Levoketoconazole in the Treatment of Endogenous Cushing's Syndrome: Improvements in Clinical Signs and Symptoms, Patient-Reported Outcomes and Associated Biochemical Markers in the Phase 3 SONICS Study

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Introduction

- Levoketoconazole, an orally administered ketoconazole stereoisomer, is a potent steroidogenesis inhibitor in development for the treatment of endogenous Cushing's syndrome (CS), a rare endocrine disease characterized by overproduction of cortisol[1,2]
- Results from the phase 3 SONICS (Study of levOketocoNazole In Cushing's Syndrome) demonstrated that levoketoconazole treatment normalized mean urinary free cortisol (mUFC) after 6 months of maintenance therapy, regardless of the need for dose increase, in 34 of 55 (62%) completers with UFC data[3]

Objective

- To evaluate investigator-assessed clinical signs and symptoms and patient-reported outcomes, predefined secondary endpoints, and associated biochemical markers of SONICS

Methods

- SONICS is a multinational, phase 3, single-arm, open-label, dose-titration study of oral levoketoconazole in adults with confirmed diagnosis of CS and elevated 24-hour mUFC levels ≥1.5× upper limit of normal (ULN; calculated from ≥4 adequately collected samples; **Figure 1**)

Figure 1. Study Design

*All patients started at the protocol-mandated 150 mg twice daily, but a reduction to 150 mg once daily to improve tolerability was allowed.
†A therapeutic dose was considered established when: [a] mean UFC levels were ≤ULN or [b] a maximum allowed dose of 600 mg twice daily had been reached or [c] a maximal tolerated dose had been reached and there was a clinically meaningful partial response in the opinion of the investigator.
EoM = end of maintenance; mUFC = mean urinary free cortisol; ULN = upper limit of normal.

- Primary endpoint: mUFC normalization (mUFC ≤ULN) at end of maintenance (EoM) was presented previously[3]
- Secondary endpoints reported here include changes from baseline to EoM in investigator-assessed CS clinical signs and symptoms, and patient-reported outcomes of quality of life (QoL) and depression; free testosterone levels are also reported

Results

Patient Population

- Ninety-four patients were enrolled and received ≥1 dose of study medication (ITT population; **Table**), 77 patients entered the maintenance phase (maintenance population), and 61 patients completed the maintenance phase

Table. Demographic and Baseline Characteristics (ITT Population)

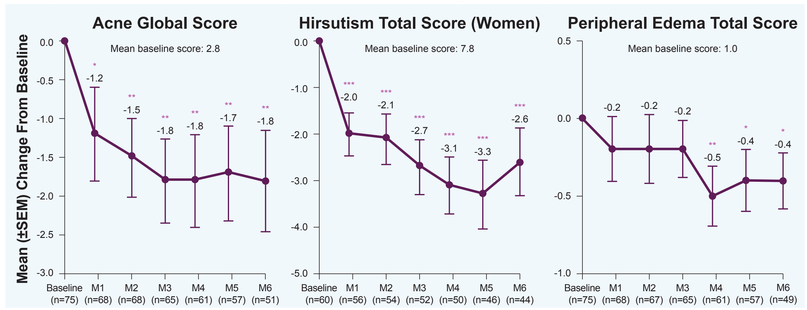
Characteristic	Patients (N=94)
Age, years, mean (SD)	43.7 (13.4)
Female, n (%)	77 (81.9)
Diagnosis of Cushing's disease, n (%)	80 (85.1)
Treatment-naive for the management of CS, n (%)	26 (27.7)
Baseline mUFC,* × ULN†	
Mean (SD)	4.9 (5.4)
Median (range)	3.0 (1.2–30.2)‡

*For each patient, the average of the UFCs from the adequate samples at baseline were calculated; n=92 (2 patients did not have ≥2 adequate urine samples at baseline).
†ULN for UFC = 50 µg/24 hours (138 nmol/24 hours).
‡1 patient with mUFC <1.5× ULN owing to inadequate urine collection.
CS = endogenous Cushing's syndrome; ITT = intent-to-treat; mUFC = mean urinary free cortisol; SD = standard deviation; ULN = upper limit of normal.

Clinical Signs and Symptoms of Cushing's Syndrome

- Significant improvements from baseline to EoM were observed in acne score (mean change, -1.8; *P*=0.0063), hirsutism score (women only; mean change, -2.6; *P*=0.0008), and peripheral edema score (mean change, -0.4; *P*=0.0295; **Figure 2**)
- Changes from baseline to EoM did not reach statistical significance (*P*=0.1085) for the total score for 7 other clinical signs and symptoms (moon facies, facial plethora, striae, bruising, supraclavicular fat, irregular menstruation [females only], and dysmenorrhea [females only]; data not shown)

Figure 2. Mean Changes From Baseline to EoM in Acne, Hirsutism, and Peripheral Edema Scores (Maintenance Population)

