Press release

Intended for media and investor audiences only

Bylvay® (odevixibat) data shows sustained improvement in severe itch and serum bile acid levels in patients with PFIC and ALGS

» ***Ipsen presents 3 late-breaking presentations and 8 abstracts across rare cholestatic liver disease portfolio at AASLD 2024***

PARIS, FRANCE., 18 November, 2024 Ipsen (Euronext: IPN; ADR: IPSEY) today announced data at the American Association for the Study of Liver Diseases (AASLD) assessing the long-term efficacy and safety of patients treated with Bylvay® from two Phase III open-label extension studies: late-breaking abstract (#5045) on PEDFIC 2 in Progressive Familial Intrahepatic Cholestasis (PFIC) and oral presentation ASSERT-EXT (#50) in Alagille syndrome (ALGS). Sustained efficacy data and improvements in height, weight and sleep measures were observed for patients treated with Bylvay for at least 72 weeks in both rare cholestatic diseases.

"We know from our work with patient communities that receiving a diagnosis of PFIC and ALGS can be overwhelming in a patient or caregivers' life. Disease symptoms like severe itch can have an impact on the whole family," said Sandra Silvestri, EVP Chief Medical Officer, Ipsen. "Data suggesting Bylvay-treated patients experienced sustained efficacy, and which support the safety and tolerability profile seen in previous clinical trials, are important. Ipsen is committed to being the leader across rare cholestatic liver diseases and we are just getting started."

PEDFIC 2 Study in PFIC

"These open-label extension data from PEDFIC 2 suggest that the initial reduction in pruritus and in serum bile acid levels achieved following initiation of odevixibat are being sustained into the longer term," said Dr. Richard J. Thompson, Professor of Molecular Hepatology, King's College London and principal investigator of the PEDFIC 2 trial. "We are also observing reductions in both pruitus and serum bile acid across a number of PFIC subtypes. This is important information for our understanding of the therapeutic management of our patients living with PFIC."

PEDFIC 2 was an open-label extension study (n=116; patients from PEDFIC 1 Bylvay and placebo cohorts at week 24, and new Bylvay-naïve patients of any age and PFIC subtype), evaluating the efficacy and safety of Bylvay through 72 weeks (n=83).[1] The data showed a clinically meaningful 1-point reduction in pruritus score at week 72 in 42 percent of patients <18 years old with PFIC 1 and 2 who transitioned to Bylvay at 24 weeks (n=5/12) and 61 percent of patients with any type of PFIC and of any age excluding episodic (n=19/31). Rapid initial pruritus scores achieved by week 4 were sustained for patients who remained on treatment. At 72 weeks, the mean change in serum bile acid (sBA) levels from patients who transition to Bylvay at week 24 (n=15) was −104.00 µmol/L and Bylvay-treated patients (n=43) was -57.97 µmol/L .

Beyond the clinically meaningful and sustained improvements seen in pruritus and sBA levels, height, weight and sleep increases were reported at 72 weeks in Bylvay-treated patients. Most adverse events in Bylvay-treated patients over the duration of the study were reported as mild or moderate. The most common were gastrointestinal (17.2 percent; n=20/116), including diarrhea (12 percent; n=14/116). In two cases, diarrhea led to one treatment interruption and one discontinuation.

Assert-EXT Study in ALGS

"The sustained improvements we've seen in Bylvay-treated individuals living with Alagille syndrome are encouraging," said Dr. Nadia Ovchinsky, Chief, Division of Gastroenterology and Hepatology, Hassenfeld Children's Hospital at NYU Langone, New York. and principal investigator of the ASSERT trial. "These results not only show the potential to manage symptoms like pruritus, which can be extremely difficult for children and their parents to manage, but we're also seeing a consistent safety profile over the longer term with sustained tolerability."

