Presenting author: Beverly MK Biller (BBILLER@mgh.harvard.edu)

PMON160

Improvements in clinical signs of hypercortisolism and quality of life according to urinary and late-night salivary cortisol levels in patients with Cushing's disease treated with osilodrostat

Findings from the LINC 3 study

*Beverly MK Biller,[1] *Maria Fleseriu,[2] *Rosario Pivonello,[3] *Richard A Feelders,[4] *André Lacroix,[5] *Richard J Auchus,[6] *Andrea Piacentini,[7] *Alberto M Pedroncelli,[8] *John Newell-Price[9]

[1]Neuroendocrine and Pituitary Tumor Clinical Center, Massachusetts General Hospital, Boston, MA, USA; [2]Pituitary Center, Departments of Medicine and Neurological Surgery, Oregon Health & Science University, Portland, OR, USA; [3]Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Naples, Italy; [4]Department of Internal Medicine, Endocrine Section, Erasmus Medical Center, Rotterdam, Netherlands; [5]Centre hospitalier de l'Université de Montréal, Montreal, Canada; [6]Division of Metabolism, Endocrinology and Diabetes, Departments of Internal Medicine and Pharmacology, University of Michigan, Ann Arbor, MI, USA; [7]Recordati SpA, Milan, Italy; [8]Recordati AG, Basel, Switzerland; [9]Department of Oncology and Metabolism, The Medical School, University of Sheffield, Sheffield, UK

Introduction

- 24-hour mUFC and LNSC levels are complementary parameters recommended for screening and monitoring treatment response in patients with CD[1]
  - LNSC assessment is a simple and more convenient test for patients with CD
- In the Phase III LINC 3 study (NCT02180217), therapy with osilodrostat (potent oral 11ß-hydroxylase inhibitor) produced rapid, sustained reductions in mUFC and LNSC alongside improvements in clinical signs of hypercortisolism in patients with CD[2]
- **Here, we explored these clinical improvements by mUFC and/or LNSC control status for all patients with evaluable assessments during the 48-week core phase of LINC 3**

CONCLUSIONS

- **Treatment with osilodrostat led to rapid, sustained reductions in mUFC and LNSC, resulting in control of one or both parameters in most patients**
  - **After 48 weeks of osilodrostat treatment, most evaluable patients had both mUFC and LNSC controlled (54.3%) or only mUFC controlled (30.0%); there was a moderate, positive correlation between mUFC and LNSC**
- **Improvements in clinical signs and physical manifestations of hypercortisolism, as well as HRQoL indicators, were generally greatest in patients with either both mUFC and LNSC controlled or only mUFC controlled**
- **Control of both mUFC and LNSC is likely to be of clinical importance; measuring both parameters to assess control of hypercortisolism can provide a more comprehensive assessment of medical treatment response and optimize patient outcomes**

Acknowledgments

We thank Rebecca Helson, Mudskipper Business Limited (funded by Recordati AG), for providing medical editorial assistance, as well as the site investigators, study coordinators and patients who participated in the trials

Disclosures

This study was sponsored by Novartis Pharma AG; however, as of July 12, 2019, osilodrostat is an asset of Recordati AG
*Potential conflict of interest may exist. Refer to the Meeting App

Please scan this quick response (QR) code with your smartphone camera or app to obtain a copy of these materials. Alternatively, please click on the link below: https://xxxxxx.com/
Copies of this poster obtained through QR code are for personal use only and may not be reproduced without permission from ENDO and the authors of this poster

References

1. Fleseriu M *et al*. *Lancet Diabetes Endocrinol* 2021;9:847–75
2. Pivonello R *et al*. *Lancet Diabetes Endocrinol* 2020;8:748–61
3. Webb SM *et al*. *Eur J Endocrinol* 2008;158:623–30
4. Beck AT *et al*. *J Pers Assess* 1996;67:588–97

Abbreviations

BDI-II, Beck Depression Inventory II; 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; IQR, interquartile range; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LNSC, late-night salivary cortisol; MID, minimal important difference; mUFC, mean urinary free cortisol; QoL, quality of life; SBP, systolic blood pressure; ULN, upper limit of normal

