than 200,000 people in the U.S. and provides certain incentives for medications intended for the treatment, diagnosis or prevention of rare diseases. At present, these incentives include seven years of marketing exclusivity for the orphan indication, certain federal grants, tax credits, and waiver of certain FDA fees.

About the CELESTIAL Study
CELESTIAL is a randomized, double-blind, placebo-controlled study of cabozantinib in patients with advanced HCC conducted at more than 100 sites globally in 19 countries. The trial was designed to enroll 760 patients with advanced HCC who received prior sorafenib and may have received up to two prior systemic cancer therapies for HCC and had adequate liver function. Enrollment of the trial was completed in September 2017. Patients were randomized 2:1 to receive 60 mg of cabozantinib once daily or placebo and were stratified based on etiology of the disease (hepatitis C, hepatitis B or other), geographic region (Asia versus other regions) and presence of extrahepatic spread and/or macrovascular invasion (yes or no). No cross-over was allowed between the study arms.

The primary endpoint for the trial is OS, and secondary endpoints include objective response rate and progression-free survival. Exploratory endpoints include patient-reported outcomes, biomarkers and safety.

Based on available clinical trial data from various published trials conducted in the second-line setting of advanced HCC, the CELESTIAL trial statistics for the primary endpoint of OS assumed a median OS of 8.2 months for the placebo arm. A total of 621 events provide the study with 90 percent power to detect a 32 percent increase in median OS (HR = 0.76) at the final analysis. Two interim analyses were planned and conducted at 50 percent and 75 percent of the planned 621 events.

About HCC
Liver cancer is the third-leading cause of death worldwide, and hepatocellular carcinoma (HCC) is the most common form, making up about three-fourths of the nearly 41,000 cases that will be diagnosed in 2017 in the U.S.[1,2] Without treatment, patients with advanced disease usually survive less than 6 months, and it is estimated that 29,000 people will die due to liver cancer in the U.S.[2,3] Worldwide, nearly 800,000 new cases are diagnosed annually, and the disease accounts for more than 700,000 deaths each year.[4]

About CABOMETYX® (cabozantinib)
CABOMETYX is the tablet formulation of cabozantinib. Its targets include MET, AXL and VEGFR-1, -2 and -3. In preclinical models, cabozantinib has been shown to inhibit the activity of these receptors, which are involved in normal cellular function and pathologic processes such as tumor angiogenesis, invasiveness, metastasis and drug resistance. CABOMETYX is available in 20 mg, 40 mg or 60 mg doses. The recommended dose is 60 mg orally, once daily.

On April 25, 2016, the FDA approved CABOMETYX tablets for the treatment of patients with advanced RCC who have received prior anti-angiogenic therapy. In February of 2016, Exelixis and Ipsen jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib indications outside of the United States, Canada and Japan. This agreement was amended in December of 2016 to include commercialization rights for Ipsen in Canada. On September 9, 2016, the European Commission approved CABOMETYX tablets for the treatment of advanced RCC in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy in the European Union, Norway and Iceland.

On January 30, 2017, Exelixis and Takeda Pharmaceutical Company Limited announced an exclusive licensing agreement for the commercialization and further clinical development of cabozantinib for all future indications in Japan, including RCC.

CABOMETYX is not indicated for the treatment of advanced HCC.

Please see Important Safety Information below and full U.S. prescribing information at https://cabometyx.com/downloads/cabometyxuspi.pdf.

U.S. Important Safety Information

Hemorrhage: Severe hemorrhage occurred with CABOMETYX. The incidence of Grade ≥3 hemorrhagic events was 2.1% in CABOMETYX-treated patients and 1.6% in everolimus-treated patients. Fatal hemorrhages also occurred in the cabozantinib clinical program. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.

Gastrointestinal (GI) Perforations and Fistulas: Fistulas were reported in 1.2% (including 0.6% anal fistula) of CABOMETYX-treated patients and 0% of everolimus-treated patients. GI perforations were reported in 0.9% of CABOMETYX-treated patients and 0.6% of everolimus-treated patients. Fatal perforations occurred in the cabozantinib clinical program. Monitor patients for symptoms of fistulas and perforations. Discontinue CABOMETYX in patients who experience a fistula that cannot be appropriately managed or a GI perforation.

Thrombotic Events: CABOMETYX treatment results in an increased incidence of thrombotic events. Venous thromboembolism was reported in 7.3% of CABOMETYX-treated patients and 2.5% of everolimus-treated patients. Pulmonary embolism occurred in 3.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Events of arterial thromboembolism were reported in 0.9% of CABOMETYX-treated patients and 0.3% of everolimus-treated patients. Fatal thrombotic events occurred in the cabozantinib clinical program. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or any other arterial thromboembolic complication.

Hypertension and Hypertensive Crisis: CABOMETYX treatment results in an increased incidence of treatment-emergent hypertension. Hypertension was reported in 37% (15% Grade ≥3) of CABOMETYX-treated patients and 7.1% (3.1% Grade ≥3) of everolimus-treated patients. Monitor blood pressure prior to initiation and regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy. Discontinue CABOMETYX if there is evidence of hypertensive crisis or severe hypertension despite optimal medical management.

