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Clinical Improvements in Patients With Cushing's Disease Treated With Osilodrostat According to Urinary and Late-Night Salivary Cortisol Levels: Pooled Analysis from LINC 3 and LINC 4

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*Potential conflict of interest may exist. Refer to the Meeting App; †AMP was an employee of Recordati at time of abstract/poster development

Plain language summary

Why was this research carried out?

- Cushing's disease is a rare disorder caused by a pituitary tumor, which leads to too much cortisol being produced. If untreated, too much cortisol can lead to other illnesses and physical changes and can increase the risk of death
- Osilodrostat is a drug that blocks cortisol production. Cortisol levels are measured to assess how well a patient is responding to treatment; they can be measured in the urine (over 24 hours; called mean urinary free cortisol [mUFC]) and saliva (assessed late at night, when cortisol levels are normally low; called late-night salivary cortisol [LNSC]
- In the LINC 3 and LINC 4 clinical trials, osilodrostat decreased both mUFC and LNSC levels in people with Cushing's disease and improved their signs/symptoms and quality of life. If mUFC and/or LNSC levels are within the normal range, these parameters are described as being controlled
- We assessed whether people with both mUFC and LNSC controlled had better improvements in signs/symptoms and quality of life than people with control of mUFC only

How was this research carried out?

- Results from LINC 3 and LINC 4 were pooled and analyzed in four separate groups: controlled mUFC and LNSC, controlled mUFC only, controlled LNSC only, and no control of either mUFC or LNSC
- Signs/symptoms, physical changes and quality of life were assessed

What were the overall results?

- People with both mUFC and LNSC controlled or with controlled mUFC only had better improvements in signs/symptoms, most physical changes and quality of life than people with control of LNSC only or with no control of either mUFC or LNSC

What do the results mean?

- Achieving normal mUFC and LNSC levels can help people with Cushing's disease get the best outcomes during osilodrostat treatment

Conclusions

- Patients with both controlled mUFC+LNSC or controlled mUFC only had the greatest improvements in cardiovascular/metabolic-related parameters, physical manifestations of hypercortisolism and HRQoL
- Improvements in some physical manifestations of hypercortisolism were observed irrespective of mUFC/LNSC control
- These findings are similar to those reported in an analysis of LNSC in a Phase III study of pasireotide in patients with Cushing's disease, which showed that better clinical outcomes were observed in patients with both controlled mUFC+LNSC compared with control of mUFC or LNSC only[5]
- Data are limited by small patient numbers in some groups and single samples of LNSC; the guidelines suggest that at least two LNSC samples be taken[6]
- Normalization of both LNSC and mUFC or mUFC alone with osilodrostat can improve long-term treatment outcomes in patients with Cushing's disease
  - This analysis showed no major advantage of controlling both mUFC and LNSC over mUFC alone

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Disclosures

This study was sponsored by Novartis Pharma AG; however, as of July 12, 2019, osilodrostat is an asset of Recordati AG.

Abbreviations

BDI-II, Beck Depression Inventory II; bid, twice daily; BMI, body mass index; CD, Cushing's disease; CushingQoL, Cushing's Quality of Life; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HRQoL, health-related quality of life; LC-MS/MS, liquid chromatography-tandem mass spectrometry; qod, every other day; SBP, systolic blood pressure; SD, standard deviation; ULN, upper limit of normal

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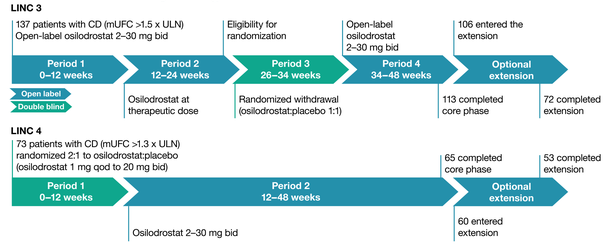
Introduction

- 24-hour mean urinary free cortisol (mUFC) and late-night salivary cortisol (LNSC) are recommended for monitoring treatment response in patients with Cushing's disease
- In two Phase III studies, LINC 3 (NCT02180217) and LINC 4 (NCT02697734), osilodrostat, a potent oral 11β-hydroxylase inhibitor, provided rapid reductions in mUFC and LNSC that were sustained during long-term treatment, alongside improvements in clinical signs of hypercortisolism and HRQoL[1–4]
- Through a pooled analysis, we assessed whether patients with both mUFC and LNSC controlled experienced greater improvements in clinical signs of hypercortisolism and HRQoL compared with control of mUFC or LNSC alone across the LINC 3 and LINC 4 studies

