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Osilodrostat Dosing in 229 Patients With Cushing's Disease: A Pooled Analysis of the LINC Program

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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?

- Osilodrostat has been shown to reduce and maintain normal cortisol levels in Phase II (LINC 2) and Phase III (LINC 3 and LINC 4) clinical trials of people with Cushing's disease. To achieve this, the osilodrostat dose may need to be increased in the early stages of treatment (known as dose titration). Once cortisol levels are normal, the dose usually remains stable but may need to be increased or decreased in some people to maintain normal cortisol levels (known as dose adjustment)
- We evaluated how dose titration and adjustment during osilodrostat treatment can help reduce cortisol to normal levels and minimize adverse events

How was this research carried out?

- Results from LINC 2, LINC 3 and LINC 4 were pooled and analyzed. The osilodrostat dose was increased if cortisol levels were above the normal range or decreased if levels were close to or below the lower limit of the normal range, or to help maintain normal cortisol levels. Dose adjustments were allowed, depending on how the individual was responding to treatment

What were the overall results?

- Osilodrostat reduced cortisol to normal levels and maintained those levels in most people with Cushing's disease over long-term treatment. People with lower cortisol levels at the start of treatment tended to achieve control faster than people with higher levels at the start of treatment. Fewer adverse events occurred during long-term treatment than during the early stages of treatment, and most were managed without stopping treatment

What do the results mean?

- It is important to personalize the treatment approach and regularly monitor people taking osilodrostat to improve outcomes

Conclusions

- Patients with lower baseline mUFC values tended to achieve control of mUFC faster than patients with higher baseline mUFC values and required a lower median average osilodrostat dose overall
- More than half of patients required a dose decrease during osilodrostat treatment, most often during the first 6 months
- Osilodrostat provided sustained mUFC control in all studies
- The occurrence of the most common AEs observed during dose titration generally decreased during long-term treatment; however, it is important to monitor patients regularly as AEs can occur at any time
- Although dose titration differed between studies, AEs of special interest were less frequent during long-term treatment than dose titration and were mostly manageable without stopping treatment
  - The mean duration of temporary dose interruption for AEs related to hypocortisolism and accumulation of adrenal hormone precursors was long, ranging from 14 to 32 days
  - It is important to educate patients on the signs and symptoms of hypocortisolism-related AEs to allow prompt intervention
- Personalized treatment approaches with osilodrostat and regular monitoring is important to optimize treatment outcomes for patients with Cushing's disease

Acknowledgments

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Disclosures

These studies were sponsored by Novartis Pharma AG; however, as of July 12, 2019, osilodrostat is an asset of Recordati AG.

Abbreviations

ACTH, adrenocorticotropic hormone; AE, adverse event; bid, twice daily; BMI, body mass index; CD, Cushing's disease; CI, confidence interval; mUFC, mean urinary free cortisol; LC-MS/MS, liquid chromatography-tandem mass spectrometry; SD, standard deviation; ULN, upper limit of normal

References

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https://bit.ly/45kBbVt

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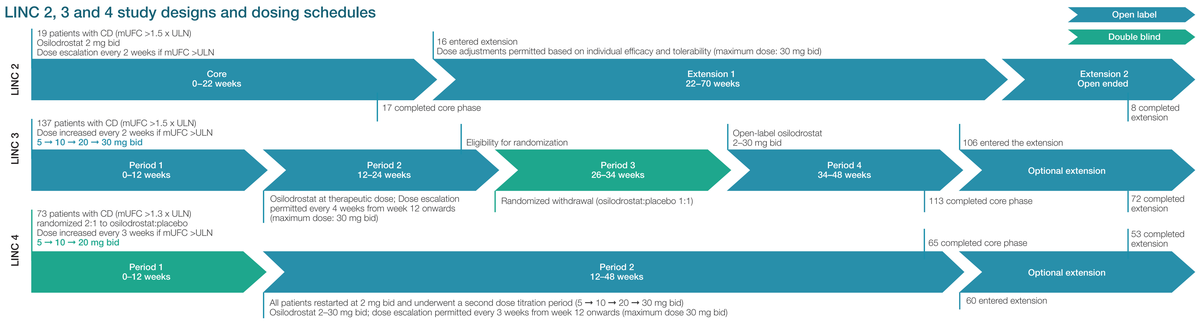
Introduction