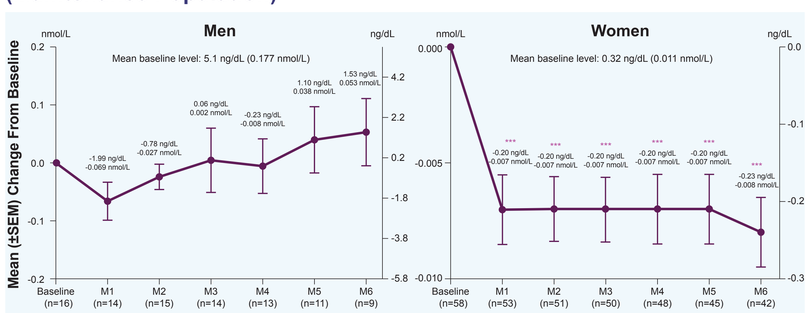


Two-sided *P* value from the paired t-test performed on the change from baseline to EoM. Acne global score: can range from 0 to 44, where 0 = none; 1-18 = mild; 19-30 = moderate; 31-38 = severe; and ≥39 = very severe. Hirsutism total score: can range from 0 (none) to 36 (worst). Peripheral edema total score: can range from 0 (none) to 12 (worst).
*P<0.05 versus baseline; **P<0.01 versus baseline; ***P<0.001 versus baseline.
EoM = end of maintenance; SEM = standard error of the mean.

Free Testosterone Levels

- Mean free testosterone levels increased non-significantly from baseline to EoM in men (5.1 to 5.8 ng/dL [0.177 to 0.202 nmol/L]) and decreased significantly in women (0.32 to 0.12 ng/dL [0.011 to 0.004 nmol/L]; *P*<0.0001; **Figure 3**)

Figure 3. Mean Changes From Baseline to EoM in Free Testosterone Levels (Maintenance Population)

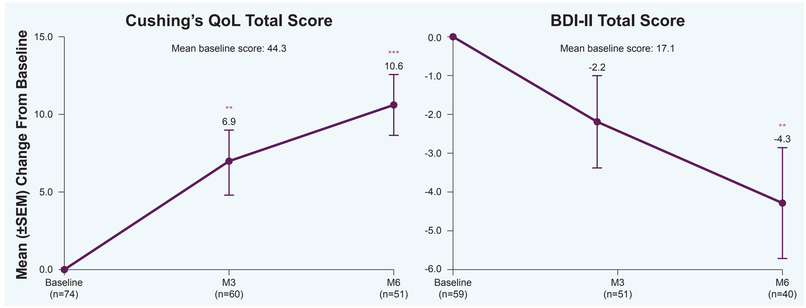


Two-sided *P* value from the paired t-test performed on the change from baseline to EoM.
Free testosterone reference levels: men age 18–69, 4.6–22.4 ng/dL (0.160–0.777 nmol/L); men age 70–89, 0.6–7.3 ng/dL (0.021–0.253 nmol/L); women age 18–69, 0.02–0.5 ng/dL (0.0007–0.017 nmol/L); women age 70–89, 0.03–0.5 ng/dL (0.001–0.017 nmol/L).
***P<0.001 versus baseline.
EoM = end of maintenance; SEM = standard error of the mean.

Patient-Reported Outcomes

- Significant mean improvements from baseline to EoM were observed in Cushing's QoL score (mean change, 10.6; *P*<0.0001) and Beck Depression Inventory-II score (mean change, -4.3; *P*=0.0043; **Figure 4**)

Figure 4. Mean Changes From Baseline to EoM in Quality of Life and Depression (Maintenance Population)



Two-sided *P* value from the paired t-test performed on the change from baseline to EoM. Cushing QoL questionnaire score: can range from 0 (worst) to 100 (best).
BDI-II total score: can range from 0 (best) to 63 (worst).
**P<0.01 versus baseline; ***P<0.001 versus baseline.
BDI-II = Beck Depression Inventory II; EoM = end of maintenance; QoL = quality of life; SEM = standard error of the mean.

Adverse Events (ITT Population)

- Overall adverse event data have been presented previously[3]; in summary, the most commonly reported adverse events were nausea (31.9% of patients), headache (27.7%), peripheral edema (19.1%), hypertension (17.0%), and fatigue (16.0%)
- Serious adverse events were reported in 14 patients, of which 4 were considered to be probably or definitely related to levoketoconazole: elevated liver function test results (1 patient), prolonged QTc interval (2 patients), and adrenal insufficiency (1 patient)
- Adverse events led to treatment discontinuation in 12 patients (12.8%)

Conclusions

- **In this large, multinational, phase 3, open-label trial, clinical signs and symptoms of CS, including acne, hirsutism (in women), and peripheral edema, significantly improved following 6 months of maintenance levoketoconazole therapy**
- **Reduction in mean free testosterone in women, consistent with improvements in clinical signs of hyperandrogenism, and a modest increase in mean free testosterone in men were observed**
- **Patient-reported outcomes of QoL and symptoms of depression improved**
- **Levoketoconazole was generally well tolerated, with 12.8% of patients discontinuing due to an adverse event through the EoM**
- **Improvements in clinician- and patient-reported signs and symptoms of CS further support the utility of levoketoconazole treatment in CS**

References

1. Creemers SG, et al. *Expert Opin Pharmacother*. 2015;16(12):1829-1844. 2. Fleseriu M, Castinetti F. *Pituitary*. 2016;19:643-653. 3. Fleseriu M, et al. Presented at the 18th Congress of the European Neuroendocrine Association; October 17-20, 2018; Warsaw, Poland.

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