Methods

- Individual patient data were pooled from the LINC 3 and LINC 4 studies
- mUFC (mean of 2–3 samples; normal range 11–138 nmol/24 h [4–50 µg/24 h]) and LNSC (single sample; normal ≤2.5 nmol/L [≤0.09 µg/dL]) were measured by LC-MS/MS in a central laboratory
- Physical manifestations of hypercortisolism were assessed locally from photographs and rated subjectively by local investigators (0=absent; 1=mild; 2=moderate; 3=severe); improvement was defined as the symptom score being lower (ie less severe) than at baseline
- HRQoL was assessed using the CushingQoL questionnaire (scored from 12 [worst] to 60 [best]) and the BDI-II (scored from 0 [best] to 63 [worst])
- Changes in cardiovascular/metabolic-related parameters, physical manifestations of hypercortisolism and HRQoL were assessed in the pooled population according to mUFC/LNSC control status
  - mUFC/LNSC control status groups and number of patients with evaluable assessments at week 72:
    - Both controlled mUFC+LNSC (mUFC ≤ULN + LNSC ≤ULN) (n=54)
    - Controlled mUFC only (mUFC ≤ULN + LNSC >ULN) (n=44)
    - Controlled LNSC only (mUFC >ULN + LNSC ≤ULN) (n=2)
    - Both uncontrolled mUFC+LNSC (mUFC >ULN + LNSC >ULN) (n=11)
- Data from patients receiving placebo during placebo-controlled periods were excluded

LINC 3 and 4 study designs



Results

1. Baseline patient characteristics were typical for patients with Cushing's disease

n=160

- Median **age**, years (min–max): **39** (19–70)
- **Female**, %: **80.6** (n=129)
- **Male**, %: **19.4** (n=31)
- Mean **weight**, kg (SD): **79.7** (19.7)
- **Previous surgery**, %: **87.5** (n=140)
- Previous **medical therapy**, %: **79.4** (n=127)
- Mean **BMI**, kg/m² (SD): **30.2** (7.2)
- **Mean mUFC**, x ULN (SD): **5.5** (9.4)
- **Mean LNSC**, x ULN (SD): **4.7** (7.5)

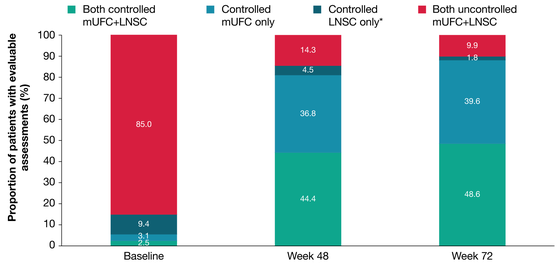
ULNs: mUFC, 138 nmol/24 h (50 µg/24 h); LNSC, 2.5 nmol/L (0.09 µg/dL)

2. Osilodrostat exposure and dose in the pooled population were similar to those in the parent studies

Median duration of osilodrostat exposure: 97.9 weeks (min–max, 2–218)

Median average osilodrostat dose: 6.5 mg/day (min–max, 1–47)

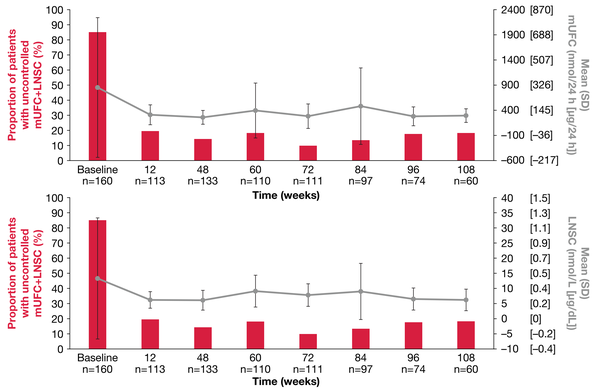
3. At weeks 48 and 72, most evaluable patients had both controlled mUFC+LNSC or controlled mUFC only



The denominator for the percentage includes all enrolled patients who received at least one dose of osilodrostat with evaluable assessments for both mUFC and LNSC at the given time point (n). *Patients with a single controlled LNSC value at the given time point

