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NEWS RELEASE

RECORDATI: POSITIVE RESULTS FROM THE PHASE III LINC 4 STUDY PRESENTED AT THE ENDOCRINE SOCIETY'S ANNUAL MEETING REINFORCE THE EFFICACY AND SAFETY OF ISTURISA® (OSILODROSTAT) IN CUSHING'S DISEASE

Statistically significant results from the pivotal Phase III LINC 4 study demonstrate that Isturisa® (osilodrostat) provides rapid and sustained normalisation of mean urinary free cortisol levels in the majority of patients. These data provide further evidence of the benefits of Isturisa® as an effective and well-tolerated oral treatment option for patients with Cushing's disease.

Milan, 23 March 2021 – Recordati Rare Diseases announces that positive results from the Phase III LINC 4 study of Isturisa® were presented on March 22 at the Endocrine Society's Annual Meeting.[1]

Results from LINC 4, the first Phase III study in patients with Cushing's disease to include an upfront, double-blind, randomised, placebo-controlled period, demonstrated that Isturisa® provided rapid and sustained normalisation of mean urinary free cortisol (mUFC) levels.[1]

Normalising mUFC levels represents an important treatment goal that can potentially reduce morbidity, improve quality of life and restore the life expectancy of patients with Cushing's disease towards that of the general population.[2]

The Phase III LINC 4 study enrolled adult patients with persistent, recurrent or *de novo* Cushing's disease who had mUFC >1.3 x upper limit of normal (ULN). Seventy-three patients received randomised treatment with Isturisa® or placebo (2:1) during the initial 12-week, double-blind, placebo-controlled period; 48 patients were included in the Isturisa® arm and 25 patients in the placebo arm. All patients received open-label Isturisa® after week 12 until the end of the core study (week 48).

The primary endpoint of the LINC 4 study was met: a significantly higher proportion of patients achieved normal mUFC levels with Isturisa® than with placebo at the end of the initial 12-week placebo-controlled phase (77% vs 8%; $P<0.0001$). Median time to first controlled mUFC response (mUFC ≤ULN) was 35 days.

The key secondary endpoint was also met, with the majority (81%) of patients having normal mUFC levels at week 36. The rapid and sustained reductions in mUFC levels were accompanied by improvements in cardiovascular and metabolic-related parameters, including systolic and diastolic blood pressure and glycated haemoglobin (HbA_{1c}) at both week 12 and the end of the core study.

"The exciting data presented today further emphasise the efficacy and tolerability of Isturisa® and build on the positive findings from the LINC 3 pivotal study, which was published in *The Lancet Diabetes & Endocrinology* in July 2020. Importantly, treatment with Isturisa® was effective in normalising mUFC levels in the majority of patients from the start of treatment, improved clinical signs of

hypercortisolism and cardiovascular-related risk factors, and was well tolerated," said Mônica Gadelha, MD, PhD, Professor of Endocrinology at Universidade Federal do Rio de Janeiro. "I feel privileged to present these additional important findings at the Endocrine Society's Annual Meeting, which represent a meaningful step forward in the optimal management of patients experiencing this life-threatening, devastating disease."

Isturisa® was well tolerated in LINC 4, further supporting the manageable safety profile established in previous studies.[3] The most common adverse events (AEs) reported up to data cut-off were arthralgia (45%), decreased appetite (45%), fatigue (38%), nausea (37%) and headache (33%). Hypocortisolism-related AEs were reported in 27% of patients. Most hypocortisolism-related AEs were of mild or moderate severity, were managed with dose reduction, dose interruption, and/or additional therapy, and did not require discontinuation of Isturisa® treatment.

"We are delighted that the positive and statistically significant data from the LINC 4 study have been presented at the Endocrine Society's Annual Meeting. These data add to the robust body of evidence supporting Isturisa® as an effective and well-tolerated treatment for patients with Cushing's disease," said Andrea Recordati, CEO. "Recordati is committed to improving the lives of patients with this serious yet underserved condition. On behalf of Recordati, I would like to thank all the patients, their families and carers, the investigators and the study collaborators who have contributed to LINC 4 and the Isturisa® clinical programme."