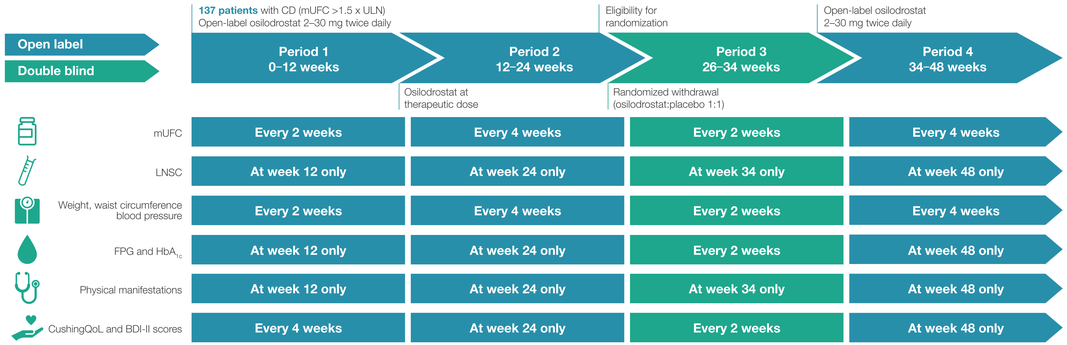
Presented at the annual meeting of the Endocrine Society (ENDO), June 11–14, 2022

MRC-E1033-20220714

Methods

- mUFC (average of 2–3 24-h samples; normal: 11–138 nmol/24 h [4–50 µg/24 h]) and LNSC (single sample; normal ≤2.5 nmol/L) were measured by LC-MS/MS in a central laboratory
- Physical manifestations of hypercortisolism were rated locally from photographs (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])[3] and the BDI-II (scored from 0 [best] to 63 [worst])[4]
- Control was defined as an mUFC and/or LNSC value ≤ULN
- Analyses are presented for patients with both mUFC and LNSC assessments:
  - **Both mUFC and LNSC controlled**
  - **Only mUFC controlled**
  - **Only LNSC controlled**
  - **Both mUFC and LNSC uncontrolled**

LINC 3 study design and assessment schedule



Results

Baseline patient characteristics

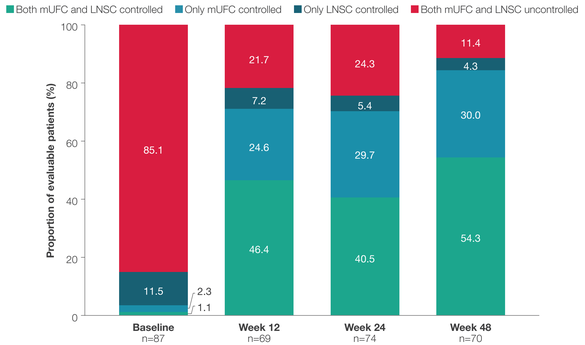
	N=137
Median age, years	40.0
Female, %	77.4
Mean/median mUFC, x ULN	7.3/3.5
Mean/median LNSC, x ULN	5.0/3.1
Mean weight, kg	80.8
Mean SBP/DBP, mmHg	132.2/85.3
Mean FPG, mg/dL	99.2
Mean HbA_{1c}, %	6.0
Mean CushingQoL score	42.2
Mean BDI-II score	16.8

Exposure to osilodrostat up to core study data cut-off

Median duration of osilodrostat exposure:
75 weeks (range 1–165, IQR 48–117)

Average median osilodrostat dose:
7.1 mg/day (range 1.1–53.9, IQR 3.8–14.0)

