Press release

Intended for international media and investor audiences only

Ipsen receives CHMP positive opinions for Iqirvo® (elafibranor) in Primary Biliary Cholangitis and Kayfanda® (odevixibat) in Alagille Syndrome, two rare cholestatic liver diseases

- ***CHMP positive opinion for Iqirvo® (elafibranor) recommended for the treatment of primary biliary cholangitis, following FDA approval in June 2024***
- ***CHMP positive opinion for Kayfanda® (odevixibat) recommended for cholestatic pruritus in patients with Alagille syndrome***
- ***Final European Commission decision for both medicines expected in Q3 2024***
- ***Ipsen continues to build leading rare cholestatic liver disease portfolio with these two new indications anticipated for approval in Europe***

PARIS, FRANCE, 26 July 2024 - Ipsen (Euronext: IPN; ADR: IPSEY) announced today two positive opinions by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) for two different rare cholestatic liver disease medicines from the company's growing portfolio. Iqirvo® (elafibranor) has been recommended for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as a monotherapy in patients unable to tolerate UDCA. Kayfanda® (odevixibat) has also received a positive opinion from CHMP as a treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older. The European Commission will now consider the CHMP recommendations. Final decisions on marketing authorization for Iqirvo and for Kayfanda are anticipated in Q3, 2024.

"We are delighted to have received CHMP positive opinions for two potential new medicines in rare cholestatic liver diseases, on the same day. A rare achievement, and one that demonstrates our commitment to addressing the unmet medical needs in these diseases, said Christelle Huguet, Executive Vice President, Head of R&D. "PBC can progress to liver damage and even liver failure without effective therapies. Today's decision takes us closer to being able to offer Iqirvo as a new treatment for patients, which significantly improves biomarkers that predict disease progression, without worsening symptoms. Also, with the positive opinion for Kayfanda we are moving forward in our efforts to provide a new treatment option for children with Alagille Syndrome, whose liver health can deteriorate rapidly and who often endure a very poor quality of life."

Iqirvo and PBC

Iqirvo is a first-in-class, oral, peroxisome proliferator-activated receptor (PPAR) agonist. Iqirvo was in-licensed by Ipsen from Genfit in 2021. The CHMP positive opinion is based mainly on data from the Phase III ELATIVE trial. The composite endpoint was achieved with results demonstrating statistically significant improvements in alkaline phosphatase (ALP) and total bilirubin (TB), biomarkers of PBC disease progression. For the key secondary endpoint using the PBC Worst Itch NRS score a trend towards improvement in pruritus (itch) was observed for elafibranor versus placebo, which was not statistically significant. Two other secondary patient-reported outcome measures were used to assess itch, and greater reductions were observed with Iqirvo compared with placebo at Week 52, according to the itch domain of PBC-40 quality of life questionnaire (LS mean difference -2.3; 95% CI, -4.0 to -0.7) and 5-D Itch total score (LS mean difference, -3.0; 95% CI, -5.5 to -0.5).[1]

"PBC is a progressive disease with a high number of patients who either don't respond or can't tolerate the current available treatments. This can result in ongoing disease progression, which may not be picked up until the patient's next doctor's appointment, which can be as long as 12 months between visits in some cases," said Professor Marco Carbone, Professor of Gastroenterology, University of Milano-Bicocca and Consultant Hepatologist, the Niguarda Liver Transplant Centre, Milan. "It is important that we not only regularly review our PBC patients to ensure the levels of alkaline phosphatase, or ALP, and bilirubin are within normal limits, but that we also discuss symptoms that might impair patients' quality of life potentially leading to withdrawal from current treatments."

"It is helpful for people diagnosed with PBC to understand that disease progression is monitored through levels of biomarkers in the blood, such as ALP," said Patient Advocate, Mrs Sindee Weinbaum from European Liver Patients' Association. "Being aware of these levels helps the person living with PBC to be more in control of their condition and to have constructive conversations with their doctor about how to control their symptoms and about what treatment is right for them. This is important for people living with PBC who can sometimes feel unheard."

