

## **Exelixis and Ipsen enter into exclusive licensing agreement to commercialize and develop novel cancer therapy Cabozantinib in regions outside the United States, Canada and Japan**

- **Cabozantinib commercialized for medullary thyroid cancer (MTC) and filed for advanced renal cell carcinoma (RCC)**
- **\$200 million upfront payment and subsequent regulatory and commercial milestones**

**Paris (France) and South San Francisco (Calif., United States), 1 March 2016** – Exelixis, Inc. (NASDAQ: EXEL) and Ipsen (Euronext: IPN; ADR: IPSEY) today jointly announced an exclusive licensing agreement for the commercialization and further development of cabozantinib, Exelixis' lead oncology drug. Under the agreement, Ipsen will have exclusive commercialization rights for current and potential future cabozantinib indications outside the United States, Canada and Japan, including COMETRIQ<sup>®</sup>, which is currently approved in the European Union (EU) for the treatment of adult patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer (MTC). The companies have agreed to collaborate on the development of cabozantinib for current and potential future indications. Exelixis will maintain exclusive commercial rights for cabozantinib in the United States and Canada, and continue its discussions to partner commercial rights in Japan.

Under the agreement, Exelixis will receive a \$200 million upfront payment. Exelixis is eligible to receive regulatory milestones, including a \$60 million milestone upon the approval of cabozantinib in Europe for advanced renal cell carcinoma (RCC), and \$50 million upon the filing and approval of cabozantinib in Europe for advanced hepatocellular carcinoma (HCC), as well as additional regulatory milestones for potential further indications. The agreement also includes up to \$545 million of potential commercial milestones and provides for Exelixis to receive tiered royalties up to 26% on Ipsen's net sales of cabozantinib in its territories.

**Marc de Garidel, Chairman and Chief Executive Officer of Ipsen** stated: *"The robust results from the METEOR study in advanced renal cell carcinoma demonstrate that cabozantinib has the potential to become a key oncology product. This transaction will help Ipsen accelerate the growth of the company and strengthen its oncology footprint in Europe. We are excited to bring cabozantinib to patients and clinicians around the world."*



Commenting on this partnership, **Michael M. Morrissey, Ph.D., President and Chief Executive Officer of Exelixis** noted: *“In Ipsen, Exelixis has an ideal partner to maximize the potential for cabozantinib to have a positive impact on the treatment of cancer on a global basis. Ipsen’s established international oncology marketing presence, late-stage clinical development expertise and shared vision with Exelixis for the franchise potential of cabozantinib will accelerate cabozantinib’s commercialization in its territories, while Exelixis remains focused on our launch in the United States. While our immediate priority will be on advanced renal cell carcinoma, Exelixis and Ipsen are committed to exploring and potentially developing cabozantinib in a variety of cancer settings.”*

Future commercial indications for cabozantinib could include advanced HCC, the subject of CELESTIAL, an Exelixis-sponsored phase 3 pivotal trial for which top-line 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 (NCI-CTEP), and its ongoing Investigator-Sponsored Trial (IST) 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.

Cabozantinib is a small molecule therapy that inhibits the activity of tyrosine kinases including VEGF receptors, MET, AXL, and RET. Following positive results from the METEOR global phase 3 pivotal trial, the tablet form of cabozantinib is the subject of pending U.S. and EU regulatory applications for use as a treatment for advanced RCC in patients who have received one prior therapy. In Europe, the Marketing Authorization Application (MAA) for cabozantinib in advanced RCC has been accepted and granted accelerated assessment. With this designation, the MAA is eligible for a 150-day review, versus the standard 210 days (excluding clock stops when information is requested by the EMA). Exelixis plans to transfer sponsorship of this MAA to Ipsen. Exelixis also anticipates transitioning the commercialization rights to COMETRIQ<sup>®</sup> outside the U.S. from Exelixis’ current international partner for COMETRIQ<sup>®</sup>, Swedish Orphan Biovitrum AB (Sobi), to Ipsen, in accordance with the terms of its agreement with Sobi. In March 2014, the capsule form of cabozantinib was approved by the European Commission under the trade name COMETRIQ<sup>®</sup> for the treatment of patients with progressive, unresectable, locally advanced or metastatic MTC.

