PRESS RELEASE

Ipsen to present new data at 13th Annual Conference of the International Liver Cancer Association (ILCA 2019)

Results from a matching-adjusted indirect comparison (MAIC) suggest that cabozantinib provides two additional months of progression-free survival versus regorafenib in the second-line treatment of advanced hepatocellular carcinoma[1]

Paris (France), 20 September 2019 – Ipsen (Euronext: IPN; ADR: IPSEY) today presents results from the matching-adjusted indirect comparison (MAIC) of cabozantinib (Cabometyx®) versus regorafenib (Stivarga®) for the second-line treatment (2L) of patients with advanced hepatocellular carcinoma (aHCC) who received sorafenib as the only prior systemic therapy. Using data from the Phase III CELESTIAL and RESORCE trials, the MAIC showed that cabozantinib offers greater efficacy versus regorafenib.

Using data from the Phase III CELESTIAL and RESORCE trials, the MAIC showed that in the 2L CELESTIAL sub-population who had received sorafenib as the only prior systemic therapy, cabozantinib significantly improved progression-free survival (PFS), with an additional 2.4 months provided vs. regorafenib (5.6 months vs. 3.2 months [95% confidence interval (CI): 4.90-7.26], p<0.05). Median overall survival (OS) was also favorable with cabozantinib (11.4 months vs. 10.8 months), though statistical significance was not met.[1]

Results from MAIC will be presented by Dr. Katie Kelley, oncologist at the University of California, San Francisco and lead investigator, at the 13th Annual Conference of the International Liver Cancer Association (ILCA 2019) taking place on 20-22 September 2019 in Chicago, USA (poster/abstract #P-021).

In the previously presented randomized, double-blind, Phase III CELESTIAL trial evaluating cabozantinib compared with placebo in previously treated patients with aHCC, in the overall CELESTIAL intent-to-treat population, cabozantinib significantly improved median PFS, with an additional 3.3 months provided vs placebo (5.2 months vs. 1.9 months [95% CI, 4.0 to

5.5], p<0.001) and median OS, with an additional 2.2 months vs placebo (10.2 months vs. 8.0 months [95% confidence interval (CI): 9.1 to 12.0), p=0.005).[1]

“Hepatocellular carcinoma is a devastating disease with only a few treatment options demonstrating survival benefits and many investigational drugs have failed to meet overall survival endpoints in clinical trials,” said Dr. Kelley. “The MAIC analysis brings further insight into the comparative effectiveness of the key second-line treatments for advanced hepatocellular carcinoma, particularly in relation to important endpoints like progression-free survival. These results may support clinicians in making informed treatment decisions in order to deliver optimal care for their patients.”

Grade 3/4 adverse events affecting more than 5% of patients were comparable for the two studies, except for diarrhea which was lower with regorafenib.[1]

MAICs are a way of providing a timely comparison of the effectiveness of different medical interventions in the absence of head-to-head randomized trials.[2] While indirect comparisons of treatments across separate studies can be performed, these analyses may be biased by cross-trial differences in patient populations, sensitivity to modeling assumptions, and differences in the definitions of outcome measures. MAICs use individual patient data (IPD), also referred to as individual-level data, from trials of one treatment to match baseline summary statistics reported from trials of another treatment and reduce observed cross-trial differences.[2] After matching, treatment outcomes are compared across balanced trial populations. It should be noted that, even after matching, bias may still occur in MAIC due to imbalance in unobserved factors, and it cannot completely replace a head-to-head randomized and controlled trial.[1]

“At Ipsen, our mission is to prolong and improve patients’ lives and health outcomes, and we acknowledge the importance of providing healthcare professionals with the best available evidence to achieve these goals for patients,” said Dr. Yan Moore, Ipsen’s Senior Vice President, Head of Oncology Therapeutic Area. “The recent rapid development of new second-line treatments for patients with advanced HCC has led to the generation of information mainly based on placebo-controlled trials. While alternative methodological approaches such as MAIC are not substitutes to evidence-based prospective clinical trials, it is important to recognize the need for further insights into the comparative effectiveness of current treatment approaches.”

About the matching-adjusted indirect comparison of cabozantinib and regorafenib
The aim of this MAIC was to compare the safety and efficacy of cabozantinib and regorafenib for patients with aHCC who have received sorafenib as the only prior systemic therapy. Through the MAIC, IPD from patients enrolled in the CELESTIAL[3] who had received cabozantinib as second-line therapy following sorafenib as the sole prior therapy (N=495) were adjusted to match the average baseline (BL) characteristics of the 573 patients enrolled in the regorafenib study RESORCE,[4] for which individual-level data (ILD) are not available.