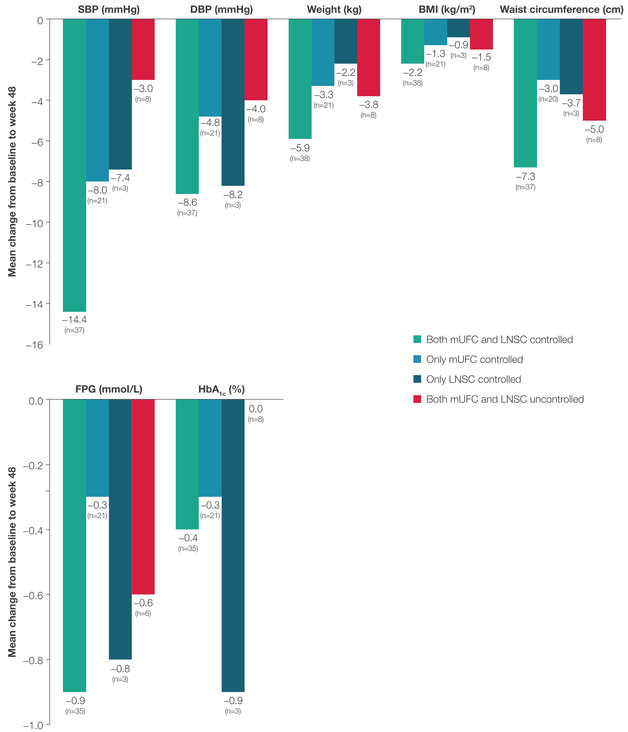
1. At week 48, over half of the evaluable patients had both mUFC and LNSC controlled



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)

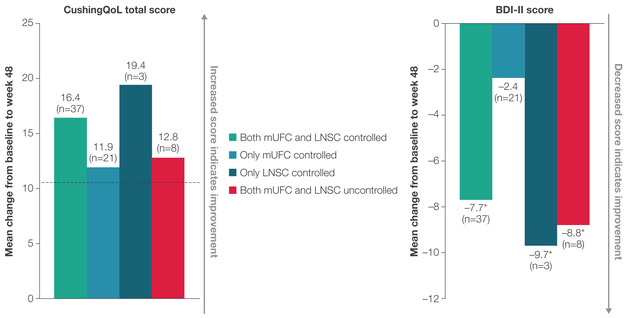
- Pearson's correlation coefficient between mUFC and LNSC (in patients with an assessment within the same 24-h period) was 0.73 (baseline), 0.47 (week 12), 0.60 (week 24) and 0.44 (week 48)

2. Mean improvements from baseline to week 48 in cardiovascular/metabolic-related parameters were generally greater in patients with both mUFC and LNSC controlled



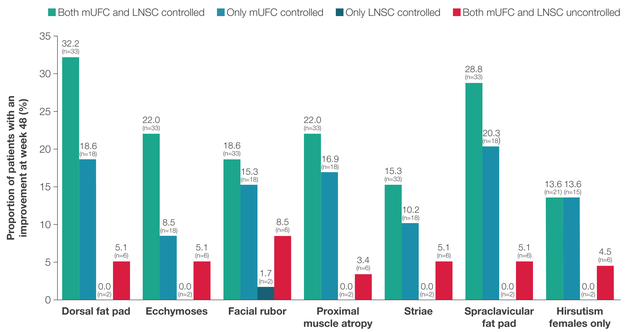
n includes all enrolled patients who received at least one dose of osilodrostat with evaluable assessments for both mUFC and LNSC and the clinical assessment at the given time point. Patients were not evenly distributed between subgroups; the 'only LNSC controlled' and 'both mUFC and LNSC uncontrolled' subgroups included few patients

3. Improvements in QoL indicators occurred at week 48 across all patient subgroups



n includes all enrolled patients who received at least one dose of osilodrostat with evaluable assessments for both mUFC and LNSC and the QoL assessment at week 48. Patients were not evenly distributed between subgroups; the 'only LNSC controlled' and 'both mUFC and LNSC uncontrolled' subgroups included few patients. The dotted line indicates the distribution-based MID corresponding to a 10.1-point change from baseline. *Changes in BDI-II score that reached the MID (17.5% reduction in score from baseline)

4. Improvements in rated scores for physical manifestations of hypercortisolism at week 48 were more common in patients with both mUFC and LNSC controlled, followed by those with only mUFC controlled



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 48, and with assessment of mUFC and LNSC (n). Patients were not evenly distributed between subgroups; the 'only LNSC controlled' and 'both mUFC and LNSC uncontrolled' subgroups included few patients