Press release

Intended for international media and investor audiences only

Ipsen expands collaboration and license agreement for development of Cabometyx® in advanced neuroendocrine tumors based on positive CABINET Phase III trial

- ***Decision adds to existing collaboration agreement with Exelixis, permitting Ipsen to seek potential marketing authorizations for Cabometyx® (cabozantinib) in advanced pancreatic and extra pancreatic neuroendocrine tumors outside of the U.S. and Japan***
- ***Agreement based on CABINET Phase III trial, led by the Alliance for Clinical Trials in Oncology, which demonstrated improvements in progression-free survival for Cabometyx versus placebo [1]***
- ***Ipsen has engaged with regulatory authorities in the European Union and will submit a regulatory filing on the basis of these data***

PARIS, FRANCE, 2 July 2024 - Ipsen (Euronext: IPN; ADR: IPSEY) announced today confirmation of an expanded collaboration and license agreement with Exelixis, Inc. for the development of Cabometyx® (cabozantinib) in advanced pancreatic neuroendocrine tumors (pNETs) and advanced extra-pancreatic neuroendocrine tumors (epNETs). The agreement is based on positive outcomes from the CABINET Phase III trial, led by the Alliance for Clinical Trials in Oncology and sponsored by the National Cancer Institute (NCI), which investigated Cabometyx versus placebo in people living with advanced pNETs or advanced epNETs whose disease had progressed after prior systemic therapy. An independent Data and Safety Monitoring Board recommended to stop accrual to the study, unblind patients and allow crossover from placebo to Cabometyx. This was due to early efficacy demonstrated at an interim analysis in both of the trial's cohorts, with clinically meaningful improvements in progression-free survival (PFS).[1]

"With many people diagnosed with neuroendocrine tumors at an advanced stage of disease and treatment options limited upon progression, the need for efficacious new therapies is extensive," said Christelle Huguet, EVP and Head of Research and Development, Ipsen. "The positive results demonstrated for Cabometyx within the CABINET Phase III trial represent clinically meaningful improvements in progression-free survival at a challenging stage of disease where there are few or no available treatment options. We look forward to discussing these clinical findings with regulatory authorities."

Neuroendocrine tumors (NETs) are a group of uncommon tumors that develop in the cells of the neuroendocrine system throughout the body.[2,3] The symptoms of NETs are often not distinct and difficult to identify, leading to delays in diagnosis, with 58% of people presenting with metastatic disease at diagnosis.[3] The number of people newly diagnosed with NETs is believed to be rising due to increasing awareness and better methods of diagnosis, with approximately 35 in every 100,000 people currently living with NETs globally.[3,4] The survival rate varies greatly depending on the primary site and stage of disease, however for people living with advanced pNETs which has spread to distant parts of the body, the prognosis is poor, with a five-year survival rate of 23%.[5]

CABINET Phase III trial

Data from the study, which demonstrated PFS benefits at interim analyses, were presented at the European Society for Medical Oncology Congress 2023 by Professor Jennifer Chan, MD, MPH, Dana-Farber Cancer Institute, Boston:[1]

- In the pNET cohort, at a median follow-up of 16.7 months, median PFS based on local radiology review was 11.4 months for Cabometyx versus 3.0 months for placebo (hazard ratio (HR) 0.27 [95% confidence interval (CI) 0.14-0.49] p<0.0001)[1]

- In the epNET cohort, at a median follow-up of 13.9 months, median PFS based on local radiology review was 8.3 months for Cabometyx versus 3.2 months for placebo (HR 0.45 [95% CI 0.30-0.66] p<0.0001)[1]
- The safety profile of Cabometyx observed in each cohort was consistent with its known safety profile; no new safety signals were identified[1]

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About Cabometyx

Cabometyx (cabozantinib) is a small molecule that inhibits multiple receptor tyrosine kinases, including VEGFRs, MET, RET and the TAM family (TYRO3, MER, AXL).[6] These receptor tyrosine kinases are involved in both normal cellular function and pathologic processes such as oncogenesis, metastasis, tumor angiogenesis (the growth of new blood vessels that tumors need to grow), drug resistance, modulation of immune activities and maintenance of the tumor microenvironment.[6,7,8,9]

In 2016, Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of Cabometyx outside of the U.S. and Japan. In 2017, Exelixis granted exclusive rights to Takeda Pharmaceutical Company Limited (Takeda) for the commercialization and further clinical development of Cabometyx for all future indications in Japan. Exelixis holds the exclusive rights to develop and commercialize Cabometyx in the U.S.

