PRESENTING AUTHOR:
Irina Bancos (bancos.irina@mayo.edu)

POSTER NO. **MON-153**

A Non-interventional, Multinational, Phase IV Study to Evaluate the Long-Term Safety and Efficacy of Osilodrostat in Patients With Endogenous Cushing's Syndrome (LINC 6): 1-Year Real-World Interim Analysis

Irina Bancos,[1] Eliza B Geer,[2] Frederic Castinetti,[3] Richard Feelders,[4] Maria Fleseriu,[5] Rosario Pivonello,[6] Martin Reincke,[7] Antoine Tabarin,[8] Jeannie Le Mouhaër,[9] Julia Stermenska,[10] Mario Maldonado,[10] Beverly MK Biller[11]

[1]Division of Endocrinology, Metabolism and Nutrition, Mayo Clinic, Rochester, MN, USA; [2]Multidisciplinary Pituitary and Skull Base Tumor Center, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Aix Marseille University, INSERM, Marseille Medical Genetics, Department of Endocrinology, La Conception Hospital, Assistance Publique Hopitaux de Marseille, Marseille, France; [4]Department of Internal Medicine, Endocrine Section, Erasmus Medical Center, Rotterdam, Netherlands; [5]Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science University, Portland, OR, USA; [6]Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Naples, Italy; [7]Ludwig-Maximilians-Universität München, Munich, Germany; [8]CHU de Bordeaux, Bordeaux, France; [9]Recordati Rare Diseases, Paris, France; [10]Recordati AG, Basel, Switzerland; [11]Neuroendocrine and Pituitary Tumor Clinical Center, Massachusetts General Hospital, Boston, MA, USA

INTRODUCTION

- Cushing's syndrome is an endocrine disorder that is not always cured and may require lifelong treatment; therefore, additional long-term data on the effects of medical treatment are needed
- Osilodrostat is a potent oral 11β-hydroxylase inhibitor, providing rapid and sustained control of cortisol production and improving clinical signs and symptoms of hypercortisolism and outcomes in patients with Cushing's syndrome
  - The efficacy and safety of osilodrostat has been demonstrated in the LINC clinical development program (Phase II: LINC 2, NCT01331239; Phase III: LINC 3, NCT02180217 and LINC 4, NCT02697734),[1–5] gaining EMA (Cushing's syndrome) and FDA approval (Cushing's disease)
  - Osilodrostat efficacy and safety were also evaluated in a Phase II study in Japanese patients with non-pituitary forms of Cushing's syndrome[6]
- The LINC 6 study is further evaluating the long-term safety and efficacy of osilodrostat in patients with endogenous Cushing's syndrome during 3 years of routine clinical practice; here, we report data from the prespecified 1-year interim analysis

CONCLUSIONS

- **At the 1-year interim analysis cut-off when the earliest-enrolled patients had been treated for at least 3 months, osilodrostat demonstrated an expected safety profile in patients with endogenous Cushing's syndrome**
  - **AEs and AEs considered to be related to osilodrostat were infrequent and manageable with corrective therapy, dose adjustments or dose interruption**
  - **Two patients discontinued because of osilodrostat-related AEs**
  - **AEs were most often related to hypocortisolism or accumulation of adrenal hormone precursors**
  - **SAEs occurred infrequently, most commonly in the form of hypocortisolism, and none resulted in osilodrostat discontinuation**
- **Early improvements in cortisol parameters are evident at month 3, with many patients achieving or maintaining control of mUFC, serum cortisol and LNSC**
- **These preliminary results from real-world settings build on Phase III clinical trial evidence and show that osilodrostat is an effective and generally well-tolerated treatment in patients with all forms of endogenous Cushing's syndrome**