After matching, the selected BL characteristics were balanced across trials. The BL characteristics available for matching for both trials and deemed potential effect modifiers by key opinion leaders were:[1]

- age group
- race
- geographical region
- ECOG (Eastern Cooperative Oncology Group) performance status
- Child-Pugh class
- duration of prior sorafenib treatment
- extrahepatic disease
- macrovascular invasion
- etiology of HCC (hepatitis B, alcohol use and hepatitis C)
- AFP (alpha-fetoprotein tumor marker) level

In the first indirect comparison of cabozantinib and regorafenib in 2L HCC (post-sorafenib):[1]

- Cabozantinib significantly improved median PFS, with an additional 2.4 months provided versus regorafenib (5.59 months vs. 3.19 months [95% CI: 4.90-7.26], p<0.05)
- OS also favored cabozantinib, with a median OS of almost 1 year (11.37 months vs. 10.79 months), though statistical significance was not met

Grade 3/4 adverse events (AEs) affecting more than 5% of patients were comparable for the two studies, except for diarrhea which was significantly lower with regorafenib.

It should be noted that, even after matching, bias may still occur in MAIC due to imbalance in unobserved factors, and it cannot replace a head-to-head randomized control trial.

About CELESTIAL
CELESTIAL is a randomized, double-blind, placebo-controlled global Phase III study of cabozantinib versus placebo in patients with advanced hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. The study was conducted at more than 100 sites globally in 19 countries. The trial was designed to enroll 760 patients with advanced hepatocellular carcinoma (HCC) who previously received sorafenib and may have received up to two prior systemic cancer therapies for hepatocellular carcinoma (HCC) and had adequate liver function. Enrollment of the trial was completed in September 2017, and 773 patients were ultimately randomized. Patients were randomized 2:1 to receive 60 mg of cabozantinib once daily or placebo and were stratified based on etiology of the disease (hepatitis C, hepatitis B or other), geographic region (Asia versus other regions) and presence of extrahepatic spread and/or macrovascular invasion (yes or no). No cross-over was allowed between the study arms.

The primary endpoint for the trial is OS, and secondary endpoints include objective response rate and progression-free survival. Exploratory endpoints included patient-reported outcomes, biomarkers and safety.

Based on available clinical trial data from various published trials conducted in the second-line setting of advanced hepatocellular carcinoma (HCC), the CELESTIAL trial statistics for the primary endpoint of OS assumed a median OS of 8.2 months for the placebo arm. A total of 621 events provide the study with 90 percent power to detect a 32 percent increase in median OS (HR = 0.76) at the final analysis. Two interim analyses were planned and conducted at 50 percent and 75 percent of the planned 621 events.

CELESTIAL trial met its primary endpoint of overall survival (OS), with cabozantinib providing a statistically significant and clinically meaningful improvement in median OS compared to placebo in patients with advanced HCC. The independent data monitoring committee for the study recommended that the trial should be stopped for efficacy following review of the second planned interim analysis. The safety data in the study were consistent with the established profile of cabozantinib.

About hepatocellular carcinoma (HCC)
HCC is an aggressive and lethal disease with the number of deaths per year close to its incidence worldwide.[5] It accounts for about 90% of all liver cancers and there were over 840,000 new cases of liver cancer in worldwide in 2018.[5,6] It is the fifth most common cancer and the second most frequent cause of cancer-related death globally.[7]

About Ipsen products
This press release mentions investigational uses of Ipsen products. Product indications and approvals for use

vary by jurisdiction; please see SmPC/PI for full indications and safety information.

About CABOMETYX® (cabozantinib**)**
CABOMETYX® is not marketed by Ipsen in the U.S.

CABOMETYX® 20mg, 40mg and 60mg film-coated unscored tablets

Active ingredient: Cabozantinib (S)-malate 20mg, 40mg and 60mg

Other components: Lactose

Indications: In the U.S., CABOMETYX® tablets are approved for the treatment of patients with advanced RCC and for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

CABOMETYX® tablets are also approved in: the European Union, Norway, Iceland, Australia, Switzerland, South Korea, Canada, Brazil and Taiwan for the treatment of advanced RCC in adults who have received prior VEGF-targeted therapy; in the European Union for previously untreated intermediate- or poor-risk advanced RCC; in Canada for adult patients with advanced RCC who have received prior VEGF targeted therapy; and in the European Union, Norway and Iceland for HCC in adults who have previously been treated with sorafenib.

CABOMETYX® is not indicated for previously untreated advanced HCC.

Dosage and administration: The recommended dose of CABOMETYX® is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of CABOMETYX therapy. For dose modification, please refer to full SmPC. CABOMETYX® is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking CABOMETYX®.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

Special warnings and precautions for use:
Monitor closely for toxicity during first 8 weeks of therapy. Events that generally have early onset include hypocalcemia, hypokalemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events.

Perforations and fistulas: serious gastrointestinal perforations and fistulas, sometimes fatal, have been observed with cabozantinib. Patients with inflammatory bowel disease, GI tumor infiltration or complications from prior GI surgery should be evaluated prior to therapy and monitored; if perforation and unmanageable fistula occur, discontinue cabozantinib.

Thromboembolic events: use with caution in patients with a history of or risk factors for thromboembolism; discontinue if acute myocardial infarction (MI) or other significant arterial thromboembolic complication occurs.