- Phase II (LINC 2, NCT01331239) and Phase III (LINC 3, NCT02180217; LINC 4, NCT02697734) studies showed that osilodrostat, a potent oral 11β-hydroxylase inhibitor, was an effective long-term therapy for patients with Cushing's disease[1–5]
- In this pooled analysis, we evaluated how dose adjustments during dose-titration and maintenance periods can provide rapid and sustained control of mUFC and minimize AEs

Methods

- The LINC program enrolled patients with Cushing's disease (LINC 2, LINC 3: mUFC >1.5 x ULN; LINC 4: mUFC >1.3 x ULN)
  - Individual patient data were pooled and analyzed
- mUFC was calculated from the mean of two or three samples (normal range 11–138 nmol/24 h [4–50 µg/24 h]) by LC-MS/MS
- Data from patients receiving placebo during placebo-controlled periods were excluded

LINC 2, 3 and 4 study designs and dosing schedules



Results

Baseline patient characteristics

229 patients included in the pooled analysis | **LINC 2:** n=19 | **LINC 3:** n=137 | **LINC 4:** n=73

Median **age**, years (min–max) **39** (19–70)

Previous surgery, % **87.8** (n=201)

Female, % **79.0** (n=181)

Previous **medical therapy**, % **83.8** (n=192)

Male, % **21.0** (n=48)

Mean **BMI**, kg/m² (SD) **30.2** (7.2)

Mean **weight**, kg (SD) **80.3** (21.0)

Mean mUFC, x ULN (SD) **6.2** (10.8)
Median mUFC, x ULN (min–max) **2.9** (0.2–77.2)

ULN for mUFC: 138 nmol/24 h (50 µg/24 h)

Osilodrostat exposure up to study end

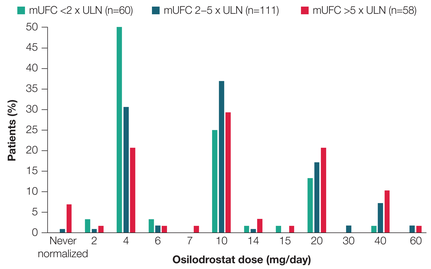
Median duration of osilodrostat exposure (all patients): 100.1 weeks (min–max, 1–351)

- Scan QR code for median duration of osilodrostat exposure by baseline mUFC severity

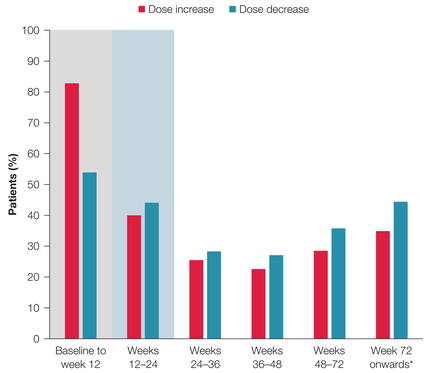
Median average osilodrostat dose (all patients): 6.8 mg/day (min–max, 1–47)

Median average osilodrostat dose (by baseline mUFC severity)
mUFC <2 x ULN: 4.9 mg/day (min–max, 1–22)
mUFC 2–5 x ULN: 7.7 mg/day (min–max, 1–47)
mUFC >5 x ULN: 7.2 mg/day (min–max, 1–46)

First dose leading to mUFC ≤ULN by baseline mUFC severity



1. Dose adjustments were more frequent during the first 6 months of treatment than during long-term treatment; however, many patients received dose adjustments throughout the study



Gray shaded area represents dose-titration period in LINC 2, 3 and 4. Blue shaded area represents a second dose-titration period in LINC 4. *Maximum duration of follow-up was 351 weeks

- 78.9% of patients received their individual maximum osilodrostat dose during the first 12 weeks (scan QR code)
- Osilodrostat dose was reduced in 56.8% of patients after they reached their individual maximum dose, most often during the first 6 months of treatment (scan QR code)