In over 60 countries outside of the U.S. and Japan, including in the E.U., Cabometyx is currently indicated as a:[7]

- Monotherapy for advanced renal cell carcinoma (aRCC).
  - as first-line treatment of adults with intermediate- or poor-risk disease.
  - in adults following prior VEGFR-targeted therapy.
- In combination with nivolumab for the first-line treatment of aRCC in adults.
- Monotherapy for the treatment of adults living with locally advanced or metastatic differentiated thyroid carcinoma, refractory or not eligible to radioactive iodine who have progressed during or after prior systemic therapy.
- Monotherapy for the treatment of hepatocellular carcinoma in adults who have previously been treated with sorafenib.

The detailed recommendations for the use of Cabometyx are described in the Summary of Product Characteristics (EU SmPC).

About neuroendocrine tumors

NETs are relatively uncommon and develop from cells of the neuroendocrine system; thus, can arise from a variety of locations throughout the body.[2,3] The most common sites of NETs include the gastrointestinal (GI) tract, lungs and pancreas.[2,10] Most NETs take years to develop and grow slowly, however some NETs can be fast-growing.[2] The symptoms of NETs are often difficult to identify leading to patients being seen by multiple specialists and undergoing extensive testing before diagnosis is confirmed.[3] As a result, almost a third of people take at least 5 years to be diagnosed with NETs.[3] The five-year survival rate is dependent on the primary site of disease. For advanced GI-NET and lung NETs, where the cancer has spread to distant parts of the body, the five-year survival rates are 68% and 55%, respectively.[11,12] For people diagnosed with advanced pNET, however, the prognosis is poor, with a five-year survival rate of 23%.[5]

About CABINET

CABINET (randomized, double-blinded Phase III trial of CABozantinib versus placebo In patients with advanced NEuroendocrine Tumors after progression on prior therapy) is sponsored by the National Cancer Institute (NCI), part of the National Institutes of Health, and is being led and conducted by the NCI-funded Alliance for Clinical Trials in Oncology with participation from the NCI-funded National Clinical Trials Network, as part of Exelixis' collaboration through a Cooperative Research and Development Agreement with the NCI's Cancer Therapy Evaluation Program.

The multicenter, Phase III CABINET pivotal trial enrolled a total of 290 patients in the U.S at the time of the interim analyses. Patients were randomized 2:1 to Cabometyx or placebo in two separate cohorts (pNET, n=93; epNET, n=197). The epNET cohort included patients with the following primary tumor sites: gastrointestinal tract, lung, unknown and other. Each cohort was randomized separately and had its own statistical analysis plan. Patients must have had measurable disease per RECIST 1.1 criteria and must have experienced disease progression or intolerance after at least one U.S. Food and Drug Administration-approved line of prior therapy other than somatostatin analogs. The primary endpoint in each cohort was PFS per RECIST 1.1 by retrospective independent central review. Upon confirmation of disease progression, patients were unblinded, and those receiving placebo were permitted to cross over to open-label therapy with Cabometyx. Secondary endpoints included overall survival, radiographic response rate and safety. More information about this trial is available at ClinicalTrials.gov.

About Ipsen

We are a global biopharmaceutical company with a focus on bringing transformative medicines to patients in three therapeutic areas: Oncology, Rare Disease and Neuroscience. Our pipeline is fuelled by external innovation and supported by nearly 100 years of development experience and global hubs in the U.S., France and the U.K. Our teams in more than 40 countries and our partnerships around the world enable us to bring medicines to patients in more than 80 countries.

Ipsen is listed in Paris (Euronext: IPN) and in the U.S. through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information, visit ipsen.com.

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Disclaimers and/or Forward-Looking Statements

The forward-looking statements, objectives and targets contained herein are based on Ipsen'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 Ipsen'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 Ipsen'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 Ipsen. 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 medicine 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. Ipsen must face or might face competition from generic medicine 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 Ipsen may fail to achieve its objectives and be forced to abandon its efforts with regards to a medicine in which it has invested significant sums. Therefore, Ipsen cannot be certain that favorable results obtained during preclinical 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 medicine concerned. There can

be no guarantees a medicine will receive the necessary regulatory approvals or that the medicine 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 healthcare legislation; global trends toward healthcare cost containment; technological advances, new medicine and patents attained by competitors; challenges inherent in new-medicine development, including obtaining regulatory approval; Ipsen'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 Ipsen's patents and other protections for innovative medicines; and the exposure to litigation, including patent litigation, and/or regulatory actions. Ipsen also depends on third parties to develop and market some of its medicines which could potentially generate substantial royalties; these partners could behave in such ways which could cause damage to Ipsen's activities and financial results. Ipsen 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 Ipsen's partners could generate lower revenues than expected. Such situations could have a negative impact on Ipsen's business, financial position or performance. Ipsen 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. Ipsen'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 Ipsen's latest Universal Registration Document, available on ipsen.com.

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