EP887

Long-Term (19-Month) Control of Urinary Free Cortisol with Osilodrostat in Patients with Cushing's Disease: Results from an Extension to the LINC-2 Study

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INTRODUCTION

- Osilodrostat (LCI699) is an oral inhibitor of 11β-hydroxylase (the enzyme responsible for catalysing the final step of cortisol synthesis)
  - Osilodrostat also inhibits aldosterone synthesis by reversibly binding to aldosterone synthase[1]
- In a 22-week, Phase II study (LINC-2), osilodrostat normalized mean urinary free cortisol (mUFC) levels in 79% (15/19) of patients with Cushing's disease[2]
- Here, we report safety and efficacy results of an interim analysis at month 19 in patients who entered an extension to LINC-2

METHODS

Study Design and Participants

- Open-ended extension to LINC-2, a prospective, open-label, 22-week study in patients with Cushing's disease
- Patients could enter the extension if considered by the investigator to be receiving clinical benefit at week 22
- Patients continued on the same dose of osilodrostat as at week 22
  - Dose adjustments were permitted during the extension (min/max: 1 mg once daily/30 mg twice daily [bid])

Assessments and Statistical Analysis

- Efficacy/safety are presented for patients who entered the extension
- Response rate: sum of controlled (mUFC ≤ upper limit of normal [ULN]) and partially controlled (mUFC >ULN and ≥50% reduction from baseline) patients
  - Response rate at month 19 was assessed with (LOCF) and without (non-LOCF) imputation of missing values using last available measurements
- Escape from response: mUFC >ULN on ≥2 consecutive visits on highest tolerated dose after previous mUFC normalization
- AEs are reported from core baseline until last patient reached month 19
  - Exposure-adjusted occurrence rates (number of events per patient year) calculated for three intervals: ≤22 weeks, >22 weeks to 1 year, and >1 year

RESULTS

Patients

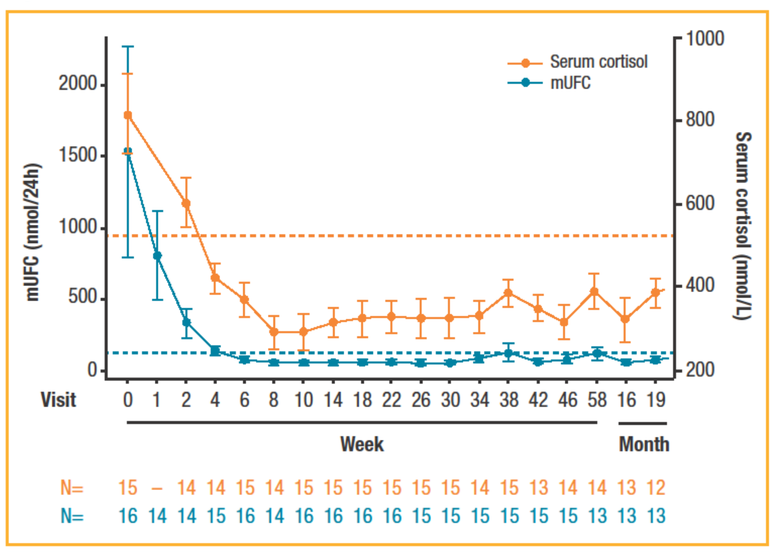
- 16 of 17 patients (male:female, 5:11) who completed week 22 entered the extension
- Median duration of osilodrostat treatment: 19.7 months (range, 6.8–25.3)
  - Median osilodrostat dose: 10 mg bid at week 22; 5 mg bid at month 19
- 14 of 16 patients were still on treatment at month 19
- Two patients discontinued before month 19 (AEs, n=1 [increased ACTH and pituitary-tumour enlargement]; withdrew consent, n=1)

Efficacy

Cortisol Levels

- Mean mUFC decreased from study baseline to <ULN by week 6 and remained in the normal range through to month 19 (**Figure 1**)
- The reduction in mean mUFC was accompanied by a rapid and sustained reduction in mean 08:00 serum cortisol level (**Figure 1**)

Figure 1. Mean mUFC and Serum Cortisol



Data are mean ± SE. Dashed lines represent ULN: mUFC, 138 nmol/24h; serum cortisol, 567 nmol/L. SE, standard error

- Overall response rate (LOCF) was 93.8% (15/16) at week 22 and month 19 (**Table 1**)
- Response rate was slightly lower at month 19 (75.0%; 12/16) when missing values were not imputed (non-LOCF)
- No patients experienced escape from response

Table 1. Response Rates at Week 22 and Month 19 (N=16)

