PRESS RELEASE

ESMO 2021: Cabometyx® demonstrates sustained 78% reduction in risk of disease progression or death in people living with uncommon form of thyroid cancer

- Ipsen's submission for extension of indication for Cabometyx® (cabozantinib) based on data from the COSMIC-311 trial received validation from the European Medicines Agency in August 2021
- Separate follow-up data presented at the European Society for Medical Oncology Congress 2021 includes cohort 6 of the Phase Ib COSMIC-021 trial and the Phase III CheckMate -9ER trial, reinforcing the broad utility potential of Cabometyx across indications[2-4]

PARIS, FRANCE, 18 September 2021 – Ipsen (Euronext: IPN; ADR: IPSEY) today announced presentation of new analyses at the European Society for Medical Oncology (ESMO) Congress 2021 across different forms of cancer for people treated with Cabometyx® (cabozantinib). Of note, the final analysis of the pivotal Phase III COSMIC-311 trial (Abstract LBA67) will be presented, with Cabometyx demonstrating a clinically meaningful, sustained efficacy benefit versus placebo in people living with previously treated radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC).

With a median follow-up of 10.1 months, Cabometyx continued to demonstrate superior median progression-free survival (mPFS) with a reduction in the risk of disease progression or death of 78% versus placebo (hazard ratio [HR]: 0.22, 96% confidence interval [CI]: 0.15-0.32; p<0.0001).[1] This final analysis is consistent with data from the interim analysis, presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2021 and published in *The Lancet Oncology*, (HR: 0.22; 96% CI: 0.13-0.36; p<0.0001).[5,6] Further data from the final analysis also confirmed that superior efficacy with Cabometyx was maintained irrespective of previous vascular endothelial growth factor receptor (VEGFR)-targeted therapy.

Efficacy and safety data from the COSMIC-311 interim analysis formed the basis of a type II variation submission to the European Medicines Agency (EMA) for an extension of indication for Cabometyx in RAI-R DTC. On 14 August 2021, the EMA validated the type II variation, confirming the submission is complete and beginning its centralized review process.

The safety profile identified in the COSMIC-311 trial was consistent with that previously observed for cabozantinib and adverse events (AEs) were managed with dose modifications. The discontinuation rate due to treatment-emergent AEs (TEAEs) was 8.8% for Cabometyx vs. 0% for placebo. Grade 3/4 TEAEs occurred in 62% of patients who received Cabometyx vs. 28% for placebo, with no treatment-related grade 5 events.

Steven Hildemann, M.D., Executive Vice President, Chief Medical Officer, Head of Global Medical Affairs and Global Patient Safety, Ipsen said "The therapeutic potential of Cabometyx as a key treatment option in our arsenal against a broad range of tumors is continuing to be realized. These final data from the COSMIC-311 trial are a strong example of how Cabometyx can make a tangible difference to the lives of people living with cancer and we look forward to receiving a decision from the EMA next year. We are committed to further evaluating the role Cabometyx may continue to play against difficult-to-treat cancers as we also look towards the results of the ongoing Phase III trials in non-small cell lung cancer (CONTACT-01) and metastatic castration-resistant prostate cancer (CONTACT-02)."

Additional data to be presented at ESMO featuring Cabometyx include new results from cohort 6 of the COSMIC-021 Phase Ib trial evaluating the combination of Cabometyx and atezolizumab in people living with previously treated metastatic castration-resistant prostate cancer (mCRPC) (Abstract LBA24).[2] These additional analyses build on the interim data presented at ASCO 2020,[7] with an expanded cohort 6 of 132 patients evaluated.[2] With a median follow-up of 15.2 months, the primary endpoint of objective

response rate (ORR) assessed by investigator per RECIST 1.1 (response evaluation criteria in solid tumours) was 23%, with three patients demonstrating a complete response (CR).[2]

Prof. Dr. Gunhild von Amsberg, University Medical Center Hamburg-Eppendorf (UKE) and investigator in the CONTACT-02 trial, said "As a uro-oncologist, I am encouraged by the results presented at this year's ESMO congress. For people living with advanced metastatic castration-resistant prostate cancer, the prognosis is often poor and the potential of new innovative therapies is critically important. Based on these clinically meaningful results of Cabometyx plus atezolizumab from cohort 6 of the COSMIC-021 trial, we now look forward to the results of the ongoing Phase III CONTACT-02."

