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POSTER NO. **SAT-670**

Effect of Osilodrostat on Cardiovascular and Metabolic Manifestations of Hypercortisolism in Patients With Non-pituitary Cushing's Syndrome: Findings From a Retrospective Observational Study (LINC 7)

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INTRODUCTION

- Endogenous Cushing's syndrome is associated with increased cardiovascular morbidity and mortality because of hypercortisolism[1]
- The most common form of endogenous Cushing's syndrome is Cushing's disease (60–70% of cases), caused by a pituitary adenoma[2]
  - 30–40% of patients present with non-pituitary causes, such as ectopic ACTH syndrome (6–10%) and adrenal Cushing's syndrome (adenomas, carcinomas and bilateral nodular or macronodular adrenal hyperplasia; 20–30%)[2]
- Osilodrostat, a potent oral 11β-hydroxylase inhibitor, is approved for patients with endogenous Cushing's syndrome (EMA) and for patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative (FDA)
- Data from the osilodrostat clinical development program have shown that it provides rapid and sustained reductions in cortisol levels and improvements in clinical manifestations of hypercortisolism in patients with Cushing's disease[3–8] and non-pituitary Cushing's syndrome[9]
- Here, we report the effect of osilodrostat on clinical manifestations of hypercortisolism in a real-world, retrospective, observational study conducted in a heterogeneous patient population with non-pituitary Cushing's syndrome (LINC 7; NCT05633953)

CONCLUSIONS

- **Osilodrostat provided rapid and sustained reductions in cortisol levels in patients with non-pituitary Cushing's syndrome**
- **Control of blood pressure and improvements in weight and BMI were observed from baseline. Glucose and HbA_{1c} levels were generally controlled although fluctuated between normal, prediabetic or diabetic ranges**
  - **Data on antihypertensive or antidiabetic medication use are not available; further studies are needed to determine whether patients can reduce or stop concomitant medications during osilodrostat treatment**
- **No new safety signals were identified; the safety profile was consistent with the known safety profile of osilodrostat in Cushing's disease and the known morbidity in the study population**
- **Limitations of this analysis include small patient numbers and missing assessments at some time points, the heterogeneous nature of the patient population with various etiologies of Cushing's syndrome and with varied levels of hypercortisolism at baseline, and the retrospective nature of the analysis**
- **Findings from this real-world setting show that alongside cortisol control, osilodrostat treatment may be associated with improvements in some clinical manifestations of hypercortisolism in patients with non-pituitary Cushing's syndrome, which may alleviate the disease burden for some patients**

METHODS

- LINC 7 was a multicenter, retrospective, observational study of osilodrostat in patients with non-pituitary Cushing's syndrome conducted in France
- Adults with non-pituitary Cushing's syndrome were evaluated retrospectively for up to 36 months and included those who initiated osilodrostat:
  - During the follow-up period between the French ATU (April 2019; temporary authorization for use granted prior to commercial availability) and commercialization of osilodrostat in France (June 2020)
  - In routine clinical practice between commercialization of osilodrostat in France (June 2020) and the study start date (December 16, 2022)
- Here, data are reported for the following populations:
  - **Safety population:** All enrolled patients who met all inclusion/exclusion criteria and have received osilodrostat treatment for non-pituitary Cushing's syndrome
  - **ITT population:** All enrolled patients who met all inclusion/exclusion criteria and have received osilodrostat treatment for non-pituitary Cushing's syndrome, with a potential follow-up of ≥12 weeks
  - **mITT population:** All patients included in the ITT population, excluding patients who did not have an mUFC measurement at week 12 for any reason except safety
- Selected outcomes were analyzed in the following etiologies of Cushing's syndrome: **ectopic ACTH syndrome** (EAS), **adrenal tumors** (adrenal adenoma or adrenocortical carcinoma), and bilateral nodular or macronodular **adrenal hyperplasia**
- The primary endpoint was the proportion of patients with mUFC ≤ULN at week 12, based on the **mITT population**
- Secondary endpoints included change in cardiovascular and metabolic parameters, recorded every 4 or 12 weeks, depending on clinical practice
- No formal statistical hypothesis testing was performed; all analyses are descriptive

RESULTS

Patient population

- **103 patients were enrolled** (**safety population**); **77 patients** were included in the **ITT population** and **52 patients** in the **mITT population**
  - Scan the QR code for baseline characteristics and data showing type of intervention and method of osilodrostat use by treatment population

