Xeris Biopharma Announces Results of the Extended Evaluation of Recorlev® (Levoketoconazole) From the Phase 3 Sonics Study Published in the European Journal of Endocrinology

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First prospective long-term levoketoconazole study demonstrating a sustained effect on cortisol levels, as well as improvements in biomarkers of Cushing's syndrome (CS) comorbidity, clinical signs and symptoms of CS and quality of life (QoL).

With a median treatment duration of 15 months, levoketoconazole was well tolerated and no new drug-related safety signals were observed.

Further supports a role for levoketoconazole in long-term therapy for patients with endogenous Cushing's syndrome (CS).

CHICAGO--(BUSINESS WIRE)--Nov. 1, 2022-- Xeris Biopharma Holdings, Inc. (Nasdaq: XERS), a growth-oriented biopharmaceutical company committed to improving patients' lives by developing and commercializing innovative products across a range of therapies, today announced that the European Journal of Endocrinology (EJE) published the extended evaluation (EE) results of the SONICS study (NCT01838551) evaluating longer-term effects of levoketoconazole on cortisol levels, biomarkers of Cushing's syndrome (CS) comorbidities, clinical signs and symptoms of CS, and quality of life.[1] The manuscript also reports findings from pituitary adenoma imaging in the SONICS study.

For the first time, the longer-term effects of levoketoconazole are reported from the EE phase of the previously published SONICS study[1,2]. EE study participants (N=60) received maintenance treatment with levoketoconazole (median exposure for entire study of 15 months, range 7.9-22 months) with assessments scheduled at Month 9 and Month 12. The majority (39/60 [65%]) received levoketoconazole doses of 600 mg/day or less at the start of the EE period. Forty-six (77%) patients completed the study (Month 12).

Key Study Findings:

- Sixty patients entered EE at Month 6; 61% (33/54 with data) exhibited normal mean urinary free cortisol (mUFC). At Months 9 and 12, respectively, 55% (27/49) and 41% (18/44) of patients with data had normal mUFC. In addition, reductions in late-night salivary cortisol (LNSC) and random serum cortisol were observed at Month 6, 9, and 12.
- Mean fasting glucose, total and LDL-cholesterol, body weight, body mass index, abdominal girth, Cushing QoL, and BDI-II scores improved from study baseline at Months 9 and 12.
- Female patients reported significant mean decreases in hirsutism score at all assessments; mean testosterone levels decreased significantly at Month 6 and were maintained throughout EE period
- Of 31 patients with tumor measurements at baseline and Month 12 or follow-up, largest tumor diameter was stable in 27 (87%) patients, decreased in 1, and increased in 3 (largest increase 4 mm).
- Forty-six patients completed Month 12; 4 (6.7%) discontinued during EE due to adverse events. The most common adverse events in EE were arthralgia, headache, hypokalemia, and QT prolongation (6.7% each)
- No patient experienced ALT or AST >3x ULN, QTcF interval >460 msec, or adrenal insufficiency during EE.

"The results from this extended evaluation of the SONICS study provide important new evidence in support of Recorlev and will help inform clinicians' decisions and individualization of medical therapy for patients with endogenous CS," said Dr. Ken Johnson, Senior Vice President, Global Development and Medical Affairs at Xeris. "I would like to extend our gratitude to all the investigators, study coordinators and patients who participated in the SONICS trial program. Their contributions are integral in our mission to improve outcomes for patients with this rare, debilitating, and life-threatening condition."

Recorlev received Food and Drug Administration marketing approval in December 2021. The initial approval was based upon safety and efficacy data from two positive Phase 3 studies that evaluated a combined study population of 166 patients, which was representative of the adult drug-treated U.S. population with Cushing's syndrome. [2] The SONICS study met its primary and key secondary endpoints, significantly reducing and normalizing mean urinary free cortisol concentrations without a dose increase (detailed results **here**).[2,3] LOGICS, a double-blind, placebo-controlled randomized-withdrawal study that met its primary and key secondary endpoints, confirmed the efficacy and safety of Recorlev in normalizing and maintaining therapeutic response compared with placebo (detailed results **here**).[2]

About Cushing's syndrome

Endogenous Cushing's syndrome is a rare, serious, and potentially fatal endocrine disease caused by chronic elevated cortisol exposure–often the result of a benign tumor of the pituitary gland. This benign tumor tells the body to overproduce high levels of cortisol for a sustained period of time, which often results in characteristic physical signs and symptoms that are distressing to patients. The disease is most common among adults between the ages of 30–50, and it affects women three times more often than men. Women with Cushing's syndrome may experience a variety of health issues including menstrual problems, difficulty becoming pregnant, excess male hormones (androgens), primarily testosterone, which can cause hirsutism (growth of coarse body hair in a male pattern), oily skin, and acne.[4]