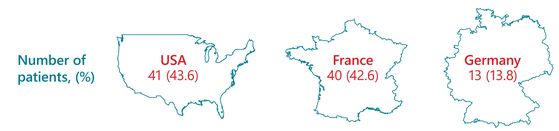
METHODS

- LINC 6 (NCT05382156) is a non-interventional, prospective, multinational study that enrolled adult patients with endogenous Cushing's syndrome, excluding patients with pseudo-Cushing's syndrome and those participating in other studies with an investigational drug
- Patients were enrolled in countries where osilodrostat is approved and available (USA, France, Germany, Italy, Netherlands); anticipated enrollment was 201 patients
  - Patients were either treatment naïve or had received prior osilodrostat monotherapy or combined treatment with other therapies targeting hypercortisolism
  - Patients were usually treated according to local prescribing information; the best therapeutic option for each patient and follow-up intervals were solely the independent decision of the treating physician according to their expertise and individual patient circumstances
  - Patients who were treated with osilodrostat and consented to data collection were enrolled consecutively, with no other inclusion or exclusion criteria
- The primary endpoint is incidence of AEs and SAEs, focusing on AEs related to hypocortisolism, accumulation of adrenal hormone precursors, QT prolongation and pituitary tumor enlargement
- Key secondary endpoints include change in mUFC, serum cortisol and LNSC and the proportion achieving or maintaining normalization for each parameter
- AEs were recorded at baseline and each visit
- Changes are reported for patients with assessments at baseline and month 3 at the prespecified 1-year interim cut-off (September 13, 2023); all assessments are descriptive

RESULTS

Patient population

- From a total of 106 patients enrolled in the USA, France and Germany, 94 were included in the safety population (received ≥1 osilodrostat dose)
- Patient characteristics were typical of a population with Cushing's syndrome; baseline mUFC was >ULN



Baseline patient characteristics	Safety population (N=94)
Mean (SD) age, years	53.2 (12.7)
Female, n (%)	66 (70.2)
Mean (SD) weight, kg*	86.3 (22.7)
Mean (SD) BMI, kg/m²*	31.0 (8.5)
Cushing's disease, n (%)	78 (81.3)
Non-pituitary Cushing's syndrome, n (%)	
Ectopic	9 (56.3)
Adrenal adenoma	3 (18.8)
Adrenal hyperplasia	3 (18.8)
Other	1 (6.3)
Patients with prior surgery, n (%)	58 (65.9)†
Mean (SD) mUFC µg/24 h‡	81.1 (119.3)

*n=65; †n=88; ‡n=35

Osilodrostat dose and exposure

Median (min–max)

On-study exposure: **5.5** (0.1–13.9) months

Dose: **5.0** (1.0–60.0) mg/day

1. Overall, AEs and AEs considered to be related to osilodrostat were infrequent and manageable without osilodrostat discontinuation in most patients

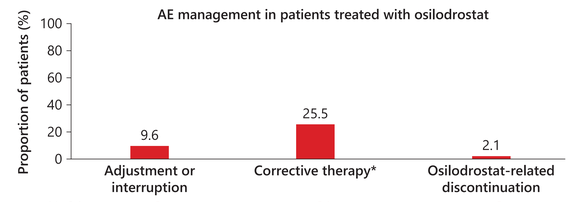
	Patients	Events	Most common events (≥5%)
At least one AE	n=29/94 (30.9%)	109	• Asthenia • Vomiting (both n=6/109; 5.5%)
At least one AE related to osilodrostat	n=12/94 (12.8%)	44	• Dizziness and vomiting (both n=4/44; 9.1%) • Acute adrenal insufficiency and diarrhea (both n=3/44; 6.8%)

- Most AEs experienced were mild or moderate and grade 1 or 2 (88.1%) versus grade 3 or 4 (11.9%)

Two patients discontinued because of osilodrostat-related AEs:

- Patient 1: Nausea; Vomiting
- Patient 2: Dizziness; Uncontrolled blood pressure; Worsening hypertension

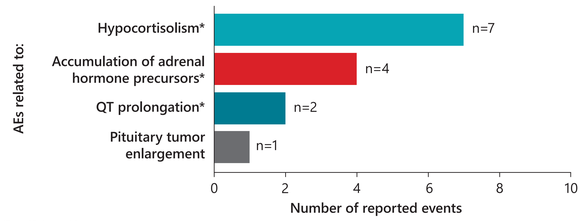
AE management in patients treated with osilodrostat



*Includes concomitant medication (n=20/24, 83.3%; glucocorticoids, n=9/20, 45.0%), surgery (n=1/24, 4.2%), concomitant medication and surgery (n=1/24, 4.2%) or other (n=4/24, 16.7% [investigation, procedure, emergency hospital visit]). n=4/24 (16.7%) required >1 corrective therapy

