

Ipsen and its partner Exelixis announce positive results from phase 2 CABOSUN trial of cabozantinib versus sunitinib in previously untreated advanced renal cell carcinoma presented at the European Society for Medical Oncology (ESMO) 2016 congress

Cabozantinib met the primary endpoint of improving progression-free survival as compared to sunitinib, decreasing the rate of disease progression or death by 31 percent

Objective response rate significantly improved: 46 percent for cabozantinib versus 18 percent for sunitinib

Ipsen to host investor and media webcast from Copenhagen to discuss the data on Monday, October 10

Paris, France, 10 October 2016 – Ipsen (Euronext: IPN; ADR: IPSEY) and its partner Exelixis (NASDAQ:EXEL) today announced detailed results from the CABOSUN randomized phase 2 trial of cabozantinib in patients with previously untreated advanced renal cell carcinoma (RCC) with intermediate- or poor-risk disease per the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). Principal investigator Toni K. Choueiri, M.D. will present detailed data from late-breaking CABOSUN abstract [#LBA30_PR] today in the Presidential Symposium 3 session, starting at 16:30 CEST (local Copenhagen time) / 10:30 a.m. EDT / 7:30 a.m. PDT at the European Society for Medical Oncology (ESMO) 2016, which is being held October 7 – 11, 2016 in Copenhagen.

CABOSUN was 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).

In CABOSUN, with a median follow-up of 20.8 months, cabozantinib demonstrated a clinically meaningful and statistically significant 31 percent reduction in the rate of disease progression or death [HR 0.69, 95% CI (0.48-0.99), one-sided P=0.012]. The median progression-free survival (PFS) for cabozantinib was 8.2 months versus 5.6 months for sunitinib, corresponding to a 2.6 months (46 percent) improvement favoring cabozantinib over sunitinib. PFS benefits were independent of IMDC risk group (intermediate or poor risk) and presence or absence of bone metastases at baseline. The results for sunitinib were in line with a previously published retrospective analysis of 1,174 intermediate- and poor-risk RCC patients from the IMDC database, which documented a median PFS of 5.6 months with a first-line targeted therapy, mainly sunitinib, in this patient population.¹



Objective response rate (ORR) was also significantly improved, at 46 percent (95% CI 34% – 57%) for cabozantinib versus 18 percent (95% CI 10% to 28%) for sunitinib. With a median follow up of 22.8 months, median overall survival was 30.3 months for cabozantinib versus 21.8 months for sunitinib [HR 0.80, 95% CI (0.50 - 1.26)].

“The results presented today support the potential of cabozantinib to become a new therapeutic option for previously untreated patients following their diagnosis with advanced kidney cancer,” said **Toni K. Choueiri, M.D., Director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and chair of the CABOSUN study.** *“Not only has cabozantinib surpassed sunitinib, the current standard of care, in progression-free survival and objective response rate, cabozantinib’s effects on progression-free survival were also consistently favorable across patient stratification subgroups including IMDC intermediate versus poor-risk groups and presence or absence of bone metastases.”*

“We at the Alliance for Clinical Trials in Oncology are pleased that CABOSUN has successfully demonstrated that cabozantinib has the potential to benefit patients with advanced renal cell carcinoma as a first-line therapy,” said **Michael J. Morris, M.D., Associate Member at Memorial Sloan Kettering Cancer Center, and Chair of the Alliance Genitourinary Committee.** *“We are grateful to everyone who has participated in the trial, especially the physicians, patients and their families.”*

David Meek, Ipsen’s Chief Executive Officer stated: *“Following the European commission approval of cabozantinib in second line advanced RCC, cabozantinib continues to show and expand potential clinical benefit in patients with RCC. With our partner Exelixis, we are pleased to report full results from the CABOSUN study showing superior results over sunitinib in PFS and ORR in patients with previously untreated advanced intermediate- or poor-risk RCC. Importantly the safety profile of cabozantinib is comparable to the sunitinib arm in the CABOSUN study as well as in previous studies of cabozantinib in advanced RCC. We look forward to sharing these important data with regulatory authorities and to define the path forward.”*

CABOSUN enrolled 157 patients with previously untreated advanced RCC: 80.9 percent of patients were intermediate risk per IMDC criteria and 19.1 percent were poor risk, 36.3 percent of patients had bone metastases, 46 percent of patients had ECOG Performance Status (PS) 0, 41 percent had ECOG PS 1, and 13 percent had ECOG PS 2. All patients were included in the efficacy analyses that followed the intent-to-treat principle. Tumor assessments were performed by the investigators following RECIST criteria. At the time of the analysis of the primary endpoint of PFS, the median duration of treatment in CABOSUN was 6.9 months with cabozantinib and 2.8 months with sunitinib; 13 patients continued on cabozantinib treatment versus 2 patients on sunitinib treatment. Dose reductions occurred for 58 percent and 49 percent of patients, respectively. Discontinuation rate due to an adverse event was 20 percent with cabozantinib and 21 percent with sunitinib.



