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Effect of osilodrostat on clinical signs, physical features and health-related quality of life (HRQoL) by degree of mUFC control in patients with Cushing's disease (CD): results from the LINC 3 study

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INTRODUCTION

- LINC 3 (NCT02180217), a Phase III, multicenter study including a double-blind, randomized withdrawal period, showed osilodrostat (a potent oral 11β-hydroxylase inhibitor) to be an effective treatment for CD by normalizing mean urinary free cortisol (mUFC) in most patients[1]
- **Here we assessed the effects of osilodrostat on signs, symptoms and HRQoL of CD by degree of mUFC control**

CONCLUSIONS

- A high response rate was sustained during the study, with most patients achieving controlled mUFC (not exceeding the upper limit of normal [ULN]) during 48 weeks of treatment
- Patients with controlled or partially controlled (>ULN but ≥50% reduction from baseline) mUFC at week (W) 24 had numerically greater improvements in blood pressure than those with uncontrolled mUFC (>ULN and <50% reduction from baseline); by W48, improvements occurred irrespective of mUFC control
- Other cardiovascular risk factors, CushingQoL and Beck Depression Inventory (BDI) scores, and physical features of hypercortisolism, including hirsutism, progressively improved from baseline to W24 and W48, irrespective of mUFC control
- **Improvements in clinical signs, physical features and HRQoL of CD patients occurred soon after osilodrostat initiation and were sustained until W48. In most cases, improvements with osilodrostat treatment were seen even in patients without complete mUFC normalization**

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METHODS

Assessments: Evaluated at baseline, every 2, 4 or 12 weeks (depending on study period), and at week 48 (see QR code for detailed schedule)

- **mUFC status:** Average of three samples by liquid chromatography-tandem mass spectrometry, normal range 4–50 µg/24h
  - **Controlled (C):** ≤ULN
  - **Partially controlled (PC):** >ULN but ≥50% reduction from baseline
  - **Uncontrolled (U):** >ULN and <50% reduction from baseline
- **Cardiovascular-related metabolic parameters**
- **Physical features** (rating: 0=absent; 1=mild; 2=moderate; 3=severe)
- **CushingQoL** and **BDI** scores

STUDY DESIGN (Figure 1)

N=137 with CD and mUFC >1.5 x ULN

Osilodrostat 2–30 mg twice daily (bid)

Eligibility for randomization

Primary endpoint: Proportion of patients with mUFC ≤ULN at W34

Period 1	Period 2	Period 3	Period 4
0–12 weeks	12–24 weeks	26–34 weeks	34–48 weeks
Open label Double blind	Osilodrostat at therapeutic dose	Randomized withdrawal (1:1)	Open-label osilodrostat

RESULTS

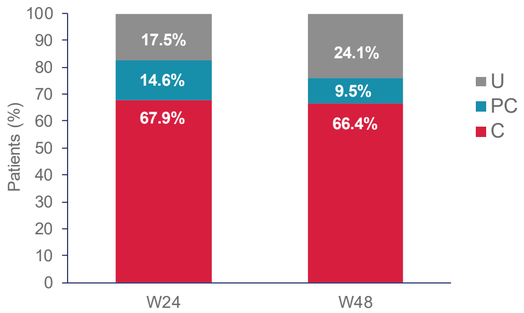
Baseline patient characteristics (Table 1)

Characteristic	N=137
Median age, years	40.0
Female, %	77.4
Mean/median mUFC, x ULN	7.3/3.5
Mean weight, kg	80.8
Systolic/diastolic blood pressure (SBP/DBP), mmHg	132.2/85.3
Fasting plasma glucose (FPG), mg/dL	99.2
Glycated hemoglobin (HbA_{1c}), %	6.0

Median (interquartile range) osilodrostat exposure/dose up to core study data cut-off: 75 (48–117) weeks/7.1 (3.8–14.0) mg/day