Isturisa® is indicated in the EU and the USA for the treatment of adult patients with endogenous Cushing's syndrome and Cushing's disease, respectively.[4,5]

About Cushing's syndrome

Cushing's syndrome is a rare disorder caused by chronic exposure to excess levels of cortisol from either an exogenous (eg medication) or an endogenous source.[6] Cushing's disease is the most common cause of endogenous Cushing's syndrome and arises as a result of excess secretion of adrenocorticotropic hormone from a pituitary adenoma, a tumour of the pituitary gland.[2,6] There is often a delay in diagnosing Cushing's syndrome, which consequently leads to a delay in treating patients.[7] Patients who are exposed to excess levels of cortisol for a prolonged period have increased comorbidities associated with the cardiovascular and metabolic systems, which consequently reduce quality of life and increase the risk of mortality.[2,8] In order to alleviate the clinical signs associated with excess cortisol exposure, the primary treatment goal in Cushing's syndrome is to reduce cortisol levels to normal.[9]

About LINC 4

LINC 4 is a multicentre, randomised, double-blind, 48-week study with an initial 12-week placebo-controlled period to evaluate the safety and efficacy of Isturisa® in patients with Cushing's disease. The LINC 4 study enrolled patients with persistent or recurrent Cushing's disease or those with *de novo* disease who were ineligible for surgery; 73 randomised patients were treated with Isturisa® (n=48) or placebo (n=25).[1] The primary endpoint of the study is the proportion of randomised patients with a

complete response (mUFC ≤ULN) at the end of the placebo-controlled period (week 12). The key secondary endpoint is the proportion of patients with mUFC ≤ULN at week 36.[1,10]

About Isturisa®

Isturisa® is a potent oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyses the final step of cortisol biosynthesis in the adrenal gland, and is authorised in the EU and USA for the treatment of adult patients with Cushing's syndrome and Cushing's disease, respectively.[4,5] Isturisa® is available as 1 mg, 5 mg and 10 mg film-coated tablets.[4,5] Please see the prescribing information for detailed recommendations for the use of this product.[4,5]

Two pivotal Phase III trials, LINC 3 and LINC 4, were designed to evaluate the efficacy and safety of Isturisa® in patients with Cushing's disease.[1,3] LINC 3 demonstrated that a higher proportion of patients on Isturisa® achieved normal mUFC compared with placebo during a randomised withdrawal period.[3] LINC 4 is the first study to include a placebo-controlled phase and complements the efficacy and safety data from the LINC 3 study.[1] Both LINC 3 and LINC 4 studies include optional extension phases that will help understand the efficacy and safety of long-term Isturisa® treatment.[1,3]

A Phase II study evaluated the efficacy and safety of Isturisa® in adult Japanese patients with non-pituitary causes of endogenous Cushing's syndrome: adrenal adenoma, n=5; ectopic adrenal corticotropic hormone syndrome, n=3; adrenocorticotropin-independent macronodular adrenocortical hyperplasia, n=1. Isturisa® decreased mUFC levels irrespective of the aetiology of Cushing's syndrome and normalised mUFC in most (67%) patients at week 12.[11]

References

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About Recordati Rare Diseases, Inc

Recordati Rare Diseases, Inc is a biopharmaceutical company committed to providing often-overlooked orphan therapies to underserved rare disease communities. Recordati Rare Diseases, Inc is a part of the rare disease business within 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.

The mission of Recordati Rare Diseases 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.

***Recordati**, established in 1926, is an international pharmaceutical group, listed on the Italian Stock Exchange (Reuters RECI.MI, Bloomberg REC IM, ISIN IT 0003828271), with a total staff of more than 4,300, dedicated to the research, development, manufacturing and marketing of pharmaceuticals. Headquartered in Milan, Italy, Recordati has operations throughout the whole of Europe, including Russia, Turkey, North Africa, the United States of America, Canada, Mexico, some South American countries, Japan and Australia. An efficient field force of medical representatives promotes a wide range of innovative pharmaceuticals, both proprietary and under license, in several therapeutic areas including a specialized business dedicated to treatments for rare diseases. Recordati is a partner of choice for new product licenses for its territories. Recordati is committed to the research and development of new specialties with a focus on treatments for rare diseases. Consolidated revenue for 2020 was € 1,448.9 million, operating income was € 469.0 million and net income was € 355.0 million.*

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