#### **About the METEOR Phase 3 Clinical Trial**

METEOR is a global, randomized open-label trial that compares cabozantinib to everolimus, a standard of care therapy, in 658 patients with advanced RCC whose disease progressed following treatment with a VEGF receptor (VEGFR) tyrosine kinase inhibitor (TKI). The trial’s primary endpoint is progression-free survival (PFS), and secondary endpoints include overall survival (OS) and objective response rate (ORR). Patients were randomized 1:1 to receive 60 mg of cabozantinib or 10 mg of everolimus daily, and were stratified based on number of prior VEGFR TKI therapies and on commonly applied RCC risk criteria. No crossover was allowed.

As published in the *New England Journal of Medicine*, the trial met its primary PFS and secondary



ORR endpoints<sup>1</sup>. Cabozantinib demonstrated a 42% reduction in the rate of disease progression or death as compared with everolimus, with median PFS of 7.4 months versus 3.8 months for everolimus (Hazard Ratio [HR]=0.58, 95% Confidence Interval [CI] 0.45-0.75, p<0.001).

Following a pre-planned interim analysis that showed a strong trend in OS favoring cabozantinib (HR=0.67, 95% CI 0.51-0.89, p=0.005) but did not reach statistical significance, Exelixis undertook a second interim analysis after consulting with regulatory authorities. The results of this second interim analysis demonstrated a highly statistically significant and clinically meaningful increase in OS for cabozantinib. Exelixis has shared these data with regulators and intends to present them at a medical conference later this year.

Cabozantinib's safety profile was similar to that of other VEGFR TKIs in this patient population. The incidence of adverse events (any grade), regardless of causality, was 100% with cabozantinib and more than 99% with everolimus. Serious adverse events occurred in 40% of cabozantinib patients and 43% of everolimus patients. The rate of treatment discontinuation due to adverse events was low (~10%) in both treatment arms.

#### **About Advanced Renal Cell Carcinoma**

The American Cancer Society's 2015 statistics cite kidney cancer as among the top ten most commonly diagnosed forms of cancer among both men and women in the U.S.<sup>2</sup> Clear cell RCC is the most common type of kidney cancer in adults.<sup>3</sup> If detected in its early stages, the five-year survival rate for RCC is high; however, the five-year survival rate for patients with advanced or late-stage metastatic RCC is under 10 percent, with no identified cure for the disease.<sup>4</sup>

Until the introduction of targeted therapies into the RCC setting a decade ago, treatments for metastatic RCC had historically been limited to cytokine therapy (e.g., interleukin-2 and interferon). In the second- and later-line settings, which encompass approximately 17,000 drug-eligible patients in the U.S. and 37,000 globally,<sup>5</sup> two small-molecule therapies and an immune checkpoint inhibitor have been approved. The currently approved small-molecule agents have shown little differentiation in terms of efficacy, demonstrating only modest PFS benefit in patients refractory to sunitinib, a commonly-used first-line therapy.

#### **About Cabozantinib**

Cabozantinib is currently marketed in capsule form under the brand name COMETRIQ® in the United States for the treatment of progressive, metastatic MTC, and in the European Union for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. COMETRIQ® is not indicated for patients with RCC. In the METEOR trial, and all other cancer trials

---

<sup>1</sup> (Choueiri T.K. et al. *N Engl J Med* 2015;373:1814-23.)

<sup>2</sup> *Cancer Facts & Figures 2015*. American Cancer Society. Available at <http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf>

<sup>3</sup> Jonasch et al., *BMJ* (2014) vol. 349, g4797.

<sup>4</sup> <http://www.cancer.org/cancer/kidneycancer/detailedguide/kidney-cancer-adult-survival-rates>

<sup>5</sup> *ACS Cancer Facts and Figures 2015*; Heng et al., *Ann Oncol* (2012) vol. 23 no. 6; internal data on file; Motzer et al., *N Engl J Med* (2007) vol. 356 no. 2; NCIN (UK) report, April 2014, Available at <http://www.ncin.org.uk/view?rid=2676>.



currently underway, Exelixis is investigating a tablet formulation of cabozantinib distinct from the COMETRIQ<sup>®</sup> capsule form. The tablet formulation of cabozantinib is the subject of the NDA and MAA for advanced RCC.

Cabozantinib inhibits the activity of tyrosine kinases including VEGF receptors, MET, AXL and RET. These receptor tyrosine kinases are involved in both normal cellular function and in pathologic processes such as oncogenesis, metastasis, tumor angiogenesis and maintenance of the tumor microenvironment.

The European Commission granted COMETRIQ conditional approval for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. Similar to another drug approved in this setting, the approved indication states that for patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decisions.