Further analyses from the landmark Phase III CheckMate -9ER trial investigating the combination of Cabometyx and nivolumab were are also being presented at ESMO, providing additional evidence to inform clinical decision-making in advanced renal cell carcinoma (RCC). New data demonstrated improved efficacy for Cabometyx and nivolumab regardless of prior nephrectomy status, when measured by PFS, ORR, CR and response durability outcomes, versus sunitinib (Abstract 663P).[3] Additionally, a matching-adjusted indirect comparison analysis is being presented, demonstrating superior, statistically significant differences in health-related quality of life across all outcomes analysed in favour of Cabometyx and nivolumab versus the combination of axitinib and pembrolizumab (Abstract 668P).[4]

More information on these data can be found during the presentation sessions outlined below:

Title	**Date and time**
Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer (mCRPC): results of expanded cohort 6 of the COSMIC-021 Study	Saturday 18 September 13:30-13:40 CEST
Cabozantinib Versus Placebo in Patients With Radioiodine-Refractory Differentiated Thyroid Cancer (DTC) Who Have Progressed After Prior VEGFR-Targeted Therapy: Updated Results From the Phase 3 COSMIC-311 Trial	Monday 20 September 17:30-17:35 CEST
First-line nivolumab + cabozantinib (NIVO+CABO) vs sunitinib (SUN) in patients (pts) with advanced renal cell carcinoma (aRCC) in subgroups based on prior nephrectomy in the CheckMate 9ER trial	Poster presentation – Available on-demand beginning September 16 at 8:30 am CEST
Matching-adjusted indirect comparison (MAIC) of health-related quality of life (HRQoL) of nivolumab plus cabozantinib (N+C) vs pembrolizumab plus axitinib (P+A) in previously untreated advanced renal cell carcinoma (aRCC)	Poster presentation – Available on-demand beginning September 16 at 8:30 am CEST

ENDS

About radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC)
In 2020, over 580,000 new cases of thyroid cancer were diagnosed worldwide.[8] Thyroid cancer is the ninth most commonly occurring cancer globally and incidence is three times higher in women than in men, with the disease representing one in every 20 cancers diagnosed among women.[7] While cancerous thyroid tumors include differentiated, medullary and anaplastic forms, differentiated thyroid tumors make up about 90 to 95% of cases.[9,10] These include papillary, follicular and Hürthle cell cancer.[7,8] DTC is typically treated with surgery, followed by ablation of the remaining thyroid tissue with radioactive iodine (RAI), but approximately 5 to 15% of cases are resistant to RAI treatment.[11] Patients who develop RAI-R DTC have a poor prognosis with an average estimated survival of three to five years.[12]

About the COSMIC-311 trial
COSMIC-311 is a multicenter, randomized, double-blind, placebo-controlled Phase III trial that enrolled 258 patients at 164 sites globally.[6] Patients were randomized in a 2:1 ratio to receive either Cabometyx

60 mg or placebo once-daily.[6] The primary endpoints were progression-free survival and objective response rate, evaluated by a blinded independent radiology committee. Additional endpoints include safety, overall survival and quality of life.[2] More information about this trial is available at ClinicalTrials.gov.

About metastatic castration-resistant prostate cancer (mCRPC)
In 2020, over 1.4 million new cases of prostate cancer were diagnosed worldwide,[13] making it the fourth most commonly occurring cancer globally.[13] Prostate cancer that has spread beyond the prostate and does not respond to androgen-suppression therapies which reduce the levels of testosterone, a common treatment for prostate cancer, is known as mCRPC.[14] Men diagnosed with mCRPC often have a poor prognosis, with an estimated survival of 1-2 years.[15]

About the COSMIC-021 trial
COSMIC-021 is a multicenter, Phase Ib, open-label trial that is divided into two parts: a dose-escalation phase and an expansion cohort phase. The dose-escalation phase was designed to enroll patients either with advanced renal cell carcinoma (RCC) with or without prior systemic therapy or with inoperable, locally advanced, metastatic or recurrent urothelial carcinoma (UC), (including renal, pelvis, ureter, urinary bladder and urethra) after prior platinum-based therapy. Ultimately, all 12 patients who enrolled in this stage of the trial were patients with advanced RCC. The dose-escalation phase of the study determined the optimal dose of cabozantinib to be 40 mg daily when given in combination with atezolizumab (1200 mg infusion once every 3 weeks).

In the expansion phase, the trial is enrolling 24 cohorts in 12 tumor types: RCC, urothelial carcinoma, non-small cell lung cancer, CRPC, hepatocellular carcinoma, triple-negative breast cancer, epithelial ovarian cancer, endometrial cancer, gastric or gastroesophageal junction adenocarcinoma, colorectal adenocarcinoma, head and neck cancer, and DTC.

Four of the cohorts are exploratory single agent cohorts. In UC, NSCLC, CRPC with cabozantinib as a single-agent, and in CRPC with single-agent atezolizumab.

