Press release

Intended for international media and investor audiences only

Ipsen's Iqirvo® receives U.S. FDA accelerated approval as a first-in-class PPAR treatment for primary biliary cholangitis

- ***Iqirvo® (elafibranor) 80 mg tablets is the first new medicine approved in nearly a decade for the treatment of the rare liver disease called primary biliary cholangitis***
- ***Approval based on positive Phase III ELATIVE trial data***
- ***Primary biliary cholangitis impacts approximately 100,000 people in the US and is growing in global prevalence. If inadequately treated, it can cause liver failure***
- ***U.S. approval of Iqirvo establishes Ipsen as a leader in the treatment of rare cholestatic liver diseases***

PARIS, FRANCE, 10 June 2024 Ipsen (Euronext: IPN; ADR: IPSEY) today announced that the U.S. Food and Drug Administration (FDA) has granted accelerated approval for Iqirvo® (elafibranor) 80 mg tablets for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. Iqirvo may be prescribed immediately in the U.S. for eligible patients.

This indication is approved under accelerated approval based on reduction of alkaline phosphatase (ALP). Improvement in survival or prevention of liver decompensation events have not been demonstrated. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Iqirvo is not recommended for people who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).

"For a significant number of people living with PBC, available treatments do not control the condition and may exacerbate symptoms of PBC. Left unmanaged, PBC can progress, leading to liver failure and in some cases, the need for a liver transplant," said Christelle Huguet, Executive Vice President, Head of Research and Development at Ipsen. "Iqirvo demonstrated statistically significant improvements in biochemical response compared to UDCA alone. Iqirvo is therefore a much-needed treatment option and the first new medicine for PBC in nearly a decade."

Iqirvo is a first-in-class oral, once-daily peroxisome proliferator-activated receptor (PPAR) agonist. Iqirvo was in-licensed from GENFIT in 2021. The accelerated approval of Iqirvo is based on data from the Phase III ELATIVE trial published in the *New England Journal of Medicine*[1]. The ELATIVE trial demonstrated that 13 times more patients achieved the composite primary endpoint of biochemical response when treated with Iqirvo plus UDCA (n=108) versus placebo plus UDCA (=53) (respectively 51% versus 4% for a 47% treatment difference). ALP is a biochemical marker and is used as a surrogate endpoint in PBC trials. Secondary endpoints showed normalization in ALP levels in only Iqirvo-treated patients (15% for Iqirvo plus UDCA (n=108) versus 0% for placebo plus UDCA (n=53)). Most patients (95%) received study treatment (Iqirvo or placebo) in combination with UDCA.

The most common adverse reactions with Iqirvo reported in ≥10% of study participants were weight gain, abdominal pain, diarrhea, nausea and vomiting. Some study participants treated with Iqirvo experienced myalgia, myopathy and rhabdomyolysis; fractures; adverse effects on fetal and newborn development; drug-induced liver injury; hypersensitivity reactions; or biliary obstruction. See full Important Safety Information below.

"Data from the pivotal Phase III ELATIVE clinical trial demonstrated that Iqirvo is an effective second-line treatment for patients with PBC with favorable benefit and risk data," said Dr. Kris Kowdley, Director at

Liver Institute Northwest, Washington and a primary investigator on the ELATIVE study. “The approval of Iqirvo will allow healthcare providers in the U.S. to address an unmet need with the potential to significantly reduce ALP levels for our patients with PBC.”

PBC is a rare, autoimmune, cholestatic liver disease where a build-up of bile and toxins (cholestasis) and chronic inflammation causes irreversible fibrosis (scarring) of the liver and destruction of the bile ducts. Impacting approximately 100,000 people in the U.S.[2], the majority being women, PBC is a lifelong condition that can worsen over time if not effectively treated, leading to liver transplant and in some cases, premature death. PBC also affects day-to-day life, with people most commonly experiencing severe fatigue symptoms and debilitating itch (pruritus).

“People living with PBC can feel like the symptoms they experience are dismissed by family members, friends or even their doctors, because they have not experienced something similarly disruptive in their lives. People with PBC may also feel uncertainty around the disease progression and if, or when, their liver health may deteriorate,” said Carol Roberts, Executive President of PBCers, a patient advocacy organization in the U.S. providing support to people living with PBC. “Earlier diagnosis and education about PBC, along with new treatment options are important to meet the current needs of people living with PBC.”

Iqirvo has been submitted to the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), seeking authorization for PBC, with final EMA and MHRA regulatory decisions anticipated in the second half of 2024. The FDA approval of Iqirvo further strengthens Ipsen’s portfolio of treatments for rare cholestatic liver diseases available to patients in the U.S. This includes our FDA approved medicine for the treatment of pruritus in patients three months and older with progressive familial intrahepatic cholestasis (PFIC) and for the treatment of cholestatic pruritus in patients from 12 months of age with Alagille syndrome (ALGS).