**Important Safety Information, including Boxed WARNINGS**

WARNING: PERFORATIONS AND FISTULAS, and HEMORRHAGE

- Serious and sometimes fatal gastrointestinal perforations and fistulas occur in COMETRIQ-treated patients.
- Severe and sometimes fatal hemorrhage occurs in COMETRIQ-treated patients.
- COMETRIQ treatment results in an increase in thrombotic events, such as heart attacks.
- Wound complications have been reported with COMETRIQ.
- COMETRIQ treatment results in an increase in hypertension.
- Osteonecrosis of the jaw has been observed in COMETRIQ-treated patients.
- Palmar-Plantar Erythrodysesthesia Syndrome (PPES) occurs in patients treated with COMETRIQ.
- The kidneys can be adversely affected by COMETRIQ. Proteinuria and nephrotic syndrome have been reported in patients receiving COMETRIQ.
- Reversible Posterior Leukoencephalopathy Syndrome has been observed with COMETRIQ.
- Avoid administration of COMETRIQ with agents that are strong CYP3A4 inducers or inhibitors.
- COMETRIQ is not recommended for use in patients with moderate or severe hepatic impairment.
- COMETRIQ can cause fetal harm when administered to a pregnant woman.

Adverse Reactions – The most commonly reported adverse drug reactions (≥25%) are diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome (PPES), decreased weight, decreased appetite, nausea, fatigue, oral pain, hair color changes, dysgeusia, hypertension, abdominal pain, and constipation. The most common laboratory abnormalities (≥25%) are increased AST, increased ALT, lymphopenia, increased alkaline phosphatase, hypocalcemia, neutropenia, thrombocytopenia, hypophosphatemia, and hyperbilirubinemia.

Please see full U.S. prescribing information, including Boxed WARNINGS, at [www.COMETRIQ.com/downloads/Cometriq\\_Full\\_Prescribing\\_Information.pdf](http://www.COMETRIQ.com/downloads/Cometriq_Full_Prescribing_Information.pdf)

Please refer to the full European Summary of Product Characteristics for full European Union prescribing information, including contraindication, special warnings and precautions for use at [www.sobi.com](http://www.sobi.com) once posted.



### **About Exelixis**

Exelixis, Inc. is a biopharmaceutical company committed to developing small molecule therapies for the treatment of cancer. Exelixis is focusing its development and commercialization efforts primarily on cabozantinib, an internally discovered inhibitor of multiple receptor tyrosine kinases. Another Exelixis-discovered compound, COTELLIC™ (cobimetinib), a selective inhibitor of MEK, has been approved in Switzerland, the United States, the European Union, and Canada, and is being evaluated by Roche and Genentech (a member of the Roche Group) in a broad global development program under a collaboration with Exelixis. For more information, please visit the company's website at [www.exelixis.com](http://www.exelixis.com).

### **Exelixis Forward-Looking Statement Disclaimer**

This press release contains forward-looking statements, including, without limitation, statements related to: the business and financial terms of the collaboration agreement for cabozantinib with Ipsen, including, the division of commercialization rights, development plans and Exelixis' eligibility to receive regulatory and commercial milestones and royalties; Exelixis' plan to continue its discussions to partner commercial rights for cabozantinib in Japan; the potential for cabozantinib to become a key oncology product in Europe and the impact of the transaction on the growth of Ipsen; advanced HCC as a future potential commercial indication for cabozantinib and the timing for anticipated top-line results from CELESTIAL; the impact of the collaboration with Ipsen on Exelixis' plan to maximize the potential for cabozantinib on a global basis; Exelixis' plan to stay focused on the potential launch of cabozantinib in advanced RCC in the United States; advanced RCC as Exelixis' immediate priority; Exelixis' and Ipsen's commitment to exploring and potentially developing cabozantinib in a variety of cancers; the eligibility for an expedited review of Exelixis' MAA for cabozantinib in advanced RCC by the EMA and Exelixis' plans to transfer sponsorship of the MAA to Ipsen; Exelixis' plans to transition the commercialization rights to COMETRIQ outside of the U.S. from Sobi to Ipsen; and Exelixis' intent to present data from the second interim analysis of OS for METEOR at a medical conference later this year. Words such as "will," "potential," "future," "continue," "eligible," "priority," "committed," "plans," "anticipates," "intends," 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 clinical, therapeutic and commercial potential of cabozantinib; Exelixis' dependence on its relationship with Ipsen, including, the level of Ipsen's investment in the resources necessary to successfully commercialize cabozantinib in the territories where it is approved; Exelixis' ability to maintain its rights under the Ipsen collaboration; risks and uncertainties related to regulatory review and approval processes and Exelixis' compliance with applicable legal and regulatory requirements; the ability to conduct clinical trials of cabozantinib sufficient to achieve a positive completion; Exelixis' ability to judge the proper size and level of experience of the commercialization teams required to support the launch of cabozantinib for advanced RCC; unanticipated complications associated with the transition of the COMETRIQ commercialization rights from Sobi to Ipsen; the availability of data at the referenced times; 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 10, 2015, and in Exelixis' future filings with the SEC, including, without limitation, Exelixis' annual report on Form 10-K expected to be filed with the SEC on February 29, 2016. 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.



