Exelixis and Ipsen Announce Phase 3 Trial Results of Cabozantinib Demonstrating Significant Overall Survival Benefit in Patients with Previously Treated Advanced Hepatocellular Carcinoma

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– Pivotal phase 3 CELESTIAL trial results, including additional subset analyses, to be presented during oral session on Friday, January 19 at the 2018 American Society of Clinical Oncology's Gastrointestinal Cancers Symposium (ASCO-GI) –

– Exelixis to submit supplemental New Drug Application to U.S. Food and Drug Administration (FDA) in the first quarter of 2018 –

SOUTH SAN FRANCISCO, Calif. & PARIS--(BUSINESS WIRE)--Jan. 16, 2018-- Exelixis, Inc. (NASDAQ:EXEL) and Ipsen (Euronext:IPN; ADR:IPSEY) today announced detailed results of the pivotal phase 3 CELESTIAL trial in patients with previously treated advanced hepatocellular carcinoma (HCC), which will be presented in a late-breaking oral session at the 2018 ASCO-GI Symposium being held in San Francisco, January 18-20, 2018. In CELESTIAL, cabozantinib provided a statistically significant and clinically meaningful improvement versus placebo in overall survival (OS), the trial's primary endpoint, at the planned second interim analysis (pre-specified critical p-value ≤ 0.021) for the population of second- and third-line patients enrolled in this study. Median OS was 10.2 months with cabozantinib versus 8.0 months with placebo (HR 0.76, 95 percent CI 0.63-0.92; p=0.0049). Median progression-free survival (PFS) was more than doubled, at 5.2 months with cabozantinib and 1.9 months with placebo (HR 0.44, 95 percent CI 0.36-0.52; p<0.0001). Objective response rates per RECIST 1.1 were 4 percent with cabozantinib and 0.4 percent with placebo (p=0.0086). Disease control (partial response or stable disease) was achieved by 64 percent of the cabozantinib group compared with 33 percent of the placebo group.

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In a subgroup analysis of patients whose only prior therapy for advanced HCC was sorafenib (70 percent of patients in the study), median OS was 11.3 months with cabozantinib versus 7.2 months with placebo (HR 0.70, 95 percent CI 0.55-0.88). Median PFS in the subgroup was 5.5 months with cabozantinib versus 1.9 months with placebo (HR 0.40, 95 percent CI 0.32-0.50). Adverse events were consistent with the known safety profile of cabozantinib.

Ghassan K. Abou-Alfa, M.D., Memorial Sloan Kettering Cancer Center, New York and lead investigator on CELESTIAL, will present detailed findings, including analyses of OS and PFS in various patient subgroups, during Oral Abstract Session B: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract, which begins at 2:15 p.m. PT on Friday, January 19, 2018.

"Patients with advanced hepatocellular carcinoma often have a poor prognosis and limited treatment options following prior systemic therapy," said Dr. Abou-Alfa. "The clinically significant benefits in both overall survival and progression-free survival shown in the CELESTIAL trial suggest that, if approved, cabozantinib could become an important addition to the treatment landscape for these patients."

"We are excited by the potential benefit cabozantinib may offer to patients with previously treated advanced hepatocellular carcinoma," said Gisela Schwab, M.D., President, Product Development and Medical Affairs and Chief Medical Officer, Exelixis. "Given the worldwide prevalence of advanced hepatocellular carcinoma, there is a continued urgency to bring new treatment options to this patient population. We look forward to submitting our supplemental New Drug Application to the FDA for cabozantinib in the first quarter of 2018, and to further advancing our mission to help cancer patients recover stronger and live longer."

"Patients diagnosed with advanced hepatocellular carcinoma urgently need new treatment options," said Alexandre Lebeaut, M.D., Executive Vice-President, R&D, Chief Scientific Officer, Ipsen. "The positive results of the pivotal phase 3 CELESTIAL trial are encouraging for both physicians and patients, and we have committed to file in the first half of 2018 a variation of the initial application to the EMA and other relevant regulatory agencies."

