RECORDATI RARE DISEASES GROUP

NEWS RELEASE

RECORDATI RARE DISEASES ANNOUNCE PUBLICATION IN *THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM* OF THE PHASE III LINC 4 STUDY CONFIRMING EFFICACY AND SAFETY OF ISTURISA® (OSILODROSTAT) IN PATIENTS WITH CUSHING'S DISEASE

The LINC 4 study demonstrated superiority of ISTURISA® (osilodrostat) over placebo in achieving cortisol control during the 12-week, double-blind, randomized phase (77% vs 8%, *P*<0.0001).

ISTURISA provided rapid and sustained control of cortisol secretion in the majority of patients throughout the 48-week core phase of the study.

Lebanon, NJ, March 29, 2022 – Recordati Rare Diseases Inc. announce today the publication of positive results from the Phase III LINC 4 study of ISTURISA in *The Journal of Clinical Endocrinology & Metabolism*.[1] These data reinforce ISTURISA as an effective and well-tolerated oral therapy for patients with Cushing's disease. ISTURISA is indicated in the United States for the treatment of adult patients with Cushing's disease,[2] a rare and debilitating condition of hypercortisolism that is caused by a pituitary adenoma.[3]

The LINC 4 study augments the efficacy and safety data for ISTURISA in patients with Cushing's disease, confirming the results from the Phase III LINC 3 study. This study in 73 adults is the first Phase III study of a medical treatment in patients with Cushing's disease to include an upfront, randomized, double-blind, placebo-controlled period during which 48 patients received ISTURISA and 25 received placebo for the first 12 weeks, followed by an open-label period during which all patients received ISTURISA until week 48; thereafter, patients could enter an optional extension phase.

Key findings published in the manuscript entitled 'Randomised trial of osilodrostat for the treatment of Cushing's disease' include:[1]

- LINC 4 met the primary endpoint: ISTURISA was significantly superior to placebo at normalizing mUFC at the end of a 12-week randomized, double-blind period (77% vs 8%; *P*<0.0001).
- Effects of Isturisa were rapid. Over one-quarter of patients randomised to Isturisa achieved normal mUFC as early week 2 and 58% achieved control by week 5.
- The key secondary endpoint was also met, with 81% of all patients in the study having normal mUFC at week 36.
- Improvements in cardiovascular and other clinical signs of Cushing's disease, including blood pressure and blood glucose metabolism, were seen by week 12 and were maintained throughout the study.
- Physical features of hypercortisolism improved during ISTURISA treatment, including fat pads, facial rubor, striae, and muscle wasting. Improvements were observed by week 12, with continued improvement throughout the study to week 48.

- Patient-reported QoL scores (CushingQoL and Beck Depression Inventory) also improved during ISTURISA treatment.
- ISTURISA was well tolerated in the majority of patients, with no unexpected adverse events (AEs). The most common AEs overall were decreased appetite, arthralgia, fatigue and nausea.

“These results show convincingly that osilodrostat is an effective treatment for Cushing’s disease,” said Peter J. Snyder MD, Professor of Medicine at the University of Pennsylvania. “Osilodrostat rapidly lowered cortisol excretion to normal in most patients with Cushing’s disease and maintained normal levels throughout the core phase of the study. Importantly, this normalization was accompanied by improvements in cardiovascular and metabolic parameters, which increase morbidity and mortality in Cushing’s disease.”

“These compelling data build on the positive Phase III LINC 3 study, published in *The Lancet Diabetes & Endocrinology* in 2020,[4] demonstrating that ISTURISA enables most patients with Cushing’s disease to gain rapid control of their cortisol levels, which in turn provides relief from a host of undesirable symptoms,” said Alberto Pedroncelli, Clinical Development & Medical Affairs Lead, Global Endocrinology, Recordati AG. “Recordati Rare Diseases is committed to improving the lives of patients with this rare, debilitating and life-threatening condition. I would like to thank everyone who has contributed to LINC 4 and the LINC clinical program.”

"Suffering from Cushing’s disease has affected every system in my body, including my mental health. For me, the only thing worse than receiving my initial diagnosis of Cushing’s disease was receiving the diagnosis a second time after what was considered a ‘successful’ surgical treatment," said Alicja D., a patient being successfully treated for Cushing's Disease using ISTURISA. "My current medical treatment has contributed greatly to the stability of my overall wellness and my hope for continued relief moving forward."

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.

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 4

LINC 4 is a large randomized, double-blinded, multicenter, 48-week trial with an initial 12-week placebo-controlled period to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease. The primary endpoint in the LINC 4 trial is the proportion of patients randomized to ISTURISA and placebo, separately, with an mUFC ≤ULN at the end of the 12-week, placebo-controlled period. The key secondary endpoint is the proportion of patients in both arms combined with an mUFC ≤ULN after 36 weeks. LINC 4 involved 73 patients with persistent or recurrent Cushing's disease or those with *de novo* disease who were not candidates for 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.

References

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3. Ferriere A, Tabarin A. Cushing's syndrome: Treatment and new therapeutic approaches. *Best Pract Res Clin Endocrinol Metab* 2020;34:101381.
4. 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. *Lancet Diabetes Endocrinol* 2020;8:748-61.
5. Lacroix A, Feelders RA, Stratakis CA *et al.* Cushing's syndrome. *Lancet* 2015;386:913-27.
6. Pivonello R, Isidori AM, De Martino MC *et al.* Complications of Cushing's syndrome: state of the art. *Lancet Diabetes Endocrinol* 2016;4:611-29.
7. Nieman LK, Biller BM, Findling JW *et al.* Treatment of Cushing's syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:2807-31.

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.

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

Recordati website: https://www.recordatirarediseases.com/us

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