IMPORTANT SAFETY INFORMATION

Myalgia, Myopathy, and Rhabdomyolysis: Rhabdomyolysis resulting in acute kidney injury occurred in one IQIRVO-treated patient who had cirrhosis at baseline and was also taking a stable dose of an HMG-CoA reductase inhibitor (statin). Myalgia or myopathy, with or without CPK elevations, occurred in patients treated with IQIRVO alone or treated concomitantly with a stable dose of an HMG-CoA reductase inhibitor. Assess for myalgia and myopathy prior to IQIRVO initiation. Consider periodic assessment (clinical exam, CPK measurement) during treatment with IQIRVO, especially in those who have signs and symptoms of new onset or worsening of muscle pain or myopathy. Interrupt IQIRVO treatment if there is new onset or worsening of muscle pain, or myopathy, or rhabdomyolysis.

Fractures: Fractures occurred in 7% of IQIRVO-treated patients compared to no placebo-treated patients. Consider the risk of fracture in the care of patients treated with IQIRVO and monitor bone health according to current standards of care.

Adverse Effects on Fetal and Newborn Development: IQIRVO may cause fetal harm when administered during pregnancy. For females of reproductive potential, verify that the patient is not pregnant prior to initiation of therapy. Advise females of reproductive potential to use effective non-hormonal contraceptives or add a barrier method when using systemic hormonal contraceptives during treatment with IQIRVO and for 3 weeks following the last dose of IQIRVO.

Drug-Induced Liver Injury: Suspected drug-induced liver injury occurred in one patient who took IQIRVO 80 mg once daily and two patients who took IQIRVO at 1.5-times the recommended dosage, of which one presented with autoimmune-like hepatitis. The median time to onset of elevation in liver tests was 85 days. Obtain baseline clinical, laboratory and imaging assessments at treatment initiation with IQIRVO and monitor thereafter according to routine patient management. Interrupt IQIRVO treatment if liver tests (ALT, AST, total bilirubin [TB], and/or alkaline phosphatase [ALP]) worsen, or the patient develops signs and symptoms consistent with clinical hepatitis (e.g., jaundice, right upper quadrant pain, eosinophilia). Consider permanent discontinuation if liver tests worsen after restarting IQIRVO.

Hypersensitivity Reactions: Hypersensitivity reactions have occurred in a clinical trial with IQIRVO at 1.5-times the recommended dosage. Three patients (0.2%) had rash or unspecified allergic reaction that occurred 2 to 30 days after IQIRVO initiation. Hypersensitivity reactions resolved after discontinuation of IQIRVO and treatment with steroids and/or antihistamines. If a severe hypersensitivity reaction occurs, permanently discontinue IQIRVO. If a mild or moderate hypersensitivity reaction occurs, interrupt IQIRVO and treat promptly. Monitor the patient until signs and symptoms resolve. If a hypersensitivity reaction recurs after IQIRVO rechallenge, then permanently discontinue IQIRVO.

Biliary Obstruction: Avoid use of IQIRVO in patients with complete biliary obstruction. If biliary obstruction is suspected, interrupt IQIRVO and treat as clinically indicated.

Drug-Drug Interactions
IQIRVO may reduce the systemic exposure of progestin and ethinyl estradiol (CYP3A4 substrates), which may lead to contraceptive failure and/or an increase in breakthrough bleeding. Switch to effective non-hormonal contraceptives or add a barrier method when using hormonal contraceptives during treatment with IQIRVO and for at least 3 weeks after last dose.

CPK elevation and/or myalgia occurred in patients on IQIRVO monotherapy. Co-administration of IQIRVO and HMG-CoA reductase inhibitors can increase the risk of myopathy. Monitor for signs and symptoms of muscle injury. Consider periodic assessment (clinical exam, CPK) during treatment. Interrupt IQIRVO treatment if there is new onset or worsening of muscle pain or myopathy.

Co-administration of IQIRVO with rifampin, an inducer of metabolizing enzymes, may reduce the systemic exposure of elafibranor resulting in delayed or suboptimal biochemical response. Monitor the biochemical response (e.g., ALP and bilirubin) when patients initiate rifampin during treatment with IQIRVO.

Bile acid sequestrants may interfere with IQIRVO absorption and systemic exposure, which may reduce efficacy. Administer IQIRVO at least 4 hours before or after a bile acid sequestrant, or at as great an interval as possible.

Use in Special Populations
Pregnancy: Based on data from animal reproduction studies, IQIRVO may cause fetal harm when administered during pregnancy. There are insufficient data from human pregnancies exposed to IQIRVO to allow an assessment of a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Report pregnancies to Ipsen Pharmaceuticals, Inc. Adverse Event reporting line at 1-855-463-5127 or https://www.ipsen.com/contact-us/.