Hemorrhage: not recommended for patients that have or are at risk of severe hemorrhage.

Wound complications: treatment should be stopped at least 28 days prior to scheduled surgery (including dental).

Hypertension: monitor blood pressure (BP); reduce with persistent hypertension and discontinue should uncontrolled hypertension or hypertensive crisis occur.

Palmar-plantar erythrodysesthesia (PPES): interrupt treatment if severe PPES occurs.

Proteinuria: discontinue in patients with nephrotic syndrome.

Reversible posterior leukoencephalopathy syndrome (RPLS): discontinue in patients with RPLS.

QT interval prolongation: use with caution in patients with a history of QT prolongation, those on antiarrhythmics or with pre-existing cardiac disease.

Excipients: do not use in patients with hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Drug interactions: Cabozantinib is a CYP3A4 substrate. Potent CYP3A4 inhibitors may result in an increase in

cabozantinib plasma exposure (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice). Coadministration with CYP3A4 inducers may result in decreased cabozantinib plasma exposure (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort). Cabozantinib may increase the plasma concentration of P-glycoprotein substrates (e.g. fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). MRP2 inhibitors may increase cabozantinib plasma concentrations (e.g. cyclosporine, efavirenz, emtricitabine). Bile salt sequestering agents may impact absorption or reabsorption resulting in potentially decreased cabozantinib exposure. No dose adjustment when co-administered with gastric pH modifying agents. A plasma protein displacement interaction may be possible with warfarin. INR values should be monitored in such a combination.

Women of childbearing potential/contraception in males and females: Ensure effective measures of contraception (oral contraceptive plus a barrier method) in male and female patients and their partners during therapy and for at least 4 months after treatment.

Pregnancy and lactation: CABOMETYX® should not be used during pregnancy unless the clinical condition of the woman requires treatment. Lactation – discontinue breast-feeding during and for at least 4 months after completing treatment. Drive and use machines: Caution is recommended

Adverse reactions:
The most common serious adverse reactions are hypertension, diarrhea, PPES, pulmonary embolism, fatigue and hypomagnesaemia. Very common (>1/10): anemia, lymphopenia neutropenia, thrombocytopenia, hypothyroidism, dehydration, decreased appetite, hyperglycemia, hypoglycemia, hypophosphatasemia, hypoalbuminemia, hypomagnesaemia, hyponatremia, hypokalemia, hyperkalemia, hypocalcemia, hyperbilirubinemia, peripheral sensory neuropathy, dysgeusia, headache, dizziness, hypertension, dysphonia, dyspnea, cough, diarrhea, nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia, oral pain, dry mouth, PPES, dermatitis acneiform, rash, rash maculopapular, dry skin, alopecia, hair color change, pain in extremity, muscle spasms, arthralgia, proteinuria, fatigue, mucosal inflammation, asthenia, weight decreased, serum ALT, AST, and ALP increased, blood bilirubin increased, creatinine increased, triglycerides increased, white blood cell decreased, GGT increased, amylase increased, blood cholesterol increased, lipase increased. Common (>1/100 to <1/10): abscess, tinnitus, pulmonary embolism, pancreatitis, abdominal pain upper, gastro-esophageal reflux disease, hemorrhoids, pruritus, peripheral edema, wound complications. Uncommon (>1/1000 to <1/100): convulsion, anal fistula, hepatitis cholestatic, osteonecrosis of the jaw. Selected adverse events: GI perforation, fistulas, hemorrhage, RPLS.

Prescribers should consult the SPC in relation to other adverse reactions.

For more information, see the regularly updated registered product information on the European Medicine Agency www.ema.europa.eu

CABOMETYX® is marketed by Exelixis, Inc. in the United States. Ipsen has exclusive rights for the commercialization and further clinical development of CABOMETYX® outside of the United States and Japan.

About Ipsen
Ipsen is a global specialty-driven biopharmaceutical group focused on innovation and specialty care. The group develops and commercializes innovative medicines in three key therapeutic areas – Oncology, Neuroscience and Rare Diseases. Its commitment to Oncology is exemplified through its growing portfolio of key therapies for prostate cancer, neuroendocrine tumors, renal cell carcinoma and pancreatic cancer. Ipsen also has a well-established Consumer Healthcare business. With total sales over €2.2 billion in 2018, Ipsen sells more than 20 drugs in over 115 countries, with a direct commercial presence in more than 30 countries. Ipsen's R&D is focused on its innovative and differentiated technological platforms located in the heart of the leading biotechnological and life sciences hubs (Paris-Saclay, France; Oxford, UK; Cambridge, US). The Group has about 5,700 employees worldwide. Ipsen is listed in Paris (Euronext: IPN) and in the United States through a Sponsored Level I American Depositary Receipt program (ADR: IPSEY). For more information on Ipsen, visit 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 favorable 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 2018 Registration Document available on its website (www.ipsen.com).

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