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Poster no. P404

Change in androgens and adrenal hormones during long-term osilodrostat treatment in patients with Cushing's disease: Results from the Phase III, prospective LINC 3 study

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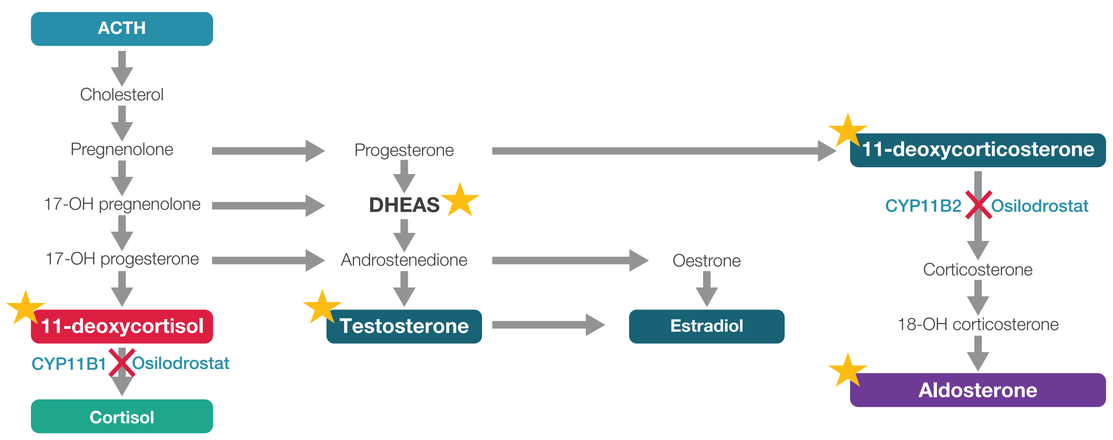
Introduction

- Osilodrostat decreases cortisol production by inhibiting 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2), which increases levels of adrenal hormones and androgens above the level of enzyme blockade[1]

Figure 1. Osilodrostat mechanism of action

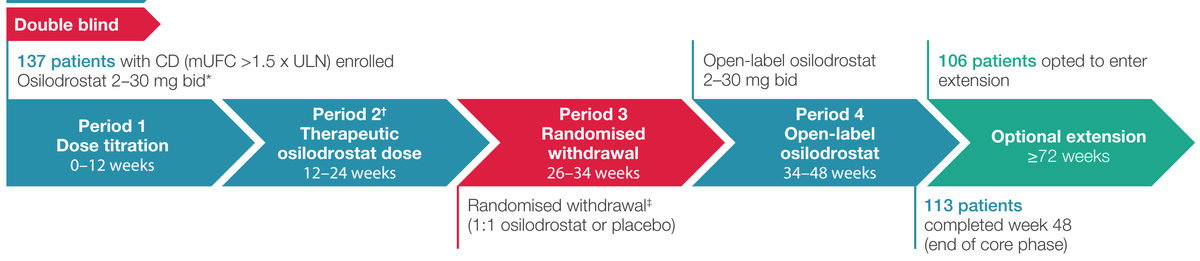


Stars show androgens and adrenal hormones that are reported here

- Efficacy and safety profile of osilodrostat in patients with Cushing's disease has been confirmed in the prospective Phase III, LINC 3 study (NCT02180217) over a median treatment period of 130 weeks[2,3]
- Based on the mechanism of action of osilodrostat, this poster describes the effects of osilodrostat on adrenal hormone and androgen levels and any adrenal hormone precursor accumulation-related AEs in the LINC 3 study

Methods

Figure 2. LINC 3: 48-week core phase, with an 8-week double-blind randomised-withdrawal period, followed by an optional extension phase



*Dose adjustments (2–30 mg bid) to normalise UFC or to address safety reasons were permitted. Dose titrations were permitted every 2 weeks. Doses below 2 mg bid were allowed if necessary; †Patients remained on open-label osilodrostat during the period between weeks 24 and 26 to allow time for availability of laboratory results; ‡Patients were eligible for randomisation if they had mUFC ≤ULN at week 24 and no dose up-titration from weeks 13 to 24

Assessments

- Adrenal hormone and androgen levels were assessed centrally at baseline and at regular intervals
  - Adrenal hormone and androgen levels reported here are highlighted with stars in **Figure 1**
  - Scan QR code for further information on methods used to measure androgen and adrenal hormone levels
- Hirsutism score (females) was assessed at regular intervals and rated locally by investigators on a semi-quantitative scale: 0=absent; 1=mild; 2=moderate; 3=severe
- Serum potassium was also measured regularly
- Safety was continually assessed from core study baseline to study end by monitoring AEs
  - Scan QR code for classification of adrenal hormone precursor accumulation-related AEs