Exelixis is the study sponsor of COSMIC-021. Both Ipsen Pharma SAS (Ipsen) and Takeda Pharmaceutical Company Limited (Takeda) have opted in to participate in the trial and are contributing to the funding for this study under the terms of the companies' respective collaboration agreements with Exelixis. Roche is providing atezolizumab for the trial.

About renal cell carcinoma (RCC)
There are over 400,000 new cases of kidney cancer diagnosed worldwide each year.[16] Of these, RCC is the most common type of kidney cancer, accounting for approximately 90% of cases.[17,18] It is twice as common in men, and male patients account for over two thirds of deaths.[16] If detected in the early stages, the five-year survival rate is high, but for patients living with advanced or late-stage metastatic RCC the survival rate is much lower, around 12%, with no identified cure for this disease.[19,20]

About the CheckMate -9ER trial
CheckMate -9ER was an open-label, randomized, multi-national Phase III trial evaluating people living with previously untreated advanced or metastatic RCC. A total of 651 patients (23% favorable risk, 58% intermediate risk, 20% poor risk; 25% PD-L1 ≥1%) were randomized to Cabometyx plus Opdivo (n = 323) versus sunitinib (n = 328). The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival and objective response rate. The primary efficacy analysis compared the doublet combination versus sunitinib in all randomized patients. The trial was sponsored by Bristol Myers Squibb and Ono Pharmaceutical Co and co-funded by Exelixis, Ipsen and Takeda Pharmaceutical Company Limited.

About Cabometyx (cabozantinib)
In the U.S., Cabometyx tablets are approved for the treatment of patients living with advanced RCC; for the treatment of patients living with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib; and for patients living with advanced RCC as a first-line treatment in combination with nivolumab. Outside the U.S., Cabometyx is currently approved in 59 countries, including in the European Union, Great Britain, Norway, Iceland, Australia, New Zealand, Switzerland, South Korea, Canada, Brazil, Taiwan, Hong Kong, Singapore, Macau, Jordan, Lebanon, the Russian Federation, Ukraine, Turkey, United Arabic Emirates, Saudi Arabia, Serbia, Israel, Mexico, Chile, Peru, Panama, Guatemala, Dominican Republic, Ecuador, Thailand, Malaysia and Egypt for the treatment of advanced RCC in adults

who have received prior VEGF-targeted therapy; in the European Union, Great Britain, Norway, Iceland, Canada, Australia, New Zealand, Brazil, Taiwan, Hong Kong, Singapore, Lebanon, Jordan, the Russian Federation, Ukraine, Turkey, the United Arab Emirates (U.A.E.)., Saudi Arabia, Israel, Mexico, Chile, Peru, Panama, Guatemala, the Dominican Republic, Ecuador, Thailand, Egypt and Malaysia for previously untreated intermediate- or poor-risk advanced RCC; and in the European Union, Great Britain Norway, Iceland, Canada, Australia, Switzerland, Saudi Arabia, Serbia, Israel, Taiwan, Hong Kong, South Korea, Singapore, Jordan, the Russian Federation, Ukraine, Turkey, Lebanon, the U.A.E., Peru, Panama, Guatemala, Chile, the Dominican Republic, Ecuador, Thailand, Brazil, New Zealand and Malaysia for HCC in adults who have previously been treated with sorafenib. Cabometyx is also approved in combination with nivolumab as first line treatment for people living with advanced RCC, in the European Union, Great Britain, Norway, Iceland, Switzerland, Taiwan, the Russian Federation.

The detailed recommendations for the use of Cabometyx are described in the Summary of Product Characteristics (EU SmPC) and in the U.S. Prescribing Information (USPI).

Ipsen has exclusive rights for the commercialization of Cabometyx outside the U.S. and Japan. Cabometyx is marketed by Exelixis in the U.S. and by Takeda Pharmaceutical Company Limited in Japan. Cabometyx is a registered trademark of Exelixis.

About Ipsen

Ipsen is a global, mid-sized biopharmaceutical company focused on transformative medicines in Oncology, Rare Disease and Neuroscience; it also has a well-established consumer healthcare business. With total sales of over €2.5bn in FY 2020, Ipsen sells more than 20 medicines in over 115 countries, with a direct commercial presence in more than 30 countries. The company's research and development efforts are focused on its innovative and differentiated technological platforms located in the heart of leading biotechnological and life-science hubs: Paris-Saclay, France; Oxford, U.K.; Cambridge, U.S.; Shanghai, China. Ipsen has c.5,700 colleagues worldwide and 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's 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 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 and also taking into consideration assessment delays of certain clinical trials in light of the ongoing COVID-19 pandemic. Ipsen 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 Ipsen 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, 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 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; 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 products; 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 products 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 the Ipsen's 2020 Universal Registration Document, available on ipsen.com.

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