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Prospective, Open Label, Phase 3 Study of Levoketoconazole in Cushing Syndrome (SONICS): Primary Safety and Efficacy Results

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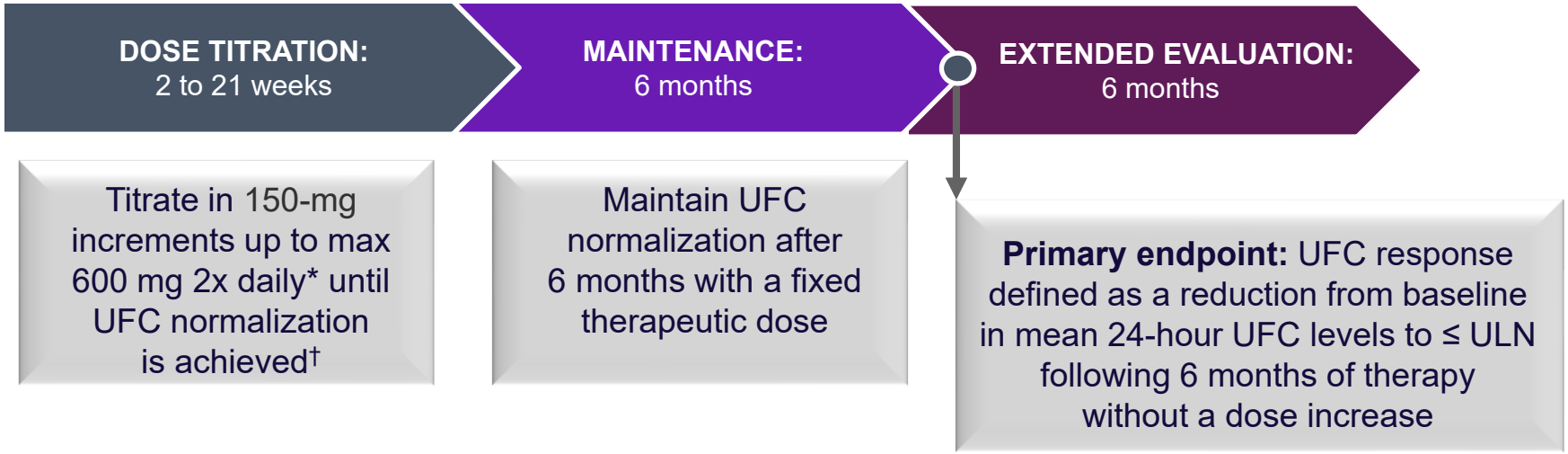
SONICS Maintenance-of-Benefit Study Design

- A prospective, phase 3, open-label, single-arm, dose-titration, maintenance-of-benefit study to assess the safety and efficacy of levoketoconazole (COR-003) in the treatment of endogenous Cushing Syndrome (CS)