In ASSERT-EXT, the open-label extension study (n=50) evaluating the long-term efficacy and safety of Bylvay in ALGS patients (ages 1-15.9 years) through 72 weeks (n=44), sustained improvements were observed in pruritus and sBA levels through 72 weeks.[2] At week 72, 93 percent (n=28/30) of patients who received Bylvay throughout the 24 weeks ASSERT trial and 77 percent (n=10/13) of those who transitioned from placebo to Bylvay at week 24 experienced a clinically meaningful ≥1 point reduction in pruritus score. Reductions in sBA levels were also observed in patients treated with Bylvay for 72 weeks showing a mean reduction of 124 µmol/L in those who continuously received Bylvay and a mean reduction of 139 µmol/L in patients who transitioned from placebo to Bylvay. Mean changes from baseline were observed in height (8.2 cm) and weight (2.8 kg) on continuous Bylvay use and for patients who transitioned from placebo to Bylvay, height (10.7 cm) and weight (3.3 kg) mean changes were also reported.

Improvements in sleep were observed from weeks 24 to 72 across all four sleep parameters (n=43), including proportion of days seeing blood due to scratching, proportion of days needing help falling asleep, proportion of days needing soothing and daytime tiredness. Data supports the safety profile in the ASSERT clinical trial for Bylvay. Treatment emergent adverse event (TEAE) occurred in 18 percent (n=6/33) of patients who continuously received Bylvay and 41 percent (n=7/17) of patients who transitioned from placebo to Bylvay. Most adverse events were mild or moderate with diarrhea as the most common TEAE. One TEAE led to discontinuation.

About PFIC and ALGS

PFIC is a group of rare genetic disorders in which bile acids build up in the liver, causing damage, which may result in liver failure. ALGS is also a rare genetic disorder, affecting multiple organs including the liver, heart, skeleton, eyes and kidneys. Without early diagnosis and effective management, people living with PFIC and ALGS may need a liver transplant. Debilitating itch, caused as a result of the serum bile acid build up, is one of the most common symptoms of both PFIC and ALGS, significantly impacting sleep and daily activities and resulting in skin mutilation, loss of sleep, irritability, and poor attention.

Bylvay (odevixibat) posters presented at AASLD

Abstract	Poster or Oral #	Full title	Authors
ASSERT-EXT final results	*Oral, Abstract Parallel, ePoster [50]* **Monday 18 November** 11:45–12:00 Human Cholestatic, PBC and other Biliary Disorders in Children and Adults	ASSERT-EXT: Final data from an open-label, Phase 3 study of odevixibat in patients with Alagille syndrome	**Nadia Ovchinsky et al.**
Hepatic parameters with ODX in PFIC	*Poster, Abstract [4277]* **Monday 18 November** 13:00–14:00 Poster Session IV	Effects of odevixibat vs placebo on hepatic biochemical parameters and liver adverse events in patients with PFIC: Data from the PEDFIC 1 study	**Tassos Grammatikopoulos et al.**
Phase I DDI results	*Poster, Abstract [4280]*	A Phase 1, open-label, fixed-sequence, crossover study to	**Florent Mazuir et al.**

	Monday 18 November 13:00–14:00 Poster Session IV	evaluate the interaction of multiple-dose odevixibat with the pharmacokinetics of single-dose combined oral contraceptive steroids in healthy female participants	
PEDFIC1/2 OLE final results (LB)	*Poster, Abstract [5045]* **Monday 18 November** 13:00–14:00 Poster Session IV	Sustained, long-term efficacy and safety of odevixibat in patients with progressive familial intrahepatic cholestasis: Results from the PEDFIC2 Phase 3, open-label extension study	**Richard Thompson et al.**

About Bylvay (odevixibat)

Odevixibat is a once-daily non-systemic ileal bile acid transport (IBAT) inhibitor approved under the brand name Bylvay® in the U.S. as the first drug treatment option for patients 3 months of age and older living with cholestatic pruritus due to progressive familial intrahepatic cholestasis (PFIC). BYLVAY may not be effective in a subgroup of PFIC type 2 patients with specific *ABCB11* variants resulting in non-functional or complete absence of the bile salt export pump protein.