Additionally, the multisystem complications of the disease are potentially life threatening. These include metabolic changes such as high blood sugar or diabetes, high blood pressure, high cholesterol, fragility of various tissues including blood vessels, skin, muscle, and bone, and psychological disturbances such as depression, anxiety, and insomnia.[4] Untreated, the five-year survival rate is only approximately 50%.[5]

About Recorlev®

Recorlev® (levoketoconazole) is a cortisol synthesis inhibitor for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.[2] Endogenous Cushing's syndrome is a rare but serious and potentially lethal endocrine disease caused by chronic elevated cortisol exposure.[2] Recorlev is the pure 2S,4R enantiomer of ketoconazole, a steroidogenesis inhibitor.[2] Recorlev has demonstrated in two successful Phase 3 studies to significantly reduce mean urine free cortisol.[2]

The Phase 3 program for Recorlev included SONICS and LOGICS, two multinational studies designed to evaluate the safety and efficacy of Recorlev when used to treat endogenous Cushing's syndrome. The SONICS study met its primary and secondary endpoints, significantly reducing and normalizing mean urinary free cortisol concentrations without a dose increase.[2,3] The LOGICS study, which met its primary endpoint and key secondary endpoint, was a double-blind, placebo-controlled randomized-withdrawal study of Recorlev that was designed to supplement the efficacy and safety information provided by SONICS.[2] The ongoing open-label OPTICS study will gather further useful information related to the long-term use of Recorlev.

Recorlev received orphan drug designation from the FDA and the European Medicines Agency for the treatment of endogenous Cushing's syndrome.

Indication & Important Safety Information for Recorlev®

BOXED WARNING: HEPATOTOXICITY AND QT PROLONGATION

HEPATOTOXICITY

Cases of hepatotoxicity with fatal outcome or requiring liver transplantation have been reported with oral ketoconazole. Some patients had no obvious risk factors for liver disease. Recorlev is associated with serious hepatotoxicity. Evaluate liver enzymes prior to and during treatment.

QT PROLONGATION

Recorlev is associated with dose-related QT interval prolongation. QT interval prolongation may result in life-threatening ventricular dysrhythmias such as torsades de pointes. Perform ECG and correct hypokalemia and hypomagnesemia prior to and during treatment.

INDICATIONS AND USAGE

Recorlev is a cortisol synthesis inhibitor indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.

Limitations of Use

Recorlev is not approved for the treatment of fungal infections.

CONTRAINDICATIONS

- Cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT > 3 times the upper limit of normal, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease.
- Taking drugs that cause QT prolongation associated with ventricular arrythmias, including torsades de pointes.
- Prolonged QTcF interval > 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome.
- Hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev.
- Taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Serious hepatotoxicity has been reported in patients receiving Recorlev, irrespective of the dosages used or the treatment duration. Drug-induced liver injury (peak ALT or AST greater than 3 times upper limit of normal) occurred in 13% of patients using Recorlev. Avoid concomitant use of Recorlev with hepatotoxic drugs. Advise patient to avoid excessive alcohol consumption while on treatment with Recorlev. Routinely monitor liver enzymes and bilirubin during treatment.

QT Prolongation

Use Recorlev with caution in patients with other risk factors for QT prolongation, such as congestive heart failure, bradyarrythmias, and uncorrected electrolyte abnormalities, with more frequent ECG monitoring considered. Routinely monitor ECG and blood potassium and magnesium levels during treatment.

Hypocortisolism

Recorlev lowers cortisol levels and may lead to hypocortisolism with a potential for life-threatening adrenal insufficiency. Lowering of cortisol levels can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness. Significant lowering of serum cortisol levels may result in adrenal insufficiency that can be manifested by hypotension, abnormal electrolyte levels, and hypoglycemia. Monitor 24-hour urine free cortisol, morning serum or plasma cortisol, and patient's signs and symptoms for hypocortisolism during treatment.

Hypersensitivity Reactions

Hypersensitivity to Recorlev has been reported. Anaphylaxis and other hypersensitivity reactions including urticaria have been reported with oral ketoconazole.

Risks Related to Decreased Testosterone

Recorlev may lower serum testosterone in men and women. Potential clinical manifestations of decreased testosterone concentrations in men may include gynecomastia, impotence and oligospermia. Potential clinical manifestations of decreased testosterone concentrations in women include decreased libido and mood changes.