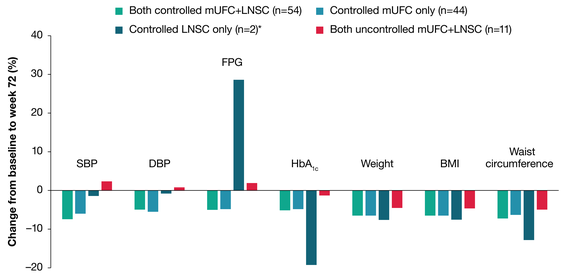
- Scan QR code for the proportion of patients in each subgroup over time
- Median time to first mUFC normalization was shorter than median time to first LNSC normalization (36 vs 85 days)

4. Mean mUFC and LNSC levels in patients with both uncontrolled mUFC+LNSC fluctuated and decreased during long-term treatment



The denominator for the percentage includes all enrolled patients who received at least one dose of osilodrostat with evaluable assessments for both mUFC and LNSC at the given time point (n)

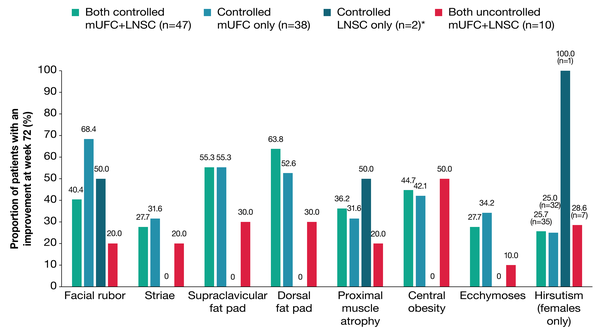
5. Mean improvements from baseline to week 72 in cardiovascular/metabolic-related parameters were generally greater in patients with both controlled mUFC+LNSC or controlled mUFC only than in patients with controlled LNSC only or both uncontrolled mUFC+LNSC



The denominator for the percentage includes all enrolled patients who received at least one dose of osilodrostat with evaluable assessments for both mUFC and LNSC and the clinical assessment at the given time point (n). The 'controlled LNSC only' and 'both uncontrolled mUFC+LNSC' subgroups included few patients. *Patients with a single controlled LNSC value at the given time point

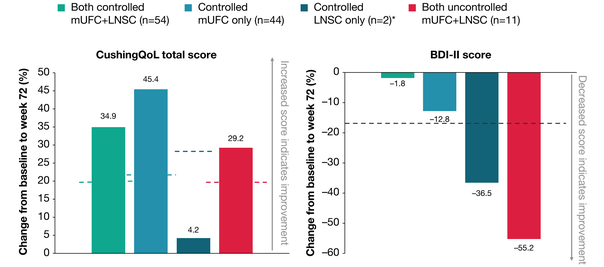
- Based on 111 patients with evaluable mUFC and LNSC assessments at week 72, there were weak correlations between the following:
  - Change in FPG, HbA_{1c}, waist circumference and LNSC at week 72 (r=0.39, P=0.0003; r=0.21, P=0.0428; r=0.28, P=0.0063, respectively)
  - Change in HbA_{1c}, SBP, DBP and mUFC at week 72 (r=0.21, P=0.0325; r=0.18, P=0.0341; r=0.18, P=0.0283, respectively)

6. Improvements in most physical manifestations of hypercortisolism were observed at week 72 in patients with both controlled mUFC+LNSC or controlled mUFC only compared with patients who had controlled LNSC only or both uncontrolled mUFC+LNSC



The denominator for the percentage includes all enrolled patients who received at least one dose of osilodrostat with an evaluable assessment at baseline and week 72, and with assessment of mUFC and LNSC (n). The 'controlled LNSC only' and 'both uncontrolled mUFC+LNSC' subgroups included few patients. *Patients with a single controlled LNSC value at the given time point

7. Patients with both controlled mUFC+LNSC or controlled mUFC only had the greatest improvement from baseline to week 72 in CushingQoL and BDI-II scores



The 'controlled LNSC only' and 'both uncontrolled mUFC+LNSC' subgroups included few patients. Dotted lines indicate the distribution-based minimal important difference corresponding to a 10.1-point actual change from baseline, reported as a percentage change for each control status group in the figure (both controlled mUFC+LNSC, 19.9%; controlled mUFC only, 21.1%; controlled LNSC only, 27.7%; both uncontrolled mUFC+LNSC, 19.5%), and a 17.5% reduction in score from baseline for BDI-II. *Patients with a single controlled LNSC value at the given time point

- There was no correlation between change in mUFC and LNSC, respectively, and change in CushingQoL score at week 72
- However, there were weak correlations between change in mUFC and LNSC and BDI-II scores at week 72 (r=0.24, P=0.0110 and r=0.33, P=0.0011, respectively)