Odevixibat was also approved in June 2021 in the E.U. under the brand name Bylvay®, as the first drug treatment option for all types of PFIC in patients aged 6 months or older. Bylvay has received orphan exclusivity for the treatment of PFIC in the U.S. and E.U.

In June 2023 Bylvay was approved in the U.S. for the treatment of cholestatic pruritus in patients from 12 months of age with Alagille syndrome (ALGS) and received orphan exclusivity for ALGS. In September 2024, odevixibat was approved in the E.U under the brand name Kayfanda® for the treatment of cholestatic pruritus in ALGS in patients aged 6 months or older.

IMPORTANT SAFETY INFORMATION – U.S.

Warnings and Precautions:

Liver Test Abnormalities

Patients who enrolled in PFIC and ALGS clinical trials had abnormal liver tests at baseline. In clinical trials, treatment-emergent elevations of liver tests or worsening of liver tests relative to baseline values were observed. Most abnormalities included elevations in aspartate aminotransferase (AST), alanine transaminase (ALT) in PFIC and ALGS, and total and direct bilirubin in PFIC clinical trials. No patients permanently discontinued treatment due to liver test abnormalities.

Obtain baseline liver tests and monitor during treatment. Dose reduction or treatment interruption may be required if abnormalities occur. For persistent or recurrent liver test abnormalities, consider treatment discontinuation.

Permanently discontinue Bylvay if a patient progresses to portal hypertension or experiences a hepatic decompensation event.

Diarrhea

Diarrhea occurred in both PFIC and ALGS clinical trials in BYLVAY-treated patients at a rate greater than placebo treated patients. If diarrhea occurs with use of BYLVAY, monitor for dehydration and treat promptly. Treatment interruption or discontinuation may be required for persistent diarrhea with no alternate etiology.

Fat-Soluble Vitamin (FSV) Deficiency

Fat-soluble vitamins (FSV) include vitamin A, D, E, and K. PFIC and ALGS patients can have FSV

deficiency at baseline, as part of their disease. BYLVAY may affect absorption of fat-soluble vitamins.

Obtain baseline levels and monitor during treatment, along with any clinical manifestations. Supplement if deficiency is observed. If FSV deficiency persists or worsens despite FSV supplementation, discontinue treatment.

ADVERSE REACTIONS
ALGS: The most common adverse reactions (>5%) are diarrhea, abdominal pain, hematoma, and decreased weight.
PFIC: The most common adverse reactions (>2%) are diarrhea, liver test abnormalities, vomiting, abdominal pain, and fat-soluble vitamin deficiency.

DRUG INTERACTIONS
For patients taking bile acid binding resins, take BYLVAY at least 4 hours before or 4 hours after administering, as bile acid binding resins may bind to and reduce BYLVAY efficacy.

USE IN SPECIFIC POPULATIONS
There are no human data on BYLVAY use in pregnant persons to establish a drug-associated risk of major birth defects, miscarriage, or adverse developmental outcomes. Based on findings from animal reproduction studies, BYLVAY may cause cardiac malformations when a fetus is exposed during pregnancy.

There is a pregnancy safety study that monitors pregnancy outcomes in women exposed to BYLVAY during pregnancy. Pregnant women exposed to BYLVAY, or their healthcare providers, should report BYLVAY exposure by calling 1-855-463-5127.

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at +1-855-463-5127, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Indications and Usage U.S.
Bylvay is an ileal bile acid transporter (IBAT) inhibitor indicated for the treatment of cholestatic pruritus in:
Patients 12 months of age and older with Alagille syndrome (ALGS)
Patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC)

Limitation of use
Bylvay may not be effective in a subgroup of PFIC type 2 patients with specific ABCB11 variants resulting in non-functional or complete absence of the bile salt export pump protein

Please see full U.S. Prescribing Information.

