RECORDATI RARE DISEASES GROUP

NEWS RELEASE

PHASE III LINC 3 STUDY DEMONSTRATES THAT ISTURISA® (OSILODROSTAT) IMPROVES PHYSICAL FEATURES ASSOCIATED WITH HYPERCORTISOLISM IN PATIENTS WITH CUSHING'S DISEASE

Data from the recent study was presented at the American Association of Clinical Endocrinology (AACE) 2022 Annual Meeting

Lebanon, NJ, May 13, 2022 – Recordati Rare Diseases Inc. announced today that the Phase III LINC 3 study demonstrates ISTURISA® (osilodrostat) improves physical features associated with hypercortisolism in patients with Cushing's disease. ISTURISA is indicated in the United States for the treatment of adult patients with Cushing's disease. These findings were presented at the American Association of Clinical Endocrinology (AACE) annual meeting by Alberto Pedroncelli MD, Head of Clinical Development & Medical Affairs, Global Endocrinology, Recordati AG.

Patients with Cushing's disease experience multiple physical manifestations of hypercortisolism that may reduce quality of life. Improving these physical manifestations is a vital treatment goal for patients with Cushing's disease. The LINC 3 study demonstrated that ISTURISA (osilodrostat) therapy provided long-term mean urinary free cortisol (mUFC) control and clinical improvements, with decreases in patient weight and the severity of physical features, including hirsutism, that were maintained through to week 72.

According to the abstract entitled "Osilodrostat Therapy Improves Physical Features Associated with Hypercortisolism in Patients with Cushing's Disease: Findings from the Phase III LINC 3 Study", 137 adult Cushing's disease patients with mUFC >1.5 x the upper limit of normal were enrolled in the 48-week core phase to evaluate the safety and efficacy of ISTURISA in patients with Cushing's disease. Of these participants, 106 opted to enter the extension phase, which ended when all patients had reached ≥72-week treatment.

Key Study Findings:

Improvements in physical features scores from baseline occurred at week 48 (n=97) and week 72 (n=86) including:

- 42.3% and 39.5% for central obesity
- 38.1% and 34.9% for proximal muscle atrophy
- 34.2% (n=26/76) and 34.4% (n=22/64) for hirsutism

Significant changes in mean patient weight and body mass improved from baseline including:

- Decrease in waist circumference 4.2% at week 48 and 5.8% at week 72.

- Improvement in body mass of the patients from 30.3 kg/m^2 at baseline to 28.4 kg/m^2 (–4.6%) at week 48 and 27.9 kg/m^2 (–5.8%) at week 72.

"The data further confirm that ISTURISA is an effective treatment for patients with Cushing's disease," said Mohamed Ladha, President and General Manager North America. "Changes to physical features caused by Cushing's disease can have a significant impact on patient health and well-being. Recordati Rare Diseases strives to improve the lives of patients with this rare, debilitating and potentially life-threatening condition. We are excited to provide ISTURISA to help in its management."

This presentation of the concomitant improvements in physical features associated with hypercortisolism follows the publication of the primary endpoint results in *Lancet Diabetes & Endocrinology*.[1] The LINC 3 study showed ISTURISA rapidly normalized and sustained control of mUFC in most patients with Cushing's disease. The most common adverse reactions seen in LINC 3 (incidence >20%) were adrenal insufficiency, fatigue, nausea, headache, edema.

All educational content of the AACE annual meeting is planned by its program committee, and AACE does not endorse, promote, approve, or recommend the use of any products, devices or services.

Important safety information for ISTURISA
Indications and usage
ISTURISA (osilodrostat) is a cortisol synthesis inhibitor indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

Warnings and precautions

- **Hypocortisolism:** ISTURISA lowers cortisol levels and can lead to hypocortisolism and sometimes life-threatening adrenal insufficiency. Lowering of cortisol can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness. Significant lowering of serum cortisol may result in hypotension, abnormal electrolyte levels, and hypoglycemia. Hypocortisolism can occur at any time during ISTURISA treatment. Evaluate patients for precipitating causes of hypocortisolism (infection, physical stress, etc). Monitor 24-hour urinary free cortisol, serum or plasma cortisol, and patient's signs and symptoms periodically during ISTURISA treatment.
  Decrease or temporarily discontinue ISTURISA if urinary free cortisol levels fall below the target range, there is a rapid decrease in cortisol levels, and/or patients report symptoms of hypocortisolism. Stop ISTURISA and administer exogenous glucocorticoid replacement therapy if serum or plasma cortisol levels are below target range and patients have symptoms of adrenal insufficiency. After ISTURISA discontinuation, cortisol suppression may persist beyond the 4-hour half-life of ISTURISA. Please see section 5.1 of full Prescribing Information.

Educate patients on the symptoms associated with hypocortisolism and advise them to contact a healthcare provider if they occur.