The most common (≥10 percent) grade 3 or 4 adverse events in the cabozantinib group compared to the placebo group were palmar-plantar erythrodysesthesia (17 percent vs. 0 percent), hypertension (16 percent vs. 2 percent), increased aspartate aminotransferase (12 percent vs. 7 percent), fatigue (10 percent vs. 4 percent), and diarrhea (10 percent vs. 2 percent). Treatment-related grade 5 adverse events occurred in six patients in the cabozantinib group (hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper gastrointestinal hemorrhage, pulmonary embolism and hepatorenal syndrome) and in one patient in the placebo group (hepatic failure). Sixteen percent of patients in the cabozantinib arm and three percent of patients in the placebo arm discontinued treatment due to treatment-related adverse events.

Webcast for the Financial Community

Exelixis and its partner Ipsen will jointly host a live webcast on Friday, January 19. The webcast will begin at 6:30 p.m. PT / 9:30 p.m. ET. During the webcast, Exelixis and Ipsen management and an invited guest speaker will review results from the CELESTIAL trial.

To access the webcast link, log onto www.exelixis.com and proceed to the News & Events / Event Calendar page under the Investors & Media heading. Please connect to the company's website at least 15 minutes prior to the webcast to ensure adequate time for any software download that may be required to view the program. To listen to an audio-only version of the program by phone, please dial 855-793-2457 (domestic) or 631-485-4921 (international/toll dial) and use passcode 2478857. A telephone replay will be available until 11:59 p.m. ET on January 26, 2018. Access

numbers for the telephone replay are: 855-859-2056 (domestic) and 404-537-3406 (international); the passcode is 2478857. A webcast replay will also be available archived on www.exelixis.com for one year.

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 during the blinded treatment phase of the trial.

The primary endpoint for the trial is OS, and secondary endpoints include objective response rate and PFS. 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 design 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 approximately 50 percent and 75 percent of the planned 621 events. At the first interim analysis conducted by the independent data monitoring committee the observed hazard ratio was 0.71 and the p-value was 0.0041, which did not cross the stopping boundary for the first interim analysis ($p \leq 0.0037$).

On October 16, 2017, Exelixis announced that the independent data monitoring committee recommended that the trial be stopped for efficacy following review of the second planned interim analysis, as the trial had met its primary endpoint of OS (pre-specified critical p-value ≤ 0.021).

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.

About HCC

Liver cancer is the second-leading cause of cancer death worldwide, accounting for more than 700,000 deaths and nearly 800,000 new cases each year.[1] In the U.S., the incidence of liver cancer has more than tripled since 1980.[2] HCC is the most common form of liver cancer, making up about three-fourths of the estimated nearly 42,000 new cases in the U.S. in 2018.[2] HCC is the fastest-rising cause of cancer-related death in U.S.[3] Without treatment, patients with advanced HCC usually survive less than 6 months.[4]

About CABOMETYX® (cabozantinib)

CABOMETYX tablets are approved in the United States for the treatment of patients with advanced RCC. CABOMETYX tablets are also approved in the European Union, Norway, Iceland and Switzerland for the treatment of advanced RCC in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy. Ipsen also submitted to European Medicines Agency (EMA) the regulatory dossier for cabozantinib as a treatment for first-line advanced RCC in the European Union on August 28, 2017; on September 8, 2017, Ipsen announced that the EMA validated the application. In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of cabozantinib outside of the United States and Japan. In 2017, Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited 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 and fatal hemorrhages have occurred with CABOMETYX. In two RCC studies, the incidence of Grade ≥ 3 hemorrhagic events was 3% in CABOMETYX-treated patients. Do not administer CABOMETYX to patients that have or are at risk for severe hemorrhage.
- **Gastrointestinal (GI) Perforations and Fistulas:** In RCC studies, fistulas were reported in 1% of CABOMETYX-treated patients. Fatal perforations occurred in patients treated with CABOMETYX. In RCC studies, gastrointestinal (GI) perforations were reported in 1% of CABOMETYX-treated patients. Monitor patients for symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a fistula which cannot be appropriately managed or a GI perforation.
- **Thrombotic Events:** CABOMETYX treatment results in an increased incidence of thrombotic events. In RCC studies, venous thromboembolism occurred in 9% (including 5% pulmonary embolism) and arterial thromboembolism occurred in 1% of CABOMETYX-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, including hypertensive crisis. In RCC studies, hypertension was reported in 44% (18% Grade ≥ 3) of CABOMETYX-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:** In RCC studies, diarrhea occurred in 74% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 11% of patients treated with CABOMETYX. 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.
- **Palmar-Plantar Erythrodysesthesia (PPE):** In RCC studies, palmar-plantar erythrodysesthesia (PPE) occurred in 42% of patients treated with CABOMETYX. Grade 3 PPE occurred in 8% of patients treated with CABOMETYX. Withhold CABOMETYX in patients who develop intolerable Grade 2 PPE or Grade 3 PPE until improvement to Grade 1; resume CABOMETYX at a reduced dose.
- **Reversible Posterior Leukoencephalopathy Syndrome (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** may be associated with CABOMETYX. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during CABOMETYX treatment and for 4 months after the last dose.
- **Adverse Reactions:** The most commonly reported (≥25%) adverse reactions are: diarrhea, fatigue, nausea, decreased appetite, hypertension, PPE, weight decreased, vomiting, dysgeusia, and stomatitis.
- **Strong CYP3A4 Inhibitors:** If concomitant use with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage.
- **Strong CYP3A4 Inducers:** If concomitant use with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage.
- **Lactation:** Advise women not to breastfeed while taking CABOMETYX and for 4 months after the final dose.
- **Hepatic Impairment:** In patients with mild to moderate hepatic impairment, reduce the CABOMETYX dosage. CABOMETYX is not recommended for use in patients with severe hepatic impairment.