Indications of use E.U.
Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older. **Please see full E.U. Prescribing Information.**

Kayfanda is indicated for the treatment of cholestatic pruritus in Alagille syndrome (ALGS) in patients aged 6 months or older. **Please see full E.U. Prescribing Information.**

ENDS

About PEDFIC 1 and 2

PEDFIC 1 was a 24-week double-blind, randomized, placebo-controlled trial that evaluated the efficacy and tolerability of two doses of odevixibat in reducing pruritus and serum bile acid levels in children with PFIC 1 or 2. PEDFIC 2 is a 72-week open label extension trial, which consisted of children from PEDFIC 1 who received either Bylvay (cohort 1a) or placebo (cohort 1b) and a new cohort (2) of Bylvay-naïve patients of any age and PFIC subtype.

PEDFIC is the largest, global, Phase III trial ever conducted in PFIC. PEDFIC 1 (NCT03566238) was a 24-week double-blind, randomized (1:1:1), placebo-controlled trial that evaluated the efficacy and tolerability of two doses of odevixibat in reducing pruritus and serum bile acid levels in children with PFIC 1 or 2. Participants were randomly allocated to receive placebo (n=20), odevixibat 40 µg/kg (n=23), or odevixibat 120 µg/kg (n=19) once a day. The results were published in *The Lancet*.[3]

PEDFIC 2 (NCT03659916), an open-label extension of PEDFIC 1, is a 72-week trial that aimed to evaluate the efficacy and tolerability of odevixibat 120 µg/kg once a day in patients with PFIC. Patients were divided into two cohorts: Cohort 1 (n=56) which consisted of children with PFIC 1 or 2 from PEDFIC 1 who received odevixibat (Cohort 1a: n= 37) or placebo (Cohort 1b: n=19), respectively, and Cohort 2 (n=60) which consisted of newly enrolled, odevixibat-naïve patients of any age and PFIC subtype. Interim results were published in *The Journal of Hepatology*.[4]

About ASSERT and ASSERT-EXT

ASSERT (NCT04674761) was a 24-week double-blind, randomized, placebo-controlled trial with an open-label long term extension. ASSERT evaluated the safety and efficacy of 120 µg /kg once-daily odevixibat vs placebo for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS). The trial enrolled 52 patients of any age with a genetically confirmed diagnosis of ALGS. The results were published in *The Lancet*.[5]

In ASSERT-EXT (NCT05035030), ASSERT's ongoing open-label extension, all trial participants received 120 µg/kg of odevixibat once daily for 72-weeks after the double-blind treatment period completed. In both ASSERT and ASSERT-EXT, the investigators looked for changes in pruritus, serum bile acid concentrations, sleep, and treatment-emergent adverse events.

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

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Disclaimers and/or Forward-Looking Statements

Ipsen

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References

[1]Thompson RJ, et al. Sustained, long-term efficacy and safety of odevixibat in patients with progressive familial intrahepatic cholestasis: Results from the PEDFIC2 phase 3, open-label extension study. Poster Abstract 5045, American Association for the Study of Liver Disease (AASLD). 2024

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[3] Thompson RJ, et al. Odevixibat treatment in progressive familial intrahepatic cholestasis: a randomised, placebo-controlled, phase 3 trial. Lancet Gastroenterol Hepatol. 2022. 7:830–842.

[4] Thompson RJ, et al. Interim results from an ongoing, open-label, single-arm trial of odevixibat in progressive familial intrahepatic cholestasis 2023. JHEP Rep. 5(8):100782.

[5] Ovchinsky N., et al. Efficacy and safety of odevixibat in patients with Alagille syndrome (ASSERT); a phase 3, double-blind, randomized, placebo-controlled trial. Lancet Gastroenterol / Hepatol. 2024 doi.org/10.1016/S2468-1253(24)00074-8.