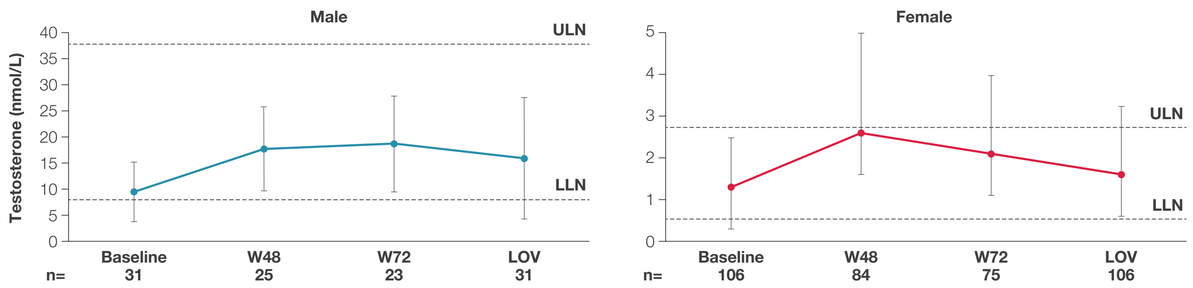
Results

Median osilodrostat exposure: 130 weeks (range 1–245)

Average median osilodrostat dose: 7.4 mg/day (range 0.8–46.6)

1. Following an increase during the core phase, mean testosterone levels stabilised in males and decreased towards baseline in females during long-term treatment

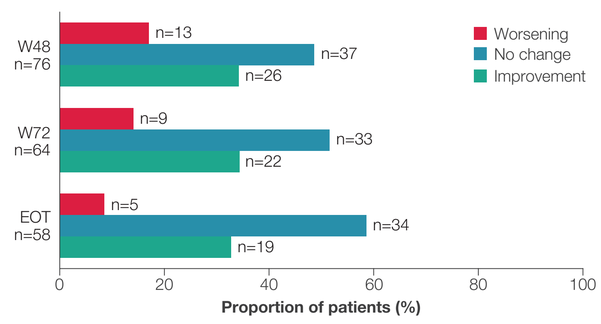
Figure 3. Mean (SD) testosterone levels in males and females



Error bars show SD. Dashed lines represent LLN and ULN; male: LLN, 8.4 nmol/L and 8.7 nmol/L; ULN, 38.2 nmol/L (or lower); female: LLN, 0.1 nmol/L and 0.7 nmol/L; ULN, 2.6 nmol/L (or lower)
LOV, last observed value

- Hirsutism score improved from baseline or remained unchanged in most female patients throughout the study, with few patients experiencing a worsening in hirsutism score

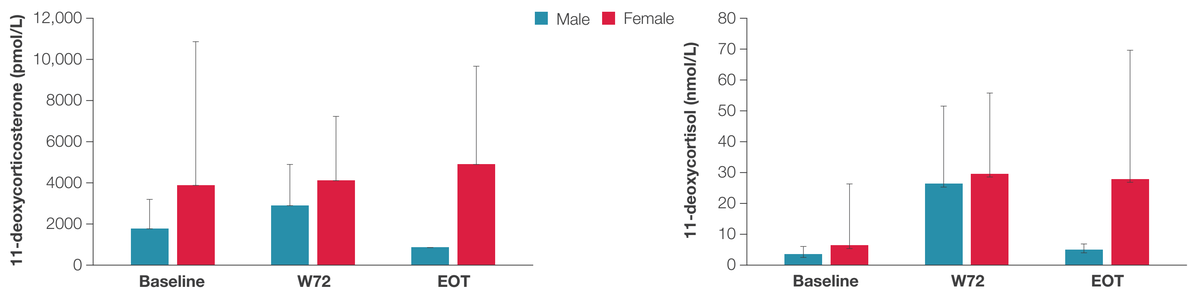
Figure 4. Change in hirsutism score from baseline to week 48, week 72 and EOT



- Scan QR code for hirsutism scores in female patients with normal testosterone levels (<ULN) and elevated testosterone levels (>ULN)

2. Mean 11-deoxycortisol and 11-deoxycorticosterone increased during the core phase and stabilised during long-term treatment

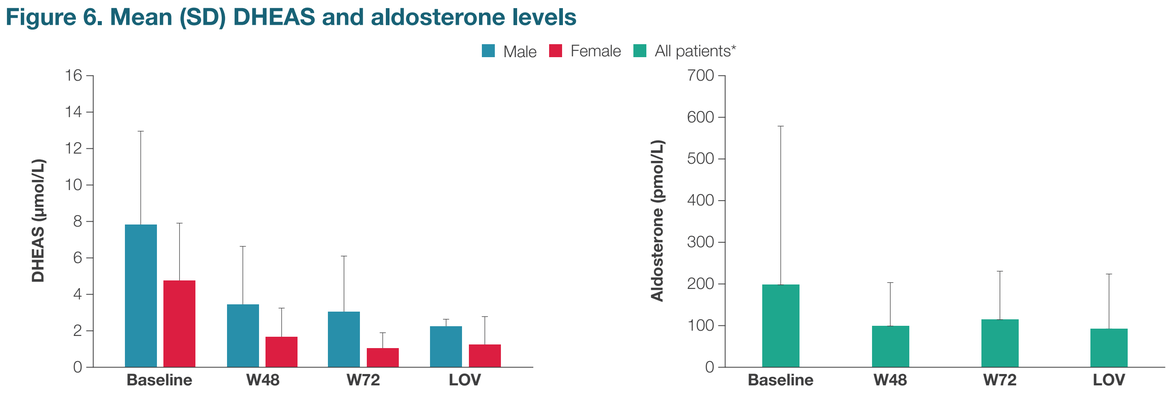
Figure 5. Mean (SD) 11-deoxycortisol and 11-deoxycorticosterone levels*



