# Exelixis and Takeda Enter into Exclusive Licensing Agreement to Commercialize and Develop Novel Cancer Therapy Cabozantinib in Japan

January 30, 2017

***– Takeda's Rights to Include all Potential Indications for Cabozantinib, which is Marketed in the U.S. and European Union for Renal Cell Carcinoma and Medullary Thyroid Carcinoma –***

***– Exelixis Receives $50 Million Upfront Payment and is Eligible for Future Regulatory and Commercial Milestones –***

SOUTH SAN FRANCISCO, Calif. & CAMBRIDGE, Mass. & OSAKA, Japan--(BUSINESS WIRE)--Jan. 30, 2017-- Exelixis, Inc. (NASDAQ:EXEL) and Takeda Pharmaceutical Company Limited (TSE:4502) today announced an exclusive licensing agreement for the commercialization and further clinical development in Japan of cabozantinib, Exelixis' lead oncology medicine. With the signing of the agreement, Takeda gains exclusive commercial rights for all potential future cabozantinib indications in Japan, including advanced renal cell carcinoma (RCC), for which cabozantinib is marketed in the United States and European Union as CABOMETYX™ tablets. The two companies will collaborate on the future clinical development of cabozantinib in Japan.

Under the terms of the agreement, Exelixis will receive a $50 million upfront payment. Exelixis is eligible to receive development, regulatory, and first-sales milestones of $95 million for the first three planned indications. In addition, Exelixis will be eligible to receive royalties on sales by Takeda.

"As an organization with a strong focus on oncology innovation, our agreement with Exelixis brings a promising and well-studied solid-tumor therapy to our pipeline that may help patients in Japan suffering from RCC and potentially other equally devastating cancers," said Tsudoi Miyoshi, Head of Japan Oncology Business Unit of Takeda. "We intend to pursue regulatory approval for RCC indications as soon as we're able, and look forward to commencing the local clinical trial program to further strengthen the clinical profile of cabozantinib."

Exelixis and Takeda will partner on cabozantinib's clinical development in Japan and on translating existing and forthcoming clinical data for potential regulatory filings in the country. In the METEOR pivotal trial, cabozantinib demonstrated statistically significant improvements in overall survival, progression-free survival and objective response rate, meaningfully differentiating it from other therapies to treat advanced renal cell carcinoma following prior therapy. In addition to advanced RCC, future indications could include advanced hepatocellular cancer (HCC), the subject of the CELESTIAL global pivotal trial for which results are anticipated in 2017. Additional earlier-stage studies are under way through Exelixis' collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program, and its ongoing Investigator-Sponsored Trial program. Through these two programs, there are more than 45 ongoing or planned studies including trials in advanced RCC, bladder cancer, colorectal cancer, non-small cell lung cancer, and endometrial cancer.

"Takeda is the ideal partner to advance cabozantinib in Japan and deliver this important treatment option to Japanese patients with cancer," said Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis. "Takeda is widely respected for both its clinical development and commercial expertise. We look forward to supporting our new partner as it pursues Japanese regulatory approval for cabozantinib, while simultaneously working together to plan the next steps for clinical development in the country. This agreement further propels the global progress for cabozantinib development and commercialization, which now includes the recent first commercial sale of CABOMETYX in the United Kingdom, triggering a $10 million milestone payment from Ipsen to Exelixis."

Cabozantinib is not approved for use in Japan. Previously, Exelixis and its collaborators conducted early-stage clinical trials in Japan, including a phase 1 trial in advanced solid tumors. Data from this trial were presented at the European Society for Medical Oncology 2012 Congress and the 2015 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics.[1,2]

Exelixis maintains its exclusive rights to develop and commercialize cabozantinib in the United States, and its partner Ipsen maintains its exclusive commercialization rights for current and potential future cabozantinib indications outside of the United States and Japan.

**About CABOMETYX™ (cabozantinib) Tablets**

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 renal cell carcinoma who have received prior anti-angiogenic therapy. On September 9, 2016, the European Commission approved CABOMETYX tablets for the treatment of advanced renal cell carcinoma in adults who have received prior vascular endothelial growth factor (VEGF)-targeted therapy in the European Union, Norway and Iceland. On February 29, 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. On December 21, 2016, Exelixis and Ipsen jointly announced an amendment to their exclusive licensing agreement for the commercialization and development of cabozantinib to include Canada.