Please see accompanying full Prescribing Information 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 these medicines to patients globally. We are steadfast in our commitment to prudently reinvest in our business to maximize the potential of our pipeline. We intend to supplement our existing therapeutic assets 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. Exelixis recently earned a spot on Deloitte's Technology Fast 500 list, a yearly award program honoring the 500 fastest-growing companies over the past four years. For more information about Exelixis, please visit www.exelixis.com or follow @ExelixisInc on Twitter.

About Ipsen

Ipsen is a global specialty-driven pharmaceutical group with total sales exceeding €1.4 billion in 2015. Ipsen sells more than 20 drugs in more than 115 countries, with a direct commercial presence in more than 30 countries. Ipsen's ambition is to become a leader in specialty healthcare solutions for targeted debilitating diseases. Its fields of expertise cover oncology, neurosciences and endocrinology (adult & pediatric). Ipsen's commitment to oncology is exemplified through its growing portfolio of key therapies improving the care of patients suffering from prostate cancer, bladder cancer and neuro-endocrine tumors. Ipsen also has a significant presence in primary care. Moreover, the Group has an active policy of partnerships. Ipsen's R&D is focused on its innovative and differentiated technological platforms, peptides and toxins, located in the heart of the leading biotechnological and life sciences hubs (Les Ulis/Paris-Saclay, France; Slough/Oxford, UK; Cambridge, US). In 2015, R&D expenditure totaled close to €193 million. The Group has more than 4,600 employees worldwide. Ipsen's shares are traded on segment A of Euronext Paris (stock code: IPN, ISIN code: FR0010259150) and eligible to the "Service de Règlement Différé" ("SRD"). The Group is part of the SBF 120 index. Ipsen has implemented a Sponsored Level I American Depositary Receipt (ADR) program, which trade on the over-the-counter market in the United States under the symbol IPSEY. For more information on Ipsen, visit www.ipsen.com.

Exelixis Forward-Looking Statement Disclaimer

This press release contains forward-looking statements, including, without limitation, statements related to: Exelixis' plan to submit a supplemental New Drug Application to the FDA in the first quarter of 2018; the plan to present detailed findings from CELESTIAL at the 2018 ASCO-GI Symposium; the clinical and therapeutic potential of cabozantinib for patients with previously treated advanced HCC; Ipsen's plan to file a variation of the initial application to the EMA and other relevant regulatory agencies in the first half of 2018; Exelixis' plan to advance its mission to deliver medicines that improve treatment outcomes; and Exelixis' commitment to reinvesting in its business to maximize the potential of its pipeline, including supplementing its existing therapeutic assets through targeted business development activities and internal drug discovery. Words such as "will," "could," "potential," "look forward," "mission," "commitment," "intend," 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; the level of costs associated with Exelixis' commercialization, research and development and other activities; competition in the area of business development activities and the inherent uncertainty of the drug discovery process; 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; Exelixis' dependence on its relationship with Genentech/ Roche with respect to cobimetinib and Exelixis' ability to maintain its rights under the collaboration; market acceptance of CABOMETYX, COMETRIQ, and COTELLIC and the availability of coverage and reimbursement for these products; Exelixis' dependence on third-party vendors for the development, manufacture and supply of its products; 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 November 1, 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.

References

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