Press release

Intended for media and investor audiences only

Iqirvo® (elafibranor) data shows efficacy and safety for up to 3 years in patients with PBC with improvements in fatigue and pruritus

- ***Ipsen presents 3 late-breaking presentations and 8 abstracts across rare cholestatic liver disease portfolio at AASLD 2024***
- ***Iqirvo approved for use in the U.S. in June 2024, in the E.U. in September 2024 and in the U.K. in October 2024***

PARIS, FRANCE, 15 November 2024 Ipsen (Euronext: IPN; ADR: IPSEY) announced today late-breaking data for Iqirvo® (elafibranor 80 mg tablets) from an interim analysis of the ongoing open-label extension of the Phase III ELATIVE® study at the American Association for the Study of Liver Disease (AASLD) congress. The late-breaking presentations (Abstract #5041 and Abstract #5042) report on biomarkers of cholestasis, stabilization of surrogate markers of liver fibrosis and moderate-to-severe pruritus data for up to three years in Iqirvo-treated patients. Additionally, exploratory endpoints in fatigue and sleep were evaluated using patient-reported outcomes tools.

"Over three years, Iqirvo data suggest sustained efficacy and support the safety profile of the medicine. Importantly, when patients tell me they are less impacted by itch and fatigue—that matters to me as a physician," said Dr. Kris Kowdley, Director at The Liver Institute Northwest, Washington and a primary investigator on the ELATIVE study. "Treatment with Iqirvo had an impact on symptoms of pruritus and surrogate markers of fibrosis, which are important findings for people living with PBC."

"Fatigue is a symptom often reported by people living with PBC and is also very challenging to manage," said Dr. Mark Swain, Department of Medicine, Cumming School of Medicine, University of Calgary, Canada. "Patients treated with Iqirvo reported improvement in fatigue and sleep, across several patient-reported outcome measures."

The open-label extension (OLE) included 138 patients who completed the double-blind period of the Phase III ELATIVE® study[1]. This interim analysis was performed after at least one year of treatment with Iqirvo in the OLE (up to three years total). In patients receiving three years of continuous treatment with Iqirvo across the double-blind period and OLE (n=13), 85 percent had a biochemical response (n=11/13; ALP <1.67 x ULN, with ≥ 15% reduction from baseline and total bilirubin ≤ ULN) and 39 percent achieved ALP normalization (n=5/13) at week 156. Surrogate markers of liver fibrosis, liver stiffness measurements (n=23) and enhanced liver fibrosis (ELF™) (n=19) scores, suggest stabilization when measured from baseline to week 130. In patients continuously receiving Iqirvo for up to 156 weeks, pruritus improvements were sustained for patients with moderate or severe pruritus at baseline (n=5).

No new safety findings were observed. The most common treatment-emergent adverse events (>10 percent) occurring more frequently in patients treated with Iqirvo than placebo in the double-blind period of the trial (abdominal pain, diarrhea, nausea and vomiting) were also reported in the OLE.

The impact of Iqirvo on fatigue and sleep were investigated as an exploratory endpoint in the OLE.[2] Changes in fatigue or sleepiness (including normal sleep) were reviewed from baseline to week 104 looking at the minimal clinically important differences and categorical changes (n=48). Fatigue and sleep improvements for patients treated with Iqirvo were observed at week 104 across three patient-reported outcome (PRO) tools. In patients with moderate-to-severe fatigue or excessive sleepiness at baseline, clinically meaningful improvements were observed after 104 weeks of treatment with Iqirvo in 56 percent (n=18) of patients according to the PRO Measurement Information System (PROMIS) Fatigue Short Form 7a, 50 percent (n=24) of patients according to the fatigue domain of the PBC-40, and 69 percent (n=16) of patients according to the Epworth Sleepiness Scale (ESS). These are interim data and have not been submitted to regulatory agencies. A confirmatory study of Iqirvo is ongoing (NCT06016842).

"People living with PBC tell us just how devastating this disease can be for patients and their families," said Sandra Silvestri, EVP and Chief Medical Officer, Ipsen. "Data like these continue to provide prescribers with a clear rationale for Iqirvo. As the first-in-class PPAR approved for the treatment of PBC, Iqirvo is on track to be the treatment of choice for patients living with PBC. Ipsen is committed to being a leader the rare liver community can count on."