Baseline characteristics by Cushing's syndrome etiology

	Safety population (N=103)	EAS (n=53)	Adrenal tumors* (n=36)	Adrenal hyperplasia (n=14)
Age, mean (SD), years	59.3 (15.5)	61.5 (12.9)	56.0 (18.9)	59.3 (14.6)
Sex, n (%)				
Male	40 (38.8)	25 (47.2)	9 (25.0)	6 (42.9)
Female	63 (61.2)	28 (52.8)	27 (75.0)	8 (57.1)
Weight, mean (SD), kg	76.6 (22.3)	74.4 (21.3)	77.6 (24.2)	80.7 (21.3)
BMI, mean (SD), kg/m²	27.8 (6.9)	26.7 (6.5)	28.3 (7.7)	29.9 (6.1)
mUFC, mean (SD), µg/24 h; x ULN	1518.6 (3679.8) (21.8 [47.8] x ULN)	2534.6 (4881.4) (NA)	498.0 (535.3) (NA)	83.4 (118.1) (NA)

*Adrenocortical carcinoma, n=19; adrenal adenoma, n=17

Osilodrostat dose and exposure

	Safety population (N=103)	EAS (n=53)	Adrenal tumors (n=36)	Adrenal hyperplasia (n=14)
Osilodrostat exposure, median (min–max), days*	164 (1–1178)	245 (10–846)	74 (1–873)	194 (28–1178)
Osilodrostat dose, median (min–max), mg/day				
Baseline	5.0 (1–60)	7.0 (1–60)	4.0 (1–60)	4.0 (1–10)
Week 12	6.0 (1–60)	10.0 (0–60)	4.0 (0–60)	1.5 (0–12)
Week 36	10.0 (1–120)	15.5 (0–50)	8.0 (2–120)	4.0 (1–12)

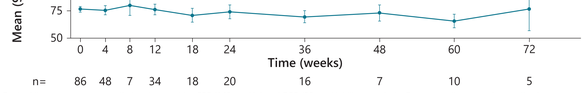
*Based on patients with available end-of-treatment dates

Effectiveness of osilodrostat

The primary endpoint was met; **23/52 patients** in the **mITT population** (44.2%; 95% CI 30.5, 58.7) had **mUFC ≤ULN at week 12**
For further information on the efficacy and safety of osilodrostat in LINC 7, please see poster SAT-671

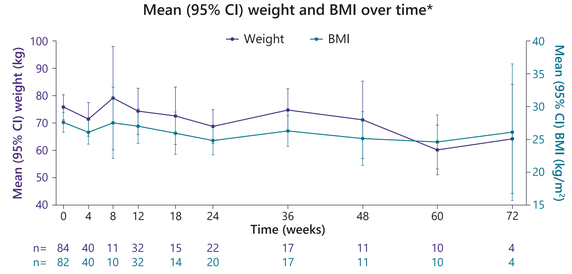
EAS (n=32)	Adrenal tumors (n=11)	Adrenal hyperplasia (n=9)
n=12/29 41.4% (23.5, 61.1)	n=5/9 55.6% (21.2, 86.3)	n=6/7 85.7% (42.1, 99.6)

1. Mean SBP and DBP generally remained stable and DBP remained within the normal range



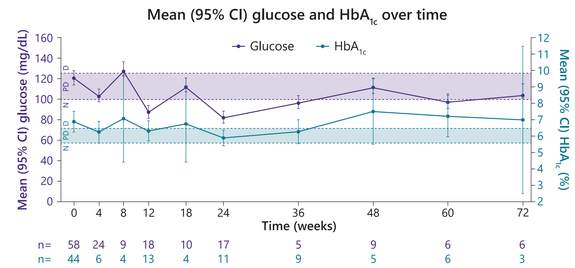
Dashed lines represent upper limits of normal for SBP (140 mmHg) and DBP (90 mmHg),[10] respectively. Data on antihypertensive medication use are not available

2. There was a trend toward a decrease in mean weight and BMI over time



*This analysis is confounded by the proportion of patients who died because of their cancer during the study and likely lost weight as they were dying

3. Mean glucose levels were within the prediabetic range at baseline and fluctuated between normal and prediabetic ranges during treatment, while mean HbA_{1c} levels were in the diabetic range at baseline and fluctuated between the prediabetic and diabetic range