**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 Takeda Pharmaceutical Company**

Takeda Pharmaceutical Company Limited is a global, research and development-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda focuses its R&D efforts on oncology, gastroenterology and central nervous system therapeutic areas plus vaccines. Takeda conducts R&D both internally and with partners to stay at the leading edge of innovation. New innovative products, especially in oncology and gastroenterology, as well as our presence in Emerging Markets, fuel the growth of Takeda. More than 30,000 Takeda employees are committed to improving quality of life for patients, working with our partners in health care in more than 70 countries. For more information, visit http://www.takeda.com/news.

Additional information about Takeda is available through its corporate website, www.takeda.com, and additional information about Takeda Oncology, the brand for the global oncology business unit of Takeda Pharmaceutical Company Limited, is available through its website, www.takedaoncology.com.

**About Exelixis**

Exelixis, Inc. (Nasdaq:EXEL) is a biopharmaceutical company committed to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer. Since its founding in 1994, three medicines discovered at Exelixis have progressed through clinical development to receive regulatory approval. Currently, Exelixis is focused on advancing cabozantinib, an inhibitor of multiple tyrosine

kinases including MET, AXL and VEGF receptors, which has shown clinical anti-tumor activity in more than 20 forms of cancer and is the subject of a broad clinical development program. Two separate formulations of cabozantinib have received regulatory approval to treat certain forms of kidney and thyroid cancer and are marketed for those purposes as CABOMETYX™ tablets (U.S. and EU) and COMETRIQ® capsules (U.S. and EU), respectively. Another Exelixis-discovered compound, COTELLIC® (cobimetinib), a selective inhibitor of MEK, has been approved in major territories including the United States and European Union, and is being evaluated for further potential indications by Roche and Genentech (a member of the Roche Group) under a collaboration with Exelixis. For more information on Exelixis, please visit www.exelixis.com or follow @ExelixisInc on Twitter.

**Exelixis Forward-Looking Statements**

This press release contains forward-looking statements, including, without limitation, statements related to: the future clinical development of cabozantinib by Exelixis and Takeda in Japan; Exelixis' receipt of a $50 million upfront payment; Exelixis' eligibility to receive development, regulatory and first-sales milestones of $95 million for the first three planned indications; Exelixis' eligibility to receive royalties on sales of cabozantinib by Takeda; the clinical and therapeutic potential of cabozantinib for patients in Japan suffering from RCC and potentially other cancers; Takeda's intent to pursue regulatory approval for cabozantinib in RCC indications and commence a local clinical trial program; Exelixis' and Takeda's plan to translate existing and forthcoming clinical data for potential regulatory filings in Japan; advanced HCC as a potential future commercial indication; the timing of anticipated results from CELESTIAL; the continued development of cabozantinib through Exelixis' collaboration with the National Cancer Institute's Cancer Therapy Evaluation Program, and its ongoing Investigator-Sponsored Trial program; Exelixis' intent to support Takeda as it pursues Japanese regulatory approval for cabozantinib, while simultaneously working together to plan the next steps for clinical development in Japan; Exelixis' commitment to the discovery, development and commercialization of new medicines with the potential to improve care and outcomes for people with cancer; Exelixis' focus on advancing cabozantinib; and the continued development of cobimetinib. Words such as "potential," "further," "will," "eligible," "planned," "may," "intend," "look forward," "future," "could," "anticipated," "next," "committed," "focused," 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: the complexities and challenges associated with regulatory review and approval processes; Exelixis' dependence on its relationship with Takeda, including, the level of Takeda's investment in the resources necessary to successfully commercialize cabozantinib in Japan; the degree of market acceptance of CABOMETYX and the availability of coverage and reimbursement for CABOMETYX; the risk that unanticipated developments could adversely affect the commercialization of CABOMETYX; 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 relationship with other collaborators, including Ipsen with respect to cabozantinib in territories outside of the United States and Japan and Genentech/Roche with respect to cobimetinib; 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 November 3, 2016, 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.



[1] Nokihara et al., Molecular profile and anti-tumor activity in non-small cell lung cancer (NSCLC) patients (pts) in a phase 1 study of cabozantinib (XL184) in Japan. *Ann Oncol.* 2012; 23 (suppl 9): ix152-ix174.

[2] Nokihara et al., Final results of a phase 1 study of cabozantinib (Cabo) in Japanese patients (pts) with expansion cohorts in non-small cell lung cancer (NSCLC) with defined molecular alterations. *Mol Cancer Ther.* December 1 2015 (14) (12 Supplement 2) B179.

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