- **QTc prolongation:** ISTURISA is associated with a dose-dependent QT interval prolongation, which may cause cardiac arrhythmias. Perform an ECG to obtain a baseline QTc interval measurement prior to initiating therapy with ISTURISA and monitor for an effect on the QTc interval thereafter. Correct hypokalemia and/or hypomagnesemia prior to ISTURISA initiation and monitor periodically during treatment with ISTURISA. Use with caution in patients with risk factors for QT prolongation and consider more frequent ECG monitoring. Please see section 5.2 of full Prescribing Information.

- **Elevations in adrenal hormone precursors and androgens:** ISTURISA blocks cortisol synthesis and may increase circulating levels of cortisol and aldosterone precursors and androgens. This may activate mineralocorticoid receptors and cause hypokalemia, edema and hypertension. Hypokalemia should be corrected prior to initiating ISTURISA. Monitor patients treated with ISTURISA for hypokalemia, worsening of hypertension and edema. Inform patients of the symptoms associated with hyperandrogenism and advise them to contact a healthcare provider if they occur. Please see section 5.3 of full Prescribing Information.

Adverse reactions

- Most common adverse reactions (incidence >20%) are adrenal insufficiency, fatigue, nausea, headache, and edema.
- **To report SUSPECTED ADVERSE REACTIONS, contact Recordati Rare Diseases Inc. at 1-888-575-8344, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

Drug interactions

- **CYP3A4 inhibitor:** Reduce the dose of ISTURISA by half with concomitant use of a strong CYP3A4 inhibitor.
- **CYP3A4 and CYP2B6 inducers:** An increase of ISTURISA dosage may be needed if ISTURISA is used concomitantly with strong CYP3A4 and CYP2B6 inducers. A reduction in ISTURISA dosage may be needed if strong CYP3A4 and CYP2B6 inducers are discontinued while using ISTURISA.

Use in specific populations

- **Lactation:** Breastfeeding is not recommended during treatment with ISTURISA and for at least 1 week after treatment.

Please refer to full Prescribing Information.

References:

1. Pivonello R, Fleseriu M, Newell-Price J, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase [published correction appears in Lancet

Diabetes Endocrinol. 2020 Aug 5;:]. *Lancet Diabetes Endocrinol*. 2020;8(9):748-761. doi:10.1016/S2213-8587(20)30240-0

About Cushing's disease

Cushing's disease is a form of Cushing's syndrome, in which chronically elevated cortisol levels is triggered by a pituitary adenoma secreting excess adrenocorticotropic hormone (ACTH).[5] It is a rare, serious and difficult-to-treat disease that affects approximately one to two patients per million per year. Prolonged exposure to elevated cortisol levels is associated with considerable morbidity, mortality and impaired QoL as a result of complications and comorbidities.[6] Normalization of cortisol levels is therefore a primary objective in the treatment of Cushing's disease.[7]

About LINC 3

LINC 3 is a prospective, multicentre, 48-week trial with an 8-week, double-blind, randomized withdrawal phase to evaluate the safety and efficacy of ISTURISA in patients with Cushing's disease. The primary endpoint in the LINC 3 trial is the proportion of patients randomized to ISTURISA and placebo, separately, at Week 26 with a mUFC ≤ULN at the end of the 8-week randomized withdrawal period (Week 34), without a dose increase during this period. The key secondary endpoint is the proportion of enrolled patients with a mUFC ≤ULN after an initial 24 weeks of open-label treatment with ISTURISA without any dose increase after Week 12. LINC 3 involved 137 patients with persistent or recurrent Cushing's disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery.

About ISTURISA

ISTURISA is a cortisol synthesis inhibitor that works by inhibiting 11-beta-hydroxylase, an enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. ISTURISA is available as 1 mg, 5 mg and 10 mg film-coated tablets. Please see prescribing information for detailed recommendations for the use of this product.[2] In March 2020, the FDA granted marketing authorization for ISTURISA in the United States. For more information visit www.isturisa.com.

About Recordati Rare Diseases Inc.

Recordati Rare Diseases Inc. is a biopharmaceutical company committed to providing often-overlooked orphan therapies to the underserved rare disease communities of the United States.

Recordati Rare Diseases is a part of the Recordati Group, a public international specialty pharmaceutical company committed to the research and development of new specialties with a focus on treatments for rare diseases. Recordati Rare Diseases' mission is to reduce the impact of extremely rare and devastating diseases by providing urgently needed therapies. We work side-by-side with rare disease communities to increase awareness, improve diagnosis and expand availability of treatments for people with rare diseases.

The company's U.S. corporate headquarters is located in Lebanon, NJ, with global headquarter offices located in Milan, Italy. https://www.recordatirarediseases.com/us

For a full list of products, please click here: www.recordatirarediseases.com/us/products

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