About 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.,[3] the majority being women, PBC is a lifelong condition that can worsen over time if not effectively treated, may lead to liver transplant and in some cases, premature death. The high symptom burden of PBC can also have an impact on daily life.

Iqirvo (elafibranor) posters presented at AASLD

Poster or Oral #	Full Title	Authors
Poster, Abstract [5041] **Monday 18 November 13:00–14:00 Poster Session IV**	Long-term efficacy and safety of elafibranor in primary biliary cholangitis: Interim results from the open-label extension of the ELATIVE® trial up to 3 years	**Kris V. Kowdley et al.**
Poster, Abstract [5042] **Monday 18 November 13:00–14:00 Poster Session IV**	Impact of elafibranor on fatigue in patients with primary biliary cholangitis: Interim results from the long-term open-label extension of the ELATIVE® trial	**Mark Swain et al.**
Poster, Abstract [4274] **Monday 18 November 13:00–14:00 Poster Session IV**	Beyond the mean: Exploring the impact of baseline alkaline phosphatase levels on endpoints in primary biliary cholangitis	**Cynthia Levy et al.**
Oral, Abstract Parallel, ePoster [43] **Monday 18 November 11:00–11:15 Human Cholestatic, PBC and other Biliary Disorders in Children and Adults**	One-year treatment with elafibranor in the Phase III ELATIVE® trial improves GLOBE and UK-PBC prognostic scores	**Kris V. Kowdley et al.**
Poster, Abstract [4292] **Monday 18 November 13:00–14:00 Poster Session IV**	Use of machine learning (ML) models to stratify response patterns to first-line treatment of primary biliary cholangitis (PBC) with ursodeoxycholic acid (UDCA)	**Seema T. Meloni et al.**
Poster, Abstract [4349] **Monday 18 November 13:00–14:00 Poster Session IV**	Elafibranor has no impact on markers of renal function in primary biliary cholangitis: results from the Phase III ELATIVE® trial	**Marcelo Kugelmas et al.**
Poster, Abstract [4358] **Monday 18 November 13:00–14:00 Poster Session IV**	Economic burden of patients with primary biliary cholangitis and experiencing fatigue or pruritus in the United States	**Nisreen Shamseddine et al.**

About Iqirvo® (elafibranor) 80 mg tablet

Iqirvo is an oral, once-daily, peroxisome proliferator-activated receptor (PPAR), 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 was granted U.S. FDA accelerated approval in June 2024, EU conditional approval by the EMA in September 2024 and UK Medicines and Healthcare products Regulatory Agency (MHRA) approval in October 2024, 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. The FDA and EMA approvals are contingent on the further verification of clinical benefit. Iqirvo is currently in regulatory processes with other authorities. Iqirvo (elafibranor) was developed by GENFIT. Ipsen licensed the exclusive worldwide rights (except China, Hong Kong, Taiwan and Macau) to elafibranor from GENFIT in 2021.

INDICATION

IQIRVO® is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

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).

Limitations of Use

Use of IQIRVO is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).

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 6% 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: 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 and laboratory 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 Biopharmaceuticals, 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 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Ipsen Biopharmaceuticals, Inc. at 1-855-463-5127.

Please see full Prescribing Information for IQIRVO in the U.S.
Please see full Prescribing Information for IQIRVO in the E.U.

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

- **Nicolas Bogler | + 33 6 52 19 98 92**

Media

- **Jennifer Smith-Parker | + 44 7843137764 | jennifer.smith-parker.ext@ipsen.com**
- **Rachel Reiff | + 1 908 616 1680 | rachel.reiff@ipsen.com**
- **Anna Gibbins | + 44 7717 80 19 00| anna.gibbins@ipsen.com**

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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

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References

[1]Kowdley. K,. et al. Long term efficacy and safety of elafibranor in primary biliary cholangitis: Interim results from the open-label extension of the ELATIVE® trial up to 3 years . Poster, Abstract 5041. American Association for the Study of Liver Disease (AASLD).2024

[2].Swain. M, et al. Impact of elafibranor on fatigue in patients with primary biliary cholangitis: Interim results from the long-term open-label extension of the ELATIVE® trial . Poster, Abstract 5042. American Association for the Study of Liver Disease (AASLD).2024

[3]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.