Shaded areas indicate the prediabetic range for glucose (purple) and HbA_{1c} (green). Ranges are as follows: glucose: normal, <100 mg/dL; prediabetic, >100–<126 mg/dL; diabetic, ≥126 mg/dL; HbA_{1c}: normal, 4–5.6%; prediabetic, 5.7–6.4%; diabetic, ≥6.5%.[11] Data on antidiabetic medication use are not available

4. No new safety signals were identified; the safety profile was consistent with the known safety profile of osilodrostat in Cushing's disease and the known morbidity in the study population

Most common AEs (≥10% of patients)

Adrenal insufficiency **28.2%** (n=29/103)	Hypokalemia **17.5%** (n=18/103)	Asthenia **13.6%** (n=14/103)
Diarrhea **12.6%** (n=13/103)	Nausea **11.7%** (n=12/103)	

ACKNOWLEDGMENTS

We thank Beth Harrahill, Mudskipper Business Limited (funded by Recordati AG [Rare Diseases Branch]), for providing medical editorial assistance, as well as the site investigators, study coordinators and patients who participated in the trials.

ABBREVIATIONS

ACTH, adrenocorticotropic hormone; AE, adverse event; ATU, Autorisation Temporaire d'Utilisation; BMI, body mass index; CI, confidence interval; D, diabetic; DBP, diastolic blood pressure; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HbA_{1c}, glycated hemoglobin; ITT, intention to treat; max, maximum; min, minimum; mITT, modified intention to treat; mUFC, mean urinary free cortisol; N, normal; NA, not available; PD, prediabetic; SBP, systolic blood pressure; SD, standard deviation; ULN, upper limit of normal

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DISCLOSURES

The LINC 7 study was funded by Recordati AG (Rare Diseases Branch).

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PRESENTED AT: **The Endocrine Society Annual Meeting (ENDO), June 1–4, 2024**

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QR code content

Baseline characteristics by treatment population

	Safety population (N=103)	ITT population (n=77)	mITT population (n=52)
Etiology of Cushing's syndrome, n (%)			
Ectopic ACTH secretion	53 (51.5)	46 (59.7)	32 (61.5)
Macronodular adrenal hyperplasia	14 (13.6)	11 (14.3)	9 (17.3)
Adrenocortical carcinoma	19 (18.4)	10 (13.0)	6 (11.5)
Adrenal adenoma	17 (16.5)	10 (13.0)	5 (9.6)
Age, mean (SD), years	59.3 (15.5)	59.3 (15.1)	57.6 (14.3)
Sex, n (%)			
Male	40 (38.8)	30 (39.0)	22 (42.3)
Female	63 (61.2)	47 (61.0)	30 (57.7)
Weight, mean (SD), kg	76.6 (22.3)	76.2 (23.8)	75.2 (21.3)
BMI, mean (SD), kg/m^2	27.8 (6.9)	27.8 (7.3)	27.2 (6.3)
mUFC, mean (SD), µg/24 h; x ULN	1518.6 (3679.8) (21.8 [47.8] x ULN)	1198.7 (2162.7) (17.5 [30.75] x ULN)	–
Type of intervention			
Treatment naïve	63 (61.2)	46 (44.7)	27 (26.2)
Switch group*	7 (6.8)	6 (5.8)	3 (2.9)
Combination therapy	33 (32.0)	25 (24.3)	22 (21.4)
Method of osilodrostat use			
Block and replace	39 (37.9)	31 (30.1)	22 (21.4)
Initial titration followed by block and replace†	26 (25.2)	21 (20.4)	18 (17.5)
Titration only‡	38 (36.9)	25 (24.3)	12 (11.7)

*Switch group: All patients who were treated with osilodrostat as monotherapy but were taking any medical therapy for Cushing's syndrome and discontinued these prior to the start of osilodrostat; †Initial titration followed by block and replace: Patients who initiated Osilodrostat and after at least 2 weeks started taking glucocorticoids as concomitant medication; ‡Titration only: Patients who did not take glucocorticoids as concomitant medications while taking osilodrostat
ACTH, adrenocorticotropic hormone; BMI, body mass index; ITT, intention to treat; mITT, modified intention to treat; mUFC, mean urinary free cortisol; SD, standard deviation; ULN, upper limit of normal