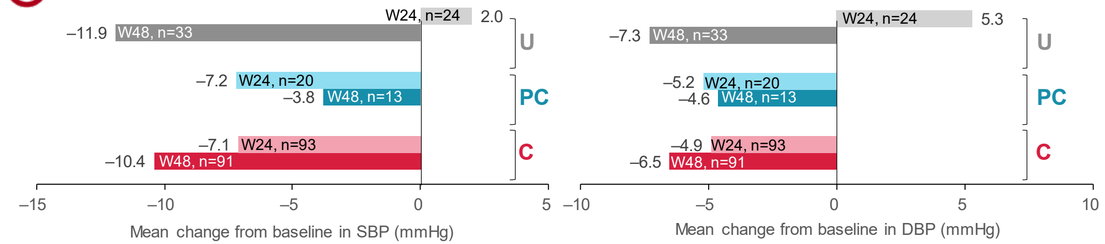
1. A high response rate was sustained during the study, with most patients achieving C mUFC during 48 weeks of treatment (Figure 2)

132/137 (96%) of patients had C mUFC (≤ULN) at least once during the core study period



2. Patients with C or PC mUFC at W24 had numerical improvements in blood pressure that were not seen in patients with U mUFC; by W48, improvements occurred irrespective of mUFC control (Figure 3)

In all patients, SBP and DBP improved by –6.3 and –4.0 mmHg, respectively, at W24 and –9.8 and –6.3 mmHg, respectively, at W48



3. Other cardiovascular risk factors and CushingQoL and BDI scores (Table 2) progressively improved from baseline to W24 and W48, regardless of mUFC control

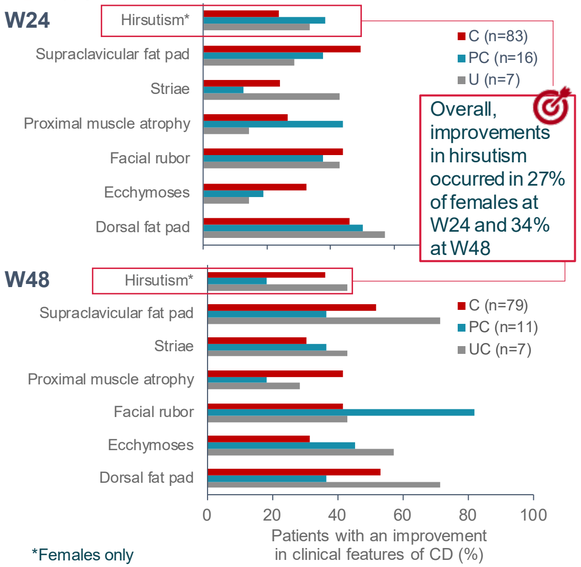
Overall, improvements were observed in most cardiovascular-related metabolic parameters associated with CD, as well as CushingQoL and BDI scores, at W24 and W48

Parameter	Mean change from BL to W24, by response status at W24			Mean change from BL to W48, by response status at W48		
	C (n=93)	PC (n=20)	U (n=24)	C (n=91)	PC (n=13)	U (n=33)
Weight, kg	–2.7	–1.7	–1.6	–3.9	–3.1	–3.5
BMI, kg/m²	–1.1	–0.6	–0.6	–1.4	–1.3	–1.3
Waist circumference, cm	–3.4	–2.4	0.1	–4.5	–5.2	–5.8
FPG, mg/dL	–13.3	–21.2	–7.4	–10.1	–9.5	–1.3
HbA_{1c}, %	–0.3	–0.4	0.0	–0.3	–0.5	–0.2
CushingQoL total score	9.2	9.4	10.1	13.7	12.7	20.5
BDI score	–3.6	–6.8	–4.6	–5.5	–6.9	–7.1

Highlighted boxes indicate data whereby the 95% confidence interval does not include 0. See QR code for summary of data in all patients, including cholesterol and triglycerides. BL, baseline; BMI, body mass index

4. Improvements in physical features of hypercortisolism (Figure 4), including hirsutism, occurred at W24 and W48, regardless of mUFC control

By W48, most patients had improvements in at least one physical feature of CD



Overall, improvements in hirsutism occurred in 27% of females at W24 and 34% at W48

*Females only

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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.

Reference

1. Pivonello R *et al. Lancet Diabetes Endocrinol* 2020;8:748–61