Kayfanda and Alagille Syndrome

Kayfanda's CHMP positive opinion is based on the ASSERT Phase III clinical trial data, presented at the 2022 American Association for the Study of Liver Disease (AASLD) congress and recently published in *Lancet Gastroenterology & Hepatology*.[2] ASSERT is the world's first and only Phase III trial completed in patients with ALGS. The data demonstrated efficacy of odevixibat in pruritus, a measure of treatment benefit, based on the worst scratching score using an observer-reported outcome instrument. Results demonstrated statistically significant and clinically meaningful improvements from baseline to month 6, in scratching severity, for odevixibat versus placebo, which was seen rapidly and maintained over the study period.

"Effective and well-tolerated treatments that can manage the debilitating itch caused by Alagille Syndrome and reduce the concentration of bile acids in the blood, are of great importance in our management and care of children with this condition and it is a positive development that there may soon be a new treatment option available," said Professor Henkjan Verkade, Pediatric Gastroenterology and Hepatology, Department of Pediatrics, University of Groningen, Beatrix Children's Hospital and University Medical Center Groningen, Netherlands. "This condition leads to multiple complications, it is however the intense itch experienced by these children and resulting sleep disturbances that is reported by the vast majority of people living with and caring for a child with liver disease due to Alagille Syndrome, as being the most significant."

In the ASSERT trial efficacy was also demonstrated on the key secondary endpoint showing a statistically significant reduction in serum bile acid concentration at the end of treatment for patients on odevixibat compared to placebo. Consistent with the improvements observed in pruritus, treatment with odevixibat led to significant improvements in multiple observer-reported outcome sleep parameters. The overall incidence of treatment emergent adverse events with odevixibat was similar to placebo, with a low drug-related diarrhea rate in patients with ALGS. All patients completed the study and 50 out of 52 patients have joined the extension study with all receiving odevixibat.[2]

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About PBC

PBC is a rare, autoimmune, cholestatic liver disease, affecting approximately nine women for every one man. A build-up of bile and toxins (cholestasis) and chronic inflammation causes fibrosis (scarring) of the liver and destruction of the bile ducts. It is a life-long condition that can worsen over time if not effectively treated, leading to liver transplant and in some cases, premature death. PBC impacts patients' daily lives through debilitating symptoms including most commonly pruritus and fatigue. Currently, there are no

approved treatments available that can effectively manage both disease progression and life-impacting symptoms.

About Iqirvo® (elafibranor)

Iqirvo® (pronounced EYE-KER-VO) is an oral, once-daily, peroxisome proliferator-activated receptor (PPAR) agonist, which exerts an effect on PPARα and PPARδ, which are thought to be key regulators of bile acid (BA) homeostasis, inflammation and fibrosis. Pharmacological activity that is potentially relevant to Iqirvo therapeutic effects includes inhibition of bile acid synthesis through activation of PPARα and PPARδ. The proposed indication is 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. 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). UCDA being 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 awaiting a final decision from the European Commission. It is also in regulatory processes with other authorities including the UK Medicines and Healthcare products Regulatory Agency (MHRA). Iqirvo (elafibranor) 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.

About ELATIVE

ELATIVE[1] is a multi-center, randomized, double-blind, placebo-controlled Phase III clinical trial, with an open-label long-term extension (NCT04526665). ELATIVE evaluated the efficacy and safety of elafibranor 80mg once daily versus placebo for the treatment of patients with PBC with an inadequate response or intolerance to ursodeoxycholic acid (UDCA), the existing first-line therapy for PBC. The trial enrolled 161 patients who were randomized 2:1 to receive elafibranor 80mg once daily or placebo. Patients with an inadequate response to UDCA would continue to receive UDCA in combination with elafibranor or placebo, while patients unable to tolerate UDCA would receive only elafibranor or placebo. Patients continued their assigned treatment after Week 52 until all patients had completed their treatment or for a maximum of 104 weeks. Data was also collected during this period, and additional analyses were conducted with a focus on Week 78.

In the trial, results show statistically significant improvements in the primary composite endpoint of biochemical response, defined as alkaline phosphatase (ALP) <1.67 x upper limit of normal (ULN), an ALP decrease ≥ 15 percent and total bilirubin (TB) ≤ ULN at 52 weeks, with a significant treatment benefit demonstrating a 47% placebo-adjusted difference (P<0.001) between patients on elafibranor 80mg (51%) compared with patients on placebo (4%) achieving a biochemical response. ALP and bilirubin are important predictors of PBC disease progression. Reductions in levels of both can indicate reduced cholestatic injury and improved liver function.