Lactation: There are no data available on the presence of IQIRVO or its metabolites in human milk, or on effects of the drug on the breastfed infant or the effects on milk production. IQIRVO is not recommended during breastfeeding and for at least 3 weeks following last dose of IQIRVO because the risk to breastfed child cannot be excluded.

Females and Males of Reproductive Potential: IQIRVO may cause fetal harm when administered to pregnant women. Verify the pregnancy status of females of reproductive potential prior to initiating IQIRVO. Advise females of reproductive potential to use effective contraception during treatment with IQIRVO and for 3 weeks after the final dose.

The most common adverse events occurring in ≥10% of patients were weight gain (23%), abdominal pain (11%), nausea (11%), vomiting (11%), and diarrhea (11%).

You are encouraged to report side effects to FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Ipsen Pharmaceuticals at 1-855-463-5127.

Please see full Prescribing Information for IQIRVO.

About Iqirvo

Iqirvo (pronounced EYE-KER-VO) is an oral, once-daily, peroxisome proliferator-activated receptor (PPAR) agonist indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. While the mechanism is not well understood, pharmacological activity that is potentially relevant to Iqirvo therapeutic effects includes inhibition of bile acid synthesis through activation of PPAR-alpha and PPAR-delta. In 2019, Iqirvo was granted Breakthrough Therapy Designation by the U.S Food and Drug Administration (FDA) in adults with PBC who have an inadequate response to ursodeoxycholic acid (UDCA) the existing first-line therapy for PBC. Iqirvo has not received approval by regulatory authorities outside of the U.S. Iqirvo is currently under regulatory review with the European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). Iqirvo was discovered and developed by GENFIT and Ipsen licensed the exclusive worldwide rights (except China, Hong Kong, Taiwan and Macau) to elafibranor from GENFIT in 2021.

Iqirvo has been granted approval under the FDA accelerated approval program, which allows for approval of medicines that treat serious conditions and fill an unmet medical need based on a surrogate endpoint. Under the program, Ipsen is required to conduct a trial to confirm anticipated clinical benefit. The confirmatory trial for Iqirvo, ELFIDENCE, is ongoing.

Iqirvo is an 80 mg tablet administered orally once daily. To ensure access to Iqirvo for eligible individuals in the U.S., the IPSEN CARES® patient support program is available as a resource to people living with PBC and their caregivers to provide educational support and address coverage, access and reimbursement questions (1-866-435-5677).

About the Phase III ELATIVE trial

ELATIVE is a multi-center, randomized double-blind, placebo-controlled Phase III clinical trial (n=161) that evaluated the efficacy and safety of Iqirvo 80mg once daily plus UDCA (n=108) versus placebo plus UDCA (n=53). Iqirvo or placebo was administered in combination with UDCA in 95% of patients and as monotherapy in 5% of patients who were unable to tolerate UDCA. The 52-week study was completed by 92% of participants with 97% of those who completed the study continuing in an extension study. The results were published in the *New England Journal of Medicine*[1].

- The ELATIVE trial demonstrated that Iqirvo had a statistically significant treatment benefit with 51% of patients on Iqirvo achieving a biochemical response compared with 4% on the placebo arm, a treatment benefit of 47% (95% CI 32, 57; p<0.0001). Biochemical response was defined as ALP less than 1.67 Upper Limit of Normal (ULN), an ALP decrease of greater than or equal to 15% from baseline and total bilirubin (TB) ≤ ULN at week 52.
- ALP normalization at week 52 was a key secondary endpoint with 15% of Iqirvo-treated patients demonstrating normalization versus 0% placebo (p=0.002).
- The significant biochemical response to Iqirvo was further supported by data demonstrating reductions from baseline in ALP levels were sustained through week 52 and response was rapid, seen as early as Week 4 in the Iqirvo group.
- The most common adverse reactions with Iqirvo reported in ≥10% of study participants were weight gain, abdominal pain, diarrhea, nausea and vomiting.

ENDS

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 (0)7584 34 91 93**
- **Nicolas Bogler | + 33 6 52 19 98 92**

Media

- **Amy Wolf | + 41 79 576 07 23 | amy.wolf@ipsen.com**
- **Rachel Reiff | + 1 908 616 1680 | rachel.reiff@ipsen.com**
- **Anna Gibbins | + 44 7717 80 19 00| anna.gibbins@ipsen.com**

Disclaimers and/or Forward-Looking Statements

Ipsen

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. Kowdley. K.V, et al. Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. NEJM. 2023. DOI: 10.1056/NEJMoa2306185
2. Lu M, Zhou, et al. Fibrotic Liver Disease Consortium Investigators. Increasing Prevalence of Primary Biliary Cholangitis and Reduced Mortality With Treatment. Clin Gastroenterol Hepatol. 2018 Aug;16(8):1342-1350.e1. DOI: 10.1016/j.cgh.2017.12.033.