Press release

Intended for international media and investor audiences only

Final results from CABINET Phase III trial reinforce efficacy benefits of Cabometyx® in advanced neuroendocrine tumors

- ***Data demonstrated statistically significant and clinically meaningful reduction in risk of disease progression or death with Cabometyx® (cabozantinib) versus placebo in advanced pancreatic and extra-pancreatic neuroendocrine tumors (NETs)***[1,2]
- ***Data presented at ESMO 2024 and published in New England Journal of Medicine***
- ***Ipsen has submitted an extension of indication Marketing Authorization to the European Medicines Agency***
- ***Limited approved treatment options for advanced NETs dependent on primary site of disease, with no approved therapies in lung NETs upon progression after prior systemic therapy***[3,4]

PARIS, FRANCE, 16 September 2024 - Ipsen (Euronext: IPN; ADR: IPSEY) announced today final data from the CABINET Phase III trial investigating Cabometyx® (cabozantinib) versus placebo in people living with advanced pancreatic neuroendocrine tumors (pNETs) or advanced extra-pancreatic neuroendocrine tumors (epNETs) whose disease had progressed after prior systemic therapy. These data demonstrated a statistically significant reduction in the risk of disease progression or death for Cabometyx versus placebo of 77% (hazard ratio (HR) 0.23) and 62% (HR 0.38) for people living with advanced pNETs and epNETs, respectively.[1,2] Presentation of these data is taking place today at the 2024 European Society for Medical Oncology Congress (ESMO 2024) during the Proffered Paper Session: NETs and Endocrine Tumors at 2:45 p.m. CEST, and is published in the New England Journal of Medicine (NEJM).

"People living with neuroendocrine tumors face many challenges, from securing a timely diagnosis to optimal treatment options which address the needs of the increasing number of people affected by this cancer worldwide," said Teodora Kolarova, Executive Director, International Neuroendocrine Cancer Alliance. "These latest data reaffirm the possibilities of continuing scientific advancements in neuroendocrine tumors, offering the potential for new therapies which could significantly impact people's everyday lives as they navigate this complex and life altering diagnosis."

Final results demonstrated progression-free survival (PFS) benefits in favor of Cabometyx versus placebo by blinded independent central review (BICR).[1,2] In the pNET cohort, at a median follow-up of 13.8 months, median PFS was 13.8 months for Cabometyx versus 4.4 months for placebo (HR 0.23 [95% confidence interval (CI) 0.12-0.42] p<0.0001).[1,2] In the epNET cohort, at a median follow-up of 10.2 months, median PFS was 8.4 months for Cabometyx versus 3.9 months for placebo (HR 0.38 [95% CI 0.25-0.59] p<0.0001).[1,2] The safety profile of Cabometyx observed in each cohort was consistent with its known safety profile; no new safety signals were identified.[1,2]

"These latest data reinforce the potential of Cabometyx to deliver significant efficacy benefits at an advanced stage of disease," said Christelle Huguet, EVP and Head of Research and Development at Ipsen. "Through our submission to the EMA, it is our ambition to evolve the treatment paradigm for people living with neuroendocrine tumors, harnessing our longstanding heritage in this area to deliver an effective new therapy where options are notably limited."

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.[5,6] However, despite increasing awareness, the non-specific nature of NET symptoms often leads patients to be seen by multiple specialists and to undergo various forms of testing before an accurate diagnosis is achieved.[5] As a result, almost a third of people take at least five years to be diagnosed with NETs, contributing to poorer patient outcomes.[5] Most forms of NETs are indolent in nature and can

develop in any part of the body,[7] requiring multiple lines of therapy as people progress.[3,4] Treatment options upon progression are often limited dependent on primary site of disease, resulting in challenges in identifying optimal care pathways specific to patients' circumstances.[3,4,8]

ENDS

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).[9] 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.[9,10,11,12]

Exelixis granted Ipsen exclusive rights for the commercialization and further clinical development of Cabometyx outside of the U.S. and Japan. 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 65 countries outside of the United States and Japan, including in the European Union, Cabometyx is currently indicated as:[10]

- 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.
- A 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.