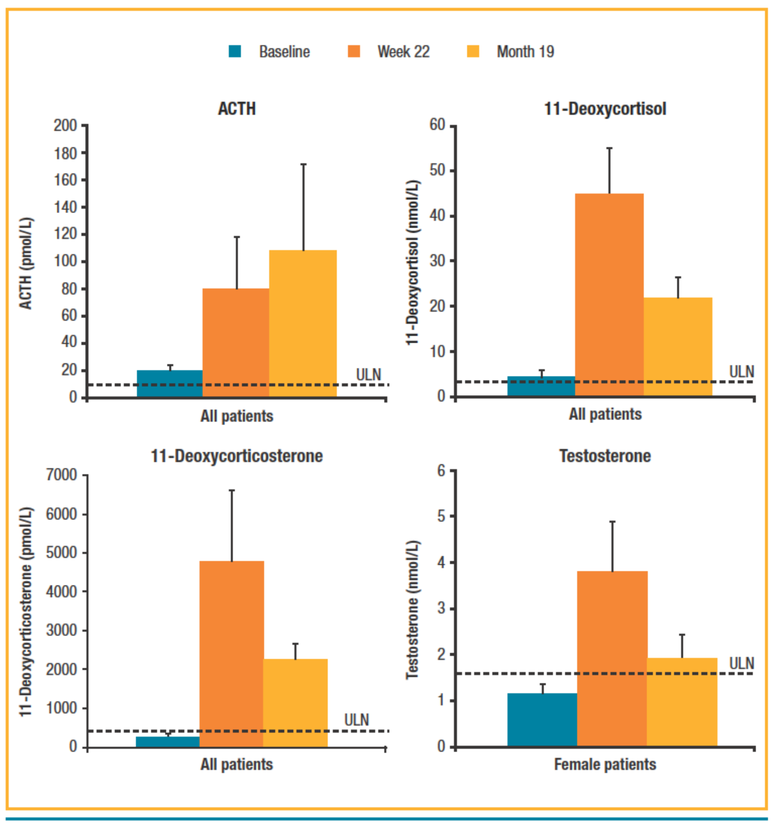
	Week 22	Month 19
LOCF		
Overall response, % (n)	93.8 (15)	93.8 (15)
Controlled UFC responder, % (n)	93.8 (15)	81.3 (13)
Partially controlled UFC responder, % (n)	0 (0)	12.5 (2)
Non-LOCF		
Overall response, % (n)	93.8 (15)	75.0 (12)*
Controlled UFC responder, % (n)	93.8 (15)	68.8 (11)
Partially controlled UFC responder, % (n)	0 (0)	6.3 (1)

*Two patients discontinued treatment prior to month 19; at last assessment, one was controlled (week 30) and one was partially controlled (week 58). One additional patient had a missing mUFC value at month 19; patient was controlled at last assessment (month 16)

Other Hormone Levels

- Mean levels of ACTH, 11-deoxycortisol and 11-deoxycorticosterone all increased during osilodrostat treatment (**Figure 2**)
- Mean 11-deoxycortisol and 11-deoxycorticosterone levels decreased between week 22 and month 19, but remained >ULN (**Figure 2**)

Figure 2. Mean ACTH, 11-Deoxycortisol, 11-Deoxycorticosterone, and Testosterone (Females) at Baseline, Week 22 and Month 19



Data are mean ± SE. Dashed lines represent ULN: ACTH, 9.2 pmol/L; 11-deoxycortisol, 3.92 nmol/L; 11-deoxycorticosterone, 390 pmol/L; testosterone, 1.6 nmol/L (females)

- In females, the increase in mean testosterone from baseline was less apparent at month 19 than at week 22 (**Figure 2**)
  - Hirsutism (n=1), acne (n=2) emerged before week 22 in 3/11 females (each had testosterone >ULN); no new or worsening events were noted during the extension
- In males, mean testosterone remained within the normal range (8.7–38.2 nmol/L) from baseline to month 19

Clinical Signs of Cushing's Disease

- Numerical reductions were seen in mean weight and BMI from baseline to month 19 (**Table 2**)

Table 2. Mean Change in Clinical and Laboratory Parameters from Baseline to Month 19

Parameter	Baseline, mean (SD)	Week 22, mean (SD)	Month 19, mean (SD)	Percentage change from baseline to month 19, mean (95% CI)
SBP, mmHg	130.6 (7.8)	129.3 (14.6)	126.7 (19.5)	–3.2 (–13.1, 6.8)
DBP, mmHg	84.9 (6.5)	85.7 (9.1)	83.3 (14.1)	–3.1 (–13.1, 6.9)
Weight, kg	83.8 (21.4)	81.7 (21.4)	73.3 (16.8)	–6.3 (–10.2, –2.3)
BMI, kg/m^2	29.6 (6.1)	28.8 (6.1)	26.5 (5.6)	–6.2 (–10.2, –2.3)
FPG, mg/dL	97.1 (30.7)	81.4 (9.3)	79.5 (9.3)	–12.8 (–26.1, 0.4)
Patients with DM at baseline	122.8 (44.8)	83.6 (13.5)	78.3 (14.3)	–41.1 (–67.2, –14.9)
HbA_{1c}, %	5.6 (0.7)	5.5 (0.6)	5.3 (0.4)	–3.9 (–11.2, 3.3)
Patients with DM at baseline	6.4 (0.5)	6.0 (0.5)	5.5 (0.6)	–16.6 (–38.1, 4.9)