### **About Ipsen**

Ipsen is a global specialty-driven biotechnological 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.ipсен.com](http://www.ipсен.com).

### **Forward Looking Statement**

The forward-looking statements, objectives and targets contained herein are based on the Group's management strategy, current views and assumptions. Such statements involve known and unknown risks and uncertainties that may cause actual results, performance or events to differ materially from those anticipated herein. All of the above risks could affect the Group's future ability to achieve its financial targets, which were set assuming reasonable macroeconomic conditions based on the information available today. Use of the words "believes," "anticipates" and "expects" and similar expressions are intended to identify forward-looking statements, including the Group's expectations regarding future events, including regulatory filings and determinations. Moreover, the targets described in this document were prepared without taking into account external growth assumptions and potential future acquisitions, which may alter these parameters. These objectives are based on data and assumptions regarded as reasonable by the Group. These targets depend on conditions or facts likely to happen in the future, and not exclusively on historical data. Actual results may depart significantly from these targets given the occurrence of certain risks and uncertainties, notably the fact that a promising product in early development phase or clinical trial may end up never being launched on the market or reaching its commercial targets, notably for regulatory or competition reasons. The Group must face or might face competition from generic products that might translate into a loss of market share. Furthermore, the Research and Development process involves several stages each of which involves the substantial risk that the Group may fail to achieve its objectives and be forced to abandon its efforts with regards to a product in which it has invested significant sums. Therefore, the Group cannot be certain that favourable results obtained during pre-clinical trials will be confirmed subsequently during clinical trials, or that the results of clinical trials will be sufficient to demonstrate the safe and effective nature of the product concerned. There can be no guarantees a product will receive the necessary regulatory approvals or that the product will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Other risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the Group's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the Group's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions. The Group also depends on third parties to develop and market some of its products which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to the Group's activities and financial results. The Group cannot

be certain that its partners will fulfil their obligations. It might be unable to obtain any benefit from those agreements. A default by any of the Group's partners could generate lower revenues than expected. Such situations could have a negative impact on the Group's business, financial position or performance. The Group expressly disclaims any obligation or undertaking to update or revise any forward looking statements, targets or estimates contained in this press release to reflect any change in events, conditions, assumptions or circumstances on which any such statements are based, unless so required by applicable law. The Group's business is subject to the risk factors outlined in its registration documents filed with the French Autorité des Marchés Financiers.

The risks and uncertainties set out are not exhaustive and the reader is advised to refer to the Group's 2014 Registration Document available on its website ([www.ipsen.com](http://www.ipsen.com)).

**For further information:**

**Ipsen**

**Media**

**Didier Véron**

Senior Vice-Président, Public Affairs  
and Communication

Tel.: +33 (0)1 58 33 51 16

Fax: +33 (0)1 58 33 50 58

E-mail: [didier.veron@ipsen.com](mailto:didier.veron@ipsen.com)

**Brigitte Le Guennec**

Corporate External Communication

Tel.: +33 (0)1 58 33 51 17

Fax: +33 (0)1 58 33 50 58

E-mail : [brigitte.le.guennec@ipsen.com](mailto:brigitte.le.guennec@ipsen.com)

**Financial Community**

**Stéphane Durant des Aulnois**

Vice-President Investor Relations

Tel.: +33 (0)1 58 33 60 09

Fax: +33 (0)1 58 33 50 63

E-mail: [stephane.durant.des.aulnois@ipsen.com](mailto:stephane.durant.des.aulnois@ipsen.com)

**Exelixis**

**Financial Community**

**Susan Hubbard**

Investor Relations and Corporate Communications

Phone : (650) 837-8194

E-mail : [shubbard@exelixis.com](mailto:shubbard@exelixis.com)

**Media**

**Hal Mackins**

For Exelixis, Inc

Phone: (415) 994-0040

Email: [hal@torchcomllc.com](mailto:hal@torchcomllc.com)