Xeris Presents New Post Hoc Analysis on Effects of Levoketoconazole (Recorlev®) in Cushing's Syndrome Patients at ENDO 2024

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In patients with Cushing's syndrome maintained on Recorlev, a lower baseline mUFC was associated with higher cortisol normalization rate.

Lower mUFC at baseline was also associated with lower maintenance dose requirements and lower rates of potentially clinically important liver-related adverse events and liver test abnormalities.

The SONICS study previously showed that Recorlev treatment was effective at normalizing cortisol across the spectrum of Cushing's syndrome severity.

CHICAGO--(BUSINESS WIRE)--Jun. 3, 2024-- 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 it presented a post-hoc analysis from its previously published SONICS study on the effects of levoketoconazole (Recorlev®) in adults with Cushing's syndrome at ENDO 2024 in Boston, June 1-4, 2024.

"The results of this analysis suggest that patients with Cushing's syndrome/disease with lower mUFC(s) normalize at a higher rate than those with more severe disease and may require lower doses of Recorlev and experience lower rates of liver-related adverse events. This exploratory analysis brings further perspective to the importance of individualizing and tailoring medical management," said James Meyer, PharmD, Xeris' Senior Director, Publications and Medical Communications.

Title: Effects of Levoketoconazole on 24-hour Mean UFC (mUFC) in the SONICS Study: Relation to Baseline mUFC in Adults with Cushing's Syndrome: A Post-hoc Analysis (SAT-085)

This post-hoc exploration included all enrolled patients in SONICS who were treated and had a post-baseline mUFC, aiming to further elucidate relationships between baseline biochemical disease severity, drug dose, and intermediate-term mUFC response. For the current analyses, 92 patients treated with levoketoconazole and with baseline mUFC measurement (modified ITT) were stratified into 3 baseline mUFC subgroups: *Group 1* (≤ 2.5x upper limit of normal (ULN)); *Group 2* (>2.5x to ≤ 5x ULN); or *Group 3* (>5x ULN) and analyzed in respect to mUFC response, average daily dose, and adverse events following 6 months of maintenance therapy. Groups 1 and 2 were similar in baseline characteristics; whereas Group 3 differed with younger age, fewer female participants, more recently diagnosed, and more frequently on prior therapy.

Group 2 (Baseline mUFC 267.9 nmol/D) had the highest apparent mUFC response rate (12/33 [36.4%]), 95% CI 0.20, 0.54) as compared with Group 1 (Baseline mUFC 498.7 nmol/D) (12/38 [31.6%], 95% CI 0.16, 0.47) or Group 3 (Baseline mUFC 1672.8 nmol/D) (5/21 [23.8%]; 95% CI 0.01, 0.55); Group 3 having a notably lower response.

Daily doses of levoketoconazole were related to baseline mUFC. Thus, Group 3 used a nominally higher average daily dose (631 mg and 741 mg) during maintenance therapy and at the last dose in the 6-month maintenance phase (regardless of completion status) than Group 1 (475 mg and 545 mg) or Group 2 (548 mg and 611 mg).

Group 3 had more liver-related AEs of special interest than Group 1 or 2 (14% vs 7.9% or 3.0%) and more AEs leading to discontinuation (24% vs 12% or 16%). Group 3 had a higher incidence of liver test (ALT, AST, GGT) abnormalities compared to Group 1 and Group 2.

This post hoc analysis demonstrated:

- Normalization of mUFC with levoketoconazole in Cushing's syndrome patients maintained on levoketoconazole in the SONICS study for up to 6 months appeared to vary inversely with baseline mUFC.
- Lower mUFC at baseline was also associated with lower maintenance dose requirements and lower rates of potentially clinically important liver-related AEs and liver test abnormalities.
- Whether observed baseline characteristic differences between the highest tertile of baseline mUFC and the 2 lower tertiles were simply coincidental to or confounders or mediators of the described relationships with mUFC remains to be explored.

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.[3]

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.[3] Untreated, the five-year survival rate is only approximately 50%.[4]

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.[1] 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.[1] Recorlev has demonstrated in two successful Phase 3 studies to significantly reduce mean urine free cortisol.[1]

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.[1,2] 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.[1] The ongoing open-label OPTICS study will gather further useful information related to the long-term use of Recorlev.

Recorlev was approved by the US FDA in December 2021 and 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.

INDICATION

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.
- Known 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 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. Routinely 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 patient 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®, a proven 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 X, LinkedIn, or Instagram.

Forward-looking Statement

Any statements in this press release other than statements of historical fact are forward-looking statements. Forward-looking statements include, but are not limited to, statements about future expectations, plans and prospects for Xeris Biopharma Holdings, Inc. including statements regarding expectations for the release of clinical data, post hoc analyses or results from clinical trials, including the SONICS study, the market and therapeutic potential of its products and product candidates, including the levoketoconazole (Recorlev®), the potential utility of its formulation platforms and other statements containing the words "will," "would," "continue," "expect," "should," "anticipate" 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, geopolitical factors, 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. The various factors that 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, include, but are not limited to, its financial position and need for financing, including to fund its product development programs or commercialization efforts, whether its products will achieve and maintain market acceptance in a competitive business environment, its reliance on third-party suppliers, including single-source suppliers, its reliance on third parties to conduct clinical trials, the ability of its product candidates to compete successfully with existing and new drugs, and its and collaborators' ability to protect its intellectual property and proprietary technology. No assurance can be given that such expectations will be realized and persons reading this communication are, therefore, cautioned not to place undue reliance on these forward-looking statements. Additional risks and information about potential impacts of financial, operational, economic, competitive, regulatory, governmental, technological, and other factors that may affect Xeris can be found in Xeris' filings, including its most recently filed Annual Report on Form 10-K filed with the Securities and Exchange Commission, the contents of which are not incorporated by reference into, nor do they form part of, this communication. Forward-looking statements in this communication are based on information available to us, as of the date of this communication and, while we believe our assumptions are reasonable, actual results may differ materially. Subject to any obligations under applicable law, we do 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. Recorlev [prescribing information]. Chicago, IL: Xeris Pharmaceuticals, Inc.; 2021. 2. Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2019;7(11):855-865. 3. Pivonello R et al. *Lancet Diabetes Endocrinol.* 2016; 4: 611-29. 4. Plotz CM, et al. *Am J Med.* 1952 November;13(5):597-614.

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