2. Median (95% CI) time to first mUFC normalization was shorter in patients with lower mUFC at baseline

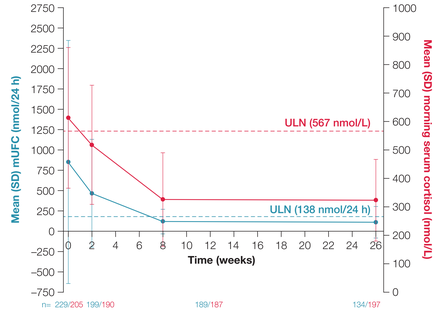
Median time to first mUFC normalization (all patients): 35 days (95% CI: 34.0, 41.0)

mUFC <2 x ULN: **28 days** (95% CI: 17.0, 34.0)

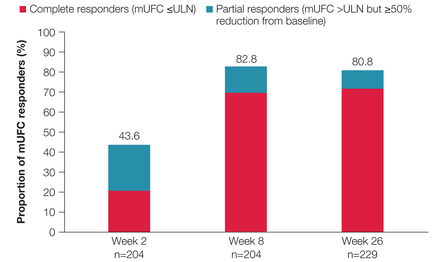
mUFC 2–5 x ULN: **40 days** (95% CI: 34.0, 42.0)

mUFC >5 x ULN: **52 days** (95% CI: 41.0, 56.0)

3. Mean morning serum cortisol and mUFC levels decreased to below the ULN by weeks 2 and 8, respectively, and remained within the normal range up to week 26



4. 69.6% of patients had mUFC ≤ULN at week 8; mUFC response rate was maintained at week 26

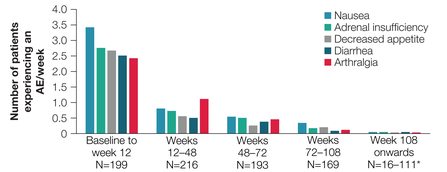


Patients with a missing mUFC value or who discontinued before a given time point are classed as non-responders

5. The occurrence of most common AEs during dose-titration phases generally decreased over time

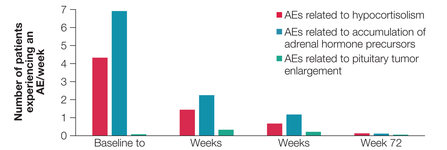
- Over the course of the study, the most common AEs were nausea, headache, fatigue and arthralgia (scan QR code)
  - These AEs were mostly manageable with dose adjustment/interruption and/or additional therapy

Occurrence of most common AEs during dose titration (>20% of patients) over time



*Weeks 108–114, n=111; weeks 144–180, n=73; weeks 180–218, n=44; after week 218, n=16. Maximum duration of follow-up 351 weeks

6. Fewer AEs related to hypocortisolism, accumulation of adrenal hormone precursors and pituitary tumor enlargement occurred during long-term maintenance than dose titration



*Maximum duration of follow-up 351 weeks

Proportion of patients requiring dose interruption to manage AEs of special interest by time interval

AEs, n (%)	Baseline to week 12 (n=204)	Weeks 12–48 (n=220)	Weeks 48–72 (n=193)	Week 72 onwards (n=169)
Related to hypocortisolism	46 (22.5)	43 (19.5)	12 (6.2)	32 (18.9)
Related to accumulation of adrenal hormone precursors	13 (6.5)	4 (1.8)	3 (1.6)	1 (0.6)
Related to pituitary tumor enlargement	0	0	0	1 (0.6)

- Mean (SD) duration of temporary dose interruption for AEs related to hypocortisolism and accumulation of adrenal hormone precursors was 32.1 (73.4) and 14.3 (8.3) days, respectively
- One patient required temporary dose interruption for an AE related to pituitary tumor enlargement for 32 days
- Few patients permanently discontinued the study because of these AEs (related to hypocortisolism, n=8; related to accumulation of adrenal hormone precursors, n=3; related to pituitary tumor enlargement, n=15)
- Occurrence of AEs related to QT prolongation and arrhythmogenic potential was low
  - No patients experienced arrhythmias
- ACTH levels increased from baseline to week 26 (scan QR code)