Error bars show SD. ULN for 11-deoxycorticosterone: male, 484.2 or 455 pmol/L; female, 696 pmol/L (mid-cycle); ULN for 11-deoxycortisol: male, 3.92 nmol/L (or lower depending on age); female, 3.1 nmol/L (or lower depending on age)
*Week 48 data not available
EOT, end of treatment

3. Mean DHEAS and aldosterone levels decreased during the core phase and stabilised during long-term treatment

Figure 6. Mean (SD) DHEAS and aldosterone levels



Error bars show SD. ULN for DHEAS: male, 18.8 µmol/L (or lower depending on age); female, 10.6 µmol/L (or lower depending on age); ULN for aldosterone: ≤777 pmol/L (upright)
*Data presented by overall population rather than male/female as data for week 48 and LOV not available by male/female
LOV, last observed value

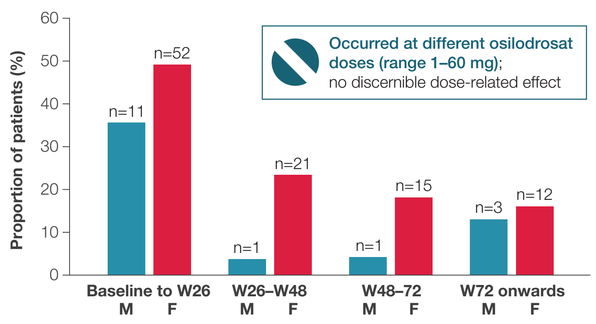
4. Adrenal hormone precursor accumulation-related AEs were reported in 58.4% (n=80/137) of patients; most occured during the first 26 weeks of treatment (period 1: dose titration; period 2: therapeutic osilodrostat dose)

Table 1. Most common adrenal hormone precursor accumulation-related AEs (≥10% of patients) from baseline to end of study

AE	All grades, n (%)	Grade ≥3, n (%)
Hypertension	24 (17.5)	15 (10.9)
Peripheral oedema	22 (16.1)	0
Hypokalaemia	18 (13.1)	5 (3.6)
Increased blood testosterone	16 (11.7)	0

- Despite adrenal hormone precursor accumulation-related AEs of hypertension, peripheral oedema and hypokalaemia, mean potassium levels remained stable throughout the study (scan QR code)

Figure 7. Occurrence of adrenal hormone precursor accumulation-related AEs by time interval



5. Concomitant medication was used to manage adrenal hormone precursor accumulation-related AEs in 36.5% (n=50/137) of patients

Table 2. Adrenal hormone precursor accumulation-related AEs managed with concomitant medication (>1 patient)

AE	All patients N=137 n (%)	
Hypertension	17 (12.4)	
Hypokalaemia	14 (10.2)	
Acne	8 (5.8)	
Peripheral oedema	6 (4.4)	10 (7.3)
Oedema	4 (2.9)	
Hirsutism	4 (2.9)	

- Only two patients (1.5%) discontinued because of these AEs, both during the core phase

Increased SBP and DBP (grade 3)

Hypokalaemia (grade 3)

CONCLUSIONS

- Adrenal hormones and androgen levels can increase upon initiation of osilodrostat treatment, but stabilise during long-term maintenance treatment
- Adrenal hormone precursor accumulation-related AEs were reported during the LINC 3 study; most occurred during the initial dose titration and maintenance periods
- These AEs were mostly manageable, with few (1.5%) patients discontinuing treatment because of these AEs
- Testosterone levels in females decreased towards baseline levels during long-term treatment; hirsutism score improved from baseline or remained unchanged in most patients, with very few patients experiencing a worsening in hirsutism score
- **Osilodrostat is an effective and well-tolerated long-term treatment option for patients with Cushing's disease; any AEs that occur during osilodrostat treatment should be closely monitored, and treatment for these AEs should be initiated as needed to achieve optimal patient outcomes**

Abbreviations

AE, adverse event; bid, twice daily; CD, Cushing's disease; DBP, diastolic blood pressure; DHEAS, dehydroepiandrosterone sulfate; EOT, end of treatment; F, female; LOV, last observed value; M, male; QR, quick response; SBP, systolic blood pressure; SD, standard deviation; ULN, upper limit of normal; W, week

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Disclosures

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

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