Diarrhea: Diarrhea occurred in 74% of patients treated with CABOMETYX and in 28% of patients treated with everolimus. Grade 3 diarrhea occurred in 11% of CABOMETYX-treated patients and in 2% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 diarrhea or Grade 3-4 diarrhea that cannot be managed with standard antidiarrheal treatments until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to diarrhea occurred in 26% of patients.

Palmar-Plantar Erythrodysesthesia Syndrome (PPES): Palmar-plantar erythrodysesthesia syndrome (PPES) occurred in 42% of patients treated with CABOMETYX and in 6% of patients treated with everolimus. Grade 3 PPES occurred in 8.2% of CABOMETYX-treated patients and in <1% of everolimus-treated patients. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPES or Grade 3 PPES until improvement to Grade 1; resume CABOMETYX at a reduced dose. Dose modification due to PPES occurred in 16% of patients.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, occurred in the cabozantinib clinical program. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Embryo-fetal Toxicity: CABOMETYX can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

Adverse Reactions: The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, PPES, hypertension, vomiting, weight decreased, and constipation.

Drug Interactions: Strong CYP3A4 inhibitors and inducers: Reduce the dosage of CABOMETYX if concomitant use with strong CYP3A4 inhibitors cannot be avoided. Increase the dosage of CABOMETYX if concomitant use with strong CYP3A4 inducers cannot be avoided.

Lactation: Advise a lactating woman not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

Reproductive Potential: Contraception—Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose. **Infertility —**CABOMETYX may impair fertility in females and males of reproductive potential.

Hepatic Impairment: Reduce the CABOMETYX dose in patients with mild (Child-Pugh score [C-P] A) or moderate (C-P B) hepatic impairment. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see full Prescribing Information at https://cabometyx.com/downloads/cabometyxuspi.pdf.

About Exelixis
Founded in 1994, Exelixis, Inc. (NASDAQ: EXEL) is a commercially successful, oncology-focused biotechnology company that strives to accelerate the discovery, development and commercialization of new medicines for difficult-to-treat cancers. Following early work in model genetic systems, we established a broad drug discovery and development platform that has served as the foundation for our continued efforts to bring new cancer

therapies to patients in need. We discovered our lead compounds, cabozantinib and cobimetinib, and advanced them into clinical development before entering into partnerships with leading biopharmaceutical companies in our efforts to bring them to patients globally. With growing revenues from the three resulting commercialized products – CABOMETYX®, COMETRIQ®, and COTELLIC® – we are reinvesting in our business to maximize the potential of our pipeline, which we intend to supplement with targeted business development activities and internal drug discovery, all to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. For more information about Exelixis, please visit www.exelixis.com or follow @ExelixisInc on Twitter.

Forward-Looking Statement Disclaimer
This press release contains forward-looking statements, including, without limitation, statements related to: Exelixis' plans to submit an sNDA to the FDA in the first quarter of 2018 for the treatment of patients with advanced HCC; Exelixis' plan to submit the detailed results from CELESTIAL for presentation at a future medical conference; the therapeutic potential of cabozantinib as a treatment for patients with advanced liver cancer; Exelixis' commitment to studying cabozantinib in a range of tumor types as part of the company's mission to deliver medicines that improve treatment outcomes and give patients hope for the future; Exelixis' plan to discuss the trial results with regulatory authorities and determine next steps for the trial, including offering patients currently receiving placebo the opportunity to cross over to the cabozantinib arm; growing revenues from CABOMETYX, COMETRIQ, and COTELLIC and Exelixis' plans to reinvest in its business to maximize the potential of the company's pipeline, including through targeted business development activities and internal drug discovery; and Exelixis' mission to deliver the next generation of Exelixis medicines and help patients recover stronger and live longer. Words such as "plans," "will," "potential," "committed," "mission," "next steps," or other similar expressions identify forward-looking statements, but the absence of these words does not necessarily mean that a statement is not forward-looking. In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances are forward-looking statements. These forward-looking statements are based upon Exelixis' current plans, assumptions, beliefs, expectations, estimates and projections. Forward-looking statements involve risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in the forward-looking statements as a result of these risks and uncertainties, which include, without limitation: risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; the availability of data at the referenced time; Exelixis' ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; risks related to the potential failure of cabozantinib to demonstrate safety and efficacy in clinical testing; Exelixis' dependence on its relationships with its cabozantinib collaboration partners, including, the level of their investment in the resources necessary to successfully commercialize cabozantinib in the territories where it is approved; market acceptance of CABOMETYX, COMETRIQ, and COTELLIC and the availability of coverage and reimbursement for these products; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX, COMETRIQ, and COTELLIC; the level of costs associated with Exelixis' commercialization, research and development and other activities; Exelixis' dependence on its relationship with Genentech/Roche with respect to cobimetinib and Exelixis' ability to maintain its rights under the collaboration; Exelixis' dependence on third-party vendors; Exelixis' ability to protect the company's intellectual property rights; market competition; changes in economic and business conditions, and other factors discussed under the caption "Risk Factors" in Exelixis' quarterly report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 2, 2017, and in Exelixis' future filings with the SEC. The forward-looking statements made in this press release speak only as of the date of this press release. Exelixis expressly disclaims any duty, obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in Exelixis' expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.

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