Normal ranges: FPG, 70–110 mmHg; HbA_{1c}, <6.4%. DM, diabetes mellitus; CI, confidence interval; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; SD, standard deviation

Tumour Size

- In patients with evaluable baseline measurements (n=6), tumour diameter increased or decreased in an equal number of patients (n=3 each; **Table 3**)

Table 3. Pituitary Tumour Size (Longest Diameter) in Patients with Evaluable Measurements at Baseline and at Last Available Assessment

Age, years/ sex	Baseline, mm	Last post-baseline assessment by interval, mm			Change to last post-baseline assessment, mm
		≤22 weeks	>22 weeks to 1 year	>1 year	
28/female	3.3	5.0	–	8.0	+4.7
51/female	6.9	6.9	–	5.0	–1.9
43/female	5.0	4.0	6.0	6.0	+1.0
35/female	10.0	9.0	9.0	8.0	–2.0
39/female	7.0	6.0	6.0	–	–1.0
29/male	3.5	5.0	–	5.0	+1.5

One patient discontinued prior to month 19 because of tumour enlargement and increased ACTH. This patient did not have an evaluable measurement at baseline; investigator noted that tumour dimension "was difficult to measure because of MRI changes from prior surgery and radiation". One additional patient received prior pituitary radiation but did not have evaluable baseline/post-baseline tumour measurements

Safety and Tolerability

- No new safety signals were identified after 22 weeks of treatment
- The most commonly reported AEs are shown in **Table 4**
  - The frequency of these AEs decreased over time (**Table 4**)

Table 4. Most Frequent AEs (≥30% of Patients; Regardless of Drug Relationship) from Baseline and Occurrence Rate by Time Interval

	Patients (N=16)		Occurrence rate (events per patient year)		
	All grades, n (%)	Grade 3/4, n (%)	≤22 weeks	>22 weeks to 1 year	>1 year
Clinical AEs					
Adrenal insufficiency	6 (37.5)	1 (6.3)	0.54	0.33	0
Nasopharyngitis	6 (37.5)	0	0.8	0.11	0.27
Diarrhoea	6 (37.5)	0	0.4	0.33	0.18
Asthenia	5 (31.3)	0	1.07	0	0
Nausea	5 (31.3)	0	0.67	0.22	0
Laboratory AEs					
ACTH increased	7 (43.8)	0	0.94	0.45	0
Oxycorticosteroids increased	5 (31.3)	0	0.67	0	0

For patients with multiple occurrences of a single AE, all events were included in the calculation of AE occurrence rate

- QTc prolongation of >450 ms (494 ms) was noted in one (6.3%) patient during hospitalization for gastroenteritis and dehydration
  - Resolved with dose interruption and did not recur upon re-challenge at a reduced dose (5 mg bid)
- For the patient who discontinued because of AEs, tumour diameter increased from 20.8 mm at first measurement (week 32) to 31.5 mm (week 58); ACTH increased from 43 pmol/L to 1483 pmol/L
  - Patient had history of an aggressive tumour with invasion into left cavernous sinus and chronic oculomotor nerve palsy prior to study entry
- No deaths were reported during the study

CONCLUSIONS

- **Osilodrostat led to rapid and sustained decreases in mean mUFC and serum cortisol levels, first seen within 1–2 weeks of treatment**
- **Normal mUFC levels were maintained up to 19 months in most patients who entered the extension; no patients experienced escape**
  - **Median osilodrostat dose was lower at month 19 than at week 22**
- **Long-term safety profile of osilodrostat was similar to that after 22 weeks, with no new treatment-emergent signals by month 19**
  - **Initial increase in mean testosterone level in females was less apparent at month 19**
- **Two Phase III studies (LINC-3 and LINC-4) will evaluate osilodrostat in larger patient populations (see poster EP937 for LINC-4 study design)**

REFERENCES

1. Amar L *et al*. *Hypertension* 2010;56:831–838.
2. Fleseriu M *et al*. *Pituitary* 2016;19:138–148.

ACKNOWLEDGEMENTS

We thank Robert Jenn PhD, Mudskipper Business Limited (funded by Novartis Pharmaceuticals Corporation), for providing medical editorial assistance, as well as the site investigators, study coordinators and patients who participated in the trial.

Poster presented at ECE, Munich, Germany, 28–31 May 2016

This study was sponsored by Novartis