One hundred and fifty patients were evaluable for safety. Ninety-nine percent of patients on both arms experienced at least one adverse event. The most common all causality grade 3 or 4 adverse events observed in more than 5 percent of patients were hypertension (28 percent), diarrhea (10 percent), palmar-plantar erythrodysesthesia (8 percent), and fatigue (6 percent) in the cabozantinib arm, and hypertension (22 percent), fatigue (15 percent), diarrhea and thrombocytopenia (both 11 percent), and oral mucositis (6 percent) in the sunitinib arm. Treatment-related grade 5 events occurred in three patients in the cabozantinib arm (acute kidney injury, sepsis and jejunal perforation) and two patients in the sunitinib arm (sepsis and vascular disorder).

About the CABOSUN Study

On May 23, 2016, Exelixis announced that CABOSUN met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS compared with sunitinib in patients with advanced intermediate- or poor-risk 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).

Based on these results, Exelixis plans to submit a Supplemental New Drug Application (sNDA) for cabozantinib as a treatment of first-line advanced renal cell carcinoma, and is working with the Alliance to transfer the complete CABOSUN clinical database to Exelixis. Exelixis is discussing the results with regulatory authorities and evaluating potential next steps in the development and submission strategy for cabozantinib as a first-line treatment for patients with advanced RCC. Ipsen is also currently evaluating potential next steps in the development and submission strategy for cabozantinib as a first-line treatment for patients with advanced RCC.

CABOSUN was a randomized, open-label, active-controlled phase 2 trial that enrolled 157 patients with advanced RCC determined to be intermediate- or poor-risk by the 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 primary endpoint was PFS. 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.

Webcast for the Financial Community and Media

Exelixis and its partner Ipsen will jointly host a live webcast on Monday, October 10. The webcast will begin at beginning at 19:00 CEST (local Copenhagen time) / 1:00 p.m. EDT / 10:00 a.m. PDT. During the webcast, Exelixis and Ipsen management and invited guest speakers will review and provide context of the results from the CABOSUN study, along with the other data sets on cabozantinib presented at the conference.

A conference call will take place and a web conference (audio and video webcast) will be available at www.ipsen.com. Participants should enter the meeting in approximately 5 to 10 minutes prior to its start. Phone numbers to call in order to connect to the conference are: from Europe 0800



919 312 and from the United States 1 855 299 5224. The reference for the conference call is 234 026 024. No reservation is required to participate in the conference call.

About Advanced Renal Cell Carcinoma

Renal cell carcinoma (RCC) represents 2-3% of all cancers², with the highest incidence occurring in Western countries. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe, though in Denmark and Sweden a continuing decrease has been observed³. In 2012, there were approximately 84,400 new cases of RCC and 34,700 kidney cancer related deaths within the European Union⁴. In Europe, overall mortality rates for RCC have increased up until the early 1990s, with rates generally stabilizing or declining thereafter⁵. There has been a decrease in mortality since the 1980s in Scandinavian countries and since the early 1990s in France, Germany, Austria, the Netherlands, and Italy. However, in some European countries (Croatia, Estonia, Greece, Ireland, Slovakia), mortality rates still show an upward trend with increasing rates⁵.

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.^{6,7} These proteins promote tumor angiogenesis (blood vessel growth), growth, invasiveness and metastasis.⁸⁻¹¹ MET and AXL may provide escape pathways that drive resistance to VEGFR inhibitors.^{7,8}

About Ipsen in oncology

Ipsen focuses its efforts in fighting cancers such as prostate cancer or those with high unmet medical needs such as bladder cancer, neuroendocrine tumors, kidney cancer and other niche oncology diseases. Our ambition is to offer new therapeutic options to patients and caregivers in their treatment journeys. Ipsen has a continuous commitment in innovative treatment development in oncology through an open innovation approach and using differentiated technological platforms notably in peptides. Moreover Ipsen has built scientific partnerships with trusted academic institutions, leading pharmaceutical and biotech companies and work with today's top researchers and clinicians. We thus develop effective and innovative therapeutic solutions to improve treatment outcomes for patients and to support healthcare professionals in their daily practice.

About CABOMETRYX™ (cabozantinib)

CABOMETRYX 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.

CABOMETRYX 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 CABOMETRYX 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 CABOMETRYX 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.



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.ipсен.com.

Ipsen 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 2015 Registration Document available on its website (www.ipsen.com).

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