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.[5,7] The most common sites of NETs include the gastrointestinal (GI) tract, lungs and pancreas.[7,13] Most NETs take years to develop and grow slowly, however some NETs can be fast-growing.[7] 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.[14,15] For people diagnosed with advanced pNET, however, the prognosis is poor, with a five-year survival rate of 23%.[16]

About CABINET (Alliance A021602)

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 298 patients in the US at the time of the final analysis. Patients were randomized 2:1 to Cabometyx or placebo in two separately powered cohorts (pNET, n=95; epNET, n=203). The epNET cohort included patients with the following primary tumor sites: gastrointestinal tract, lung, unknown primary sites 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 analogues. 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 fueled 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.

Ipsen contacts

Investors

- **Craig Marks | +44 7584 349 193**

Media

- **Amy Wolf | +41 7 95 76 07 23**
- **Emma Roper | +44 7711 766 517**

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.

References

[1] Chan *et al.* Phase 3 Trial of Cabozantinib in Previously Treated Advanced Neuroendocrine Tumors. 2024 *New England Journal of Medicine.* Online ahead of print

[2] Cabozantinib Versus Placebo for Advanced Neuroendocrine Tumors (NET) after Progression on Prior Therapy (CABINET Trial/Alliance A021602): Updated Results Including Progression Free-Survival (PFS) by Blinded Independent Central Review (BICR) and Subgroup Analyses. As presented at ESMO Congress 2024 during the 'Proffered Paper: NETs and Endocrine Tumors at 2:45 p.m. CEST Barcelona, Spain.

[3] Baudin E, et al. Ann Oncol. 2021 Nov;32(11):1453-1455.

[4] Pavel M, et al. Ann Oncol. 2020;31(7):844-860.

[5] Singh *et al.* Patient-Reported Burden of a Neuroendocrine Tumor (NET) Diagnosis: Results From the First Global Survey of Patients With NETs. *J Glob Oncol.* 2017 Feb; 3(1): 43–53.

[6] Durma *et al.* Epidemiology of Neuroendocrine Neoplasms and Results of Their Treatment with [177Lu]Lu-DOTA-TATE or [177Lu]Lu-DOTA-TATE and [90Y]Y-DOTA-TATE—A Six-Year Experience in High-Reference Polish Neuroendocrine Neoplasm Center. *Cancers* 2023, 15(22), 5466; https://doi.org/10.3390/cancers15225466

[7] Neuroendocrine tumor (NET). https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-endocrine-tumor/carcinoid-tumor. Accessed September 2024.

[8] McClellan, K., Chen. E.Y, Kardosh A., et al. Therapy Resistant Gastroenteropancreatic Neuroendocrine Tumors. Cancers. 2022, 14(19), 4769.

[9] El-Khoueiry A. et al., Cabozantinib: An evolving therapy for hepatocellular carcinoma. Cancer Treatment Reviews. 2021 Jul;98:102221. DOI: 10.1016/j.ctrv.2021.102221.

[10] European Medicines Agency. Cabometyx® (cabozantinib) EU Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/cabometyx-epar-product-information_en.pdf. Last accessed: September 2024

[11] Yakes M. *et al.*, Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther*. 2011;10:2298–2308. DOI: 10.1158/1535-7163.MCT-11-0264

[12] Hsu *et al.*, AXL and MET in Hepatocellular Carcinoma: A Systematic Literature Review. *Liver Cancer* 2021 DOI: 10.1159/000520501

[13] Jamal *et al.* Neuroendocrine tumor of the kidney. Diagnostic challenge and successful therapy. *Urology Annals* 11(4):p 435-438, Oct–Dec 2019. DOI: 10.4103/UA.UA_169_18

[14] Survival Rates for Gastrointestinal Carcinoid Tumors. ACS website. Available at: https://www.cancer.org/cancer/types/gastrointestinal-carcinoid-tumor/detection-diagnosis-staging/survival-rates.html. Accessed September 2024.

[15] Survival Rates for Lung Carcinoid Tumors. ACS website. Available at: https://www.cancer.org/cancer/types/lung-carcinoid-tumor/detection-diagnosis-staging/survival-rates.html. Accessed September 2024.
[16] Survival Rates for Pancreatic Neuroendocrine Tumor. American Cancer Society Available at: https://www.cancer.org/cancer/types/pancreatic-neuroendocrine-tumor/detection-diagnosis-staging/survival-rates.html. Accessed June 2024. Accessed September 2024.