2. AEs related to hypocortisolism or accumulation of adrenal hormone precursors were infrequent and manageable without discontinuation in most patients

- AEs related to hypocortisolism, accumulation of adrenal hormone precursors, QT prolongation and pituitary tumor enlargement are of interest because of the mechanism of action of osilodrostat[2,4]

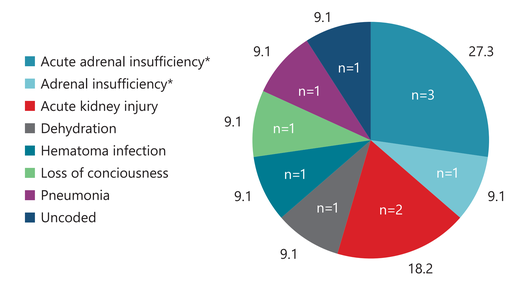


*These AEs (n=events) were reported as:
Hypocortisolism: Acute adrenal insufficiency (n=4) and adrenal insufficiency (n=3), assessed according to clinicians' individual judgment. Osilodrostat is a potent inhibitor of cortisol synthesis and its pharmacology can result in symptoms of glucocorticoid withdrawal; in patients with Cushing's syndrome, excessive inhibition of cortisol synthesis can result in hypocortisolism or adrenal insufficiency. **Accumulation of adrenal hormone precursors**: 11-deoxycortisol and 11-deoxycorticosterone: Hypertension (n=2), peripheral edema (n=1) and hypokalemia (n=1). **QT prolongation**: Loss of consciousness (n=1), syncope (n=1). **Pituitary tumor enlargement**: Increase in pituitary tumor size (n=1)

- Events related to hypocortisolism or accumulation of adrenal hormone precursors were expected and occurred mostly at treatment initiation (baseline to week 12[2] or week 26[4])
- No AE reported by investigators as hypocortisolism required osilodrostat dose interruption, adjustment or discontinuation; one patient discontinued osilodrostat because of AEs related to adrenal hormone precursors

3. SAEs were infrequent and managed without osilodrostat discontinuation

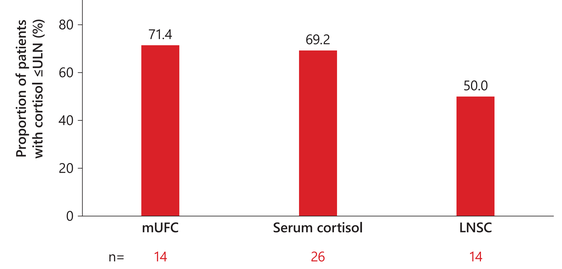
6 patients (6.4%) reported 11 SAE events



*These are listed separately as they were reported as distinct terms by investigators

- Most SAEs were related to hypocortisolism (n=4/11, 36.4%)
- No SAEs required osilodrostat discontinuation; n=3/11 (27.3%) required dose adjustment or interruption (acute renal injury, dehydration and increase in pituitary tumor size, all n=1)

4. Most patients achieved or maintained mUFC, serum cortisol or LNSC normalization at month 3*



*The denominator only includes patients with a cortisol evaluation at month 3

LIMITATIONS

- At the prespecified 1-year interim cut-off (September 13, 2023) not all enrolled patients had yet had a 3-month visit; only baseline data are reported for those patients
- Three months of data are not sufficient to determine whether corticotroph tumor growth will be seen

ACKNOWLEDGMENTS

We thank Lyssa Gold, Mudskipper Business Limited (funded by Recordati AG), for providing medical editorial assistance, as well as the site investigators, study coordinators/nurses and patients who participated in the trial.

DISCLOSURES

The LINC 6 clinical trial is sponsored by Recordati AG.

ABBREVIATIONS

AE, adverse event; BMI, body mass index; EMA, European Medicines Agency; FDA, US Food and Drug Administration; LNSC, late-night salivary cortisol; max, maximum; min, minimum; mUFC, mean urinary free cortisol; SAE, serious adverse event; SD, standard deviation; ULN, upper limit of normal

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