

**Ipsen’s partner Exelixis announced results from randomized phase 2 trial CABOSUN that demonstrate that cabozantinib significantly improved progression-free survival versus sunitinib in previously untreated advanced renal cell carcinoma**

**Ipsen in collaboration with Exelixis will share these results with European regulatory authorities and evaluate potential next steps in development and submission strategy for cabozantinib as a treatment of first-line advanced renal cell carcinoma**

**Paris (France), May 23, 2016** – Ipsen (Euronext: IPN; ADR: IPSEY) announced that its partner Exelixis, Inc. (NASDAQ:EXEL) today reported positive top-line results from the CABOSUN randomized phase 2 trial of cabozantinib in patients with previously untreated advanced renal cell carcinoma (RCC). The trial met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in progression-free survival (PFS) for cabozantinib compared with sunitinib in patients with advanced intermediate- or poor-risk RCC. The safety data in the cabozantinib-treated arm of the study were consistent with those observed in previous studies in patients with advanced RCC. CABOSUN is being conducted by The Alliance for Clinical Trials in Oncology as part of Exelixis’ collaboration with the National Cancer Institute’s Cancer Therapy Evaluation Program (NCI-CTEP). The final results from CABOSUN will be submitted for presentation at a future medical conference.

**Claude Bertrand, Executive Vice-President, R&D and Chief Scientific Officer, Ipsen** stated: *“Ipsen is very proud to share the robust results obtained by our partner Exelixis in the treatment of advanced RCC, with the CABOSUN study demonstrating an improvement in progression-free survival with cabozantinib compared to sunitinib as a first-line treatment. This is an important milestone for patients as cabozantinib may have the potential to become a key reference for the treatment of previously untreated patients with locally advanced or metastatic RCC.”*

On March 1<sup>st</sup>, 2016, Exelixis, Inc. granted Ipsen an exclusive licensing agreement for the commercialization and further development of cabozantinib, where Ipsen has exclusive commercialization rights for current and potential future cabozantinib indications outside the United States, Canada and Japan.



Exelixis will share the results of CABOSUN with U.S. regulatory authorities and will collaborate with Ipsen on the European strategy and discussions with European regulators on the potential next steps in the development and submission strategy for cabozantinib as a treatment of first-line advanced RCC. Data supporting cabozantinib in previously treated patients with advanced RCC are currently under review by European regulatory authorities. Exelixis is also working closely with clinical advisors on the development plan for cabozantinib in future clinical trials in other genitourinary malignancies.

### **About the CABOSUN Study**

CABOSUN is a randomized, open-label, active-controlled phase 2 trial that was designed to enroll 150 patients with advanced RCC determined to be intermediate- or poor-risk by the International Metastatic RCC Database Consortium (IMDC) criteria. Patients were randomized 1:1 to receive cabozantinib (60 mg once daily) or sunitinib (50 mg once daily, 4 weeks on followed by 2 weeks off). The randomization was stratified by the IMDC risk strata (intermediate or poor risk) and presence of bone metastasis (yes, no). Enrollment was completed in March 2015. The primary endpoint was PFS, defined as time from randomization to disease progression or death, whichever occurs first. Secondary endpoints included overall survival and objective response rate. Eligible patients were required to have locally advanced or metastatic clear-cell RCC, ECOG performance status 0-2, and had to be intermediate or poor risk, per the IMDC Criteria (Heng JCO 2009). Prior systemic treatment for RCC was not permitted. With 123 events (disease progression or death), the log-rank statistic has 85 percent power (with a one-sided type I error rate=0.12) to detect a hazard ratio of 0.67. Between July 9, 2013 and April 6, 2015, 157 patients were randomized: 79 patients on the cabozantinib arm and 78 patients on the sunitinib arm.

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

The American Cancer Society's 2016 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>1</sup> Clear cell RCC is the most common type of kidney cancer in adults.<sup>2</sup> If detected in its early stages, the five-year survival rate for RCC is high; for patients with advanced or late-stage metastatic RCC, however, the five-year survival rate is only 12 percent, with no identified cure for the disease.<sup>1</sup> Approximately 30,000 patients in the U.S. and 68,000 globally require treatment.<sup>3</sup>

The majority of clear cell RCC tumors have lower than normal levels of a protein called von Hippel-Lindau, which leads to higher levels of MET, AXL and VEGF.<sup>4,5</sup> These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.<sup>6-9</sup> MET and AXL may provide escape pathways that drive resistance to VEGF receptor inhibitors.<sup>5,6</sup>

### **About CABOMETYX®**



CABOMETRYX<sup>®</sup> 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.

CABOMETRYX<sup>®</sup>, the tablet formulation of cabozantinib, is available in 20 mg, 40 mg or 60 mg doses. The recommended dose is 60 mg orally, once daily.

On January 28, 2016, the European Medicines Agency (EMA) validated Exelixis' Marketing Authorization Application (MAA) for cabozantinib as a treatment for patients with advanced renal cell carcinoma who have received one prior therapy. The MAA has been granted accelerated assessment, making it eligible for a 150-day review, versus the standard 210 days. On March 1st, 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 April 25, the FDA approved CABOMETRYX<sup>®</sup> tablets for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.

#### **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.ipsen.com](http://www.ipsen.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)).

## References

1. American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.
2. Jonasch E., Gao J., Rathmell W.K., Renal cell carcinoma. *BMJ*. 2014; 349:g4797.
3. Decision Resources Report: Renal Cell Carcinoma. October 2014 (internal data on file).
4. Harshman, L.C. and Choueiri, T.K., Targeting the hepatocyte growth factor/c-Met signaling pathway in renal cell carcinoma. *Cancer J*. 2013; 19(4):316-23.
5. Rankin et al., Direct regulation of GAS6/AXL signaling by HIF promotes renal metastasis through SRC and MET. *Proc Natl Acad Sci U S A*. 2014; 111(37):13373-8.
6. Zhou L, Liu X-D, Sun M, et al. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. *Oncogene*. 2015 Sep 14. doi:10.1038/onc.2015.343. [Epub ahead of print].
7. Koochekpour et al., The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. *Mol Cell Biol*. 1999; 19(9):5902-5912.
8. Takahashi A, Sasaki H, Kim SJ, et al. Markedly increased amounts of messenger RNAs for vascular endothelial growth factor and placenta growth factor in renal cell carcinoma associated with angiogenesis. *Cancer Res*. 1994;54:4233-4237.



9. Nakagawa M, Emoto A, Hanada T, Nasu N, Nomura Y. Tubulogenesis by microvascular endothelial cells is mediated by vascular endothelial growth factor (VEGF) in renal cell carcinoma. *Br J Urol.* 1997;79:681-687.

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