ADVERSE REACTIONS

Most common adverse reactions (incidence > 20%) are nausea/vomiting, hypokalemia, hemorrhage/contusion, systemic hypertension, headache, hepatic injury, abnormal uterine bleeding, erythema, fatigue, abdominal pain/dyspepsia, arthritis, upper respiratory infection, myalgia, arrhythmia, back pain, insomnia/sleep disturbances, and peripheral edema.

DRUG INTERACTIONS

- Consult approved product labeling for drugs that are substrates of CYP3A4, P-gp, OCT2, and MATE prior to initiating Recorlev.
- Sensitive CYP3A4 or CYP3A4 and P-gp Substrates: Concomitant use of Recorlev with these substrates is contraindicated or not recommended.
- Atorvastatin: Use lowest atorvastatin dose possible and monitor for adverse reactions for dosages exceeding 20 mg daily.
- Metformin: Monitor glycemia, kidney function, and vitamin B12 and adjust metformin dosage as needed.
- Strong CYP3A4 Inhibitors or Inducers: Avoid use of these drugs 2 weeks before and during Recorlev treatment.
- Gastric Acid Modulators: See Full Prescribing Information for recommendations regarding concomitant use with Recorlev.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed during treatment and for one day after final dose.

To report SUSPECTED ADVERSE REACTIONS, contact Xeris Pharmaceuticals, Inc. at 1-877-937-4737 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Full Prescribing Information including Boxed Warning.

About Xeris

Xeris (Nasdaq: XERS) is a growth-oriented biopharmaceutical company committed to improving patients' lives by developing and commercializing innovative products across a range of therapies. Xeris has three commercially available products; Gvoke®, a ready-to-use liquid glucagon for the treatment of severe hypoglycemia, Keveyis®, the first and only FDA-approved therapy for primary periodic paralysis, and Recorlev® for the treatment of endogenous Cushing's syndrome. Xeris also has a robust pipeline of development programs to extend the current marketed products into important new indications and uses and bring new products forward using its proprietary formulation technology platforms, XeriSol™ and XeriJect™, supporting long-term product development and commercial success.

Xeris Biopharma Holdings is headquartered in Chicago, IL. For more information, visit www.xerispharma.com, or follow us on Twitter, LinkedIn, or Instagram.

Forward-Looking Statements

Any statements in this press release about future expectations, plans and prospects for Xeris Biopharma Holdings, Inc., including statements regarding the market and therapeutic potential of Recorlev, results of the SONICS study, the market and therapeutic potential of its products and product candidates, expectations regarding clinical data or results from clinical trials, the timing of clinical trials, the timing or likelihood of regulatory approval and commercialization of its product candidates, the timing or likelihood of expansion into additional markets, the potential utility of its formulation platforms and other statements containing the words "will," "would," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. These forward-looking statements are based on numerous assumptions and assessments made in light of Xeris' experience and perception of historical trends, current conditions, business strategies, operating environment, future developments, and other factors it believes appropriate. By their nature, forward-looking statements involve known and unknown risks and uncertainties because they relate to events and depend on circumstances that will occur in the future. Various factors could cause Xeris' actual results, performance or achievements, industry results and developments to differ materially from those expressed in or implied by such forward-looking statements, including the impact of COVID-19 on our business operations and clinical activities, our ability to fund our product development programs or commercialization efforts, whether our clinical trials demonstrate efficacy and safety to the satisfaction of the FDA or other regulatory authorities, and whether our products will achieve and maintain market acceptance. No assurance can be given that our expectations will be realized and persons reading this communication are, therefore, cautioned not to place undue reliance on these forward-looking statements. Additional information about economic, competitive, governmental, technological, and other factors that may affect Xeris is set forth in the "Risk Factors" section of the most recently filed Quarterly Report on Form 10-Q filed with the U.S. Securities and Exchange Commission, the contents of which are not incorporated by reference into, nor do they form a part of, this communication. Forward-looking statements in this communication are based upon information available to Xeris, as of the date of this communication and, while believed to be reasonable, actual results may differ materially. Subject to any obligations under applicable law, Xeris does not undertake any obligation to update any forward-looking statement whether as a result of new information, future developments or otherwise, or to conform any forward-looking statement to actual results, future events, or to changes in expectations.

1. Fleseriu, M. et al. Euro J Endocrinol. (published online ahead of print 2022), EJE-22-0506. 2. Recorlev [prescribing information]. Chicago, IL: Xeris Pharmaceuticals, Inc.; 2021. 3. Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2019;7(11):855-865. 4. Pivonello R et al. *Lancet Diabetes Endocrinol.* 2016; 4: 611-29. 5. Plotz CM, et al. *Am J Med.* 1952 November;13(5):597-61

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