Only patients receiving elafibranor achieved normalization of ALP (upper limit of normal 104 U/L in females and 129 U/L in males) at Week 52 (15% vs 0% placebo, P=0.002), a key secondary endpoint of the trial. The significant biochemical effect of elafibranor measured by ALP reduction was further supported by data demonstrating reductions from baseline in ALP levels were rapid, seen as early as Week 4 in the elafibranor group, and were sustained through Week 52, with a decrease in ALP of 41% on elafibranor compared with placebo.

Elafibranor was well tolerated in the trial. Similar percentages of patients in the treatment group and the placebo group experienced adverse events, treatment-related adverse events, severe or serious adverse events or adverse events leading to discontinuation. Adverse events occurring in >10% of patients and more frequently on elafibranor versus placebo included abdominal pain, diarrhea, nausea, and vomiting.

About ALGS

ALGS is an inherited rare, genetic disorder that can affect multiple organs including the liver, heart, skeleton, eyes and kidneys. Liver damage may result from having fewer than normal, narrowed or

malformed bile ducts, which leads to a build-up of toxic bile acid, known as cholestasis and this in turn can cause fibrosis and progressive liver disease. Approximately 95% of patients with the condition present with chronic cholestasis, usually within the first three months of life and as many as 88% also present with severe, intractable pruritus or itch. The estimated global incidence of ALGS is 3 in 100,000 live births.

About Kayfanda® (odevixibat)

Kaydanda® (odevixibat) is a once-daily non-systemic ileal bile acid transport (IBAT) inhibitor being investigated in the E.U. for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older. Odevixibat was approved in June 2021 in the E.U. under the brand name Bylvay ®, as the first drug treatment option for all types of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older, and in the U.S. under the brand name Bylvay®, as the first drug treatment option for patients 3 months of age and older living with cholestatic pruritus due to PFIC. Bylvay has received orphan exclusivity for the treatment of PFIC in the E.U. and in the U.S. In June 2023 Bylvay was approved in the U.S. for the treatment of cholestatic pruritus in patients from 12 months of age with ALGS and received orphan exclusivity for ALGS. In October 2023, while the EMA's CHMP recommended the approval of Bylvay in ALGS, the EMA's Committee for Orphan Medicinal Products (COMP) recommended not to maintain orphan exclusivity in the E.U. for Bylvay in ALGS. In order to ensure sustainable access and availability for Bylvay in the approved indication for the treatment of PFIC, which is supported by orphan drug status, odevixibat for the treatment of ALGS has been resubmitted to the EMA under a new brand name, Kayfanda, without orphan designation and is currently awaiting a final decision from the European Commission.

About ASSERT

ASSERT[2] is a double-blind, randomized, placebo-controlled trial designed to evaluate the safety and efficacy of 120 µg/kg/day Bylvay (odevixibat) for 24 weeks in relieving pruritus in patients with ALGS conducted in 52 patients with 32 sites across North America, Europe, Middle East, and Asia Pacific.

The trial enrolled patients aged 0 to 17 years of age with a genetically confirmed diagnosis of ALGS. In the primary analysis, the study met the primary endpoint showing highly statistically significant improvement in pruritus for patients on odevixibat as measured by the PRUCISION Observer-Reported Outcome scratching score (0-4 point scale), from baseline at month 6 (weeks 21 to 24), compared to the placebo arm (p=0.002). More than 90% of patients were pruritus responders (≥ 1 point change at any time during 24 weeks).

The study also met the key secondary endpoint showing a highly statistically significant reduction in serum bile acid concentration from baseline to the average of weeks 20 and 24 (compared to the placebo arm p=0.001). Statistically significant improvements in multiple sleep parameters were observed as early as weeks 1-4 compared to patients on placebo with continued improvement through week 24.

In the study, there were no patient discontinuations and 96% of patients rolled over into the open-label extension study. Bylvay had an overall adverse event incidence similar to placebo and a low incidence of drug-related diarrhea (11.4% vs. 5.9% placebo).

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

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 fuelled 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 | craig.marks@ipsen.com**
- **Nicolas Bogler | + 33 6 52 19 98 92 | nicolas.bogler@ipsen.com**

Media

- **Amy Wolf | + 41 79 576 07 23 | amy.wolf@ipsen.com**
- **Anna Gibbins | + 44 7717 80 19 00| anna.gibbins@ipsen.com**

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