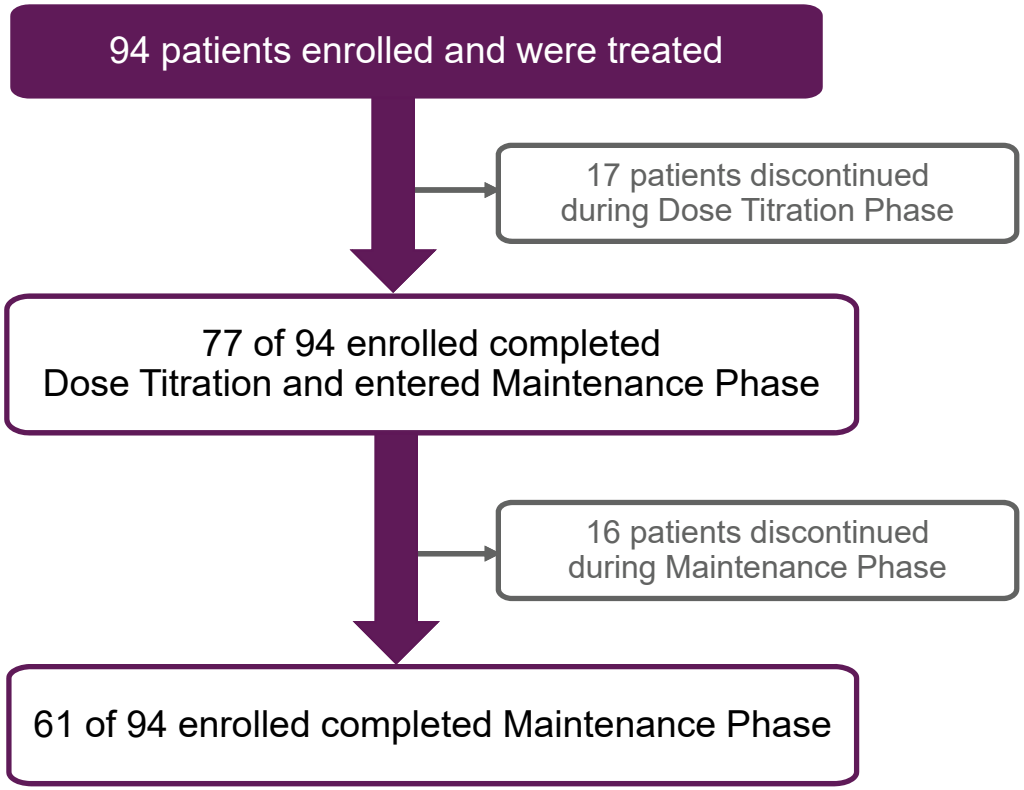


*All patients began at the protocol-mandated 300 mg daily, but a reduction to 150 mg once daily to resolve tolerability issues was allowed.
†mUFC above ULN was allowed to advance to the Maintenance Phase (at least 50% decrease in mUFC required and had to reach the highest allowed or tolerated dose).
mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal.

Key Secondary Endpoints and Analysis Population

- Changes from baseline in selected cardiovascular risk biomarkers after 6 months of dosing in the Maintenance Phase were predefined
- Safety/tolerability evaluation: treatment-emergent adverse events (TEAEs) and prespecified adverse events (AEs) of special interest (potential liver toxicity, QTc prolongation, and adrenal insufficiency)
- Intent-to-treat population included all patients who received at least one dose of levoketoconazole
  - This population was used for the evaluation of efficacy and all safety analyses
  - Efficacy was also evaluated for two secondary analysis populations
    - Maintenance (M) Population – all patients who received at least one dose of levoketoconazole in the M Phase
    - Maintenance Completers (MC) Population – all patients who completed the M Phase

Patient Disposition



Demographics and Disease Characteristics

	(N=94)
Age, mean (SD), years	44 (13)
Gender, n (%) Female Male	 77 (82) 17 (18)
Baseline weight, mean (SD), kg	84 (23)
BMI,* mean (SD), kg/m^2	31 (8)
Time since diagnosis, months Mean (SD) Median Range	 68 (80) 34 0.7-434
Diagnosis of Cushing disease, n (%)	80 (85)
Diagnosis of diabetes, n (%)	36 (38)
Diagnosis of hypertension, n (%)	67 (71)
Diagnosis of hypercholesterolemia, n (%)	34 (36)
Baseline mean UFC†, nmol/24 hours; fold ULN Mean (SD) Median Range	 671 (743); 5x (5x) 408; 3x 162-4168; 1.2x-30x

- Prior pituitary radiotherapy for CS: 9 patients (10%)
- Prior surgery for CS: 65 patients (69%)
- No prior therapy for CS (completely treatment-naïve): 26 patients (28%)

*BMI is based on 93 patients. One patient had a missing BMI due to missing height information.
†For each patient, the average of the UFCs from the adequate samples at baseline were calculated. Upper limit of normal (ULN) UFC - 138 nmol/24 hours.
BMI, body mass index; CS, Cushing Syndrome; UFC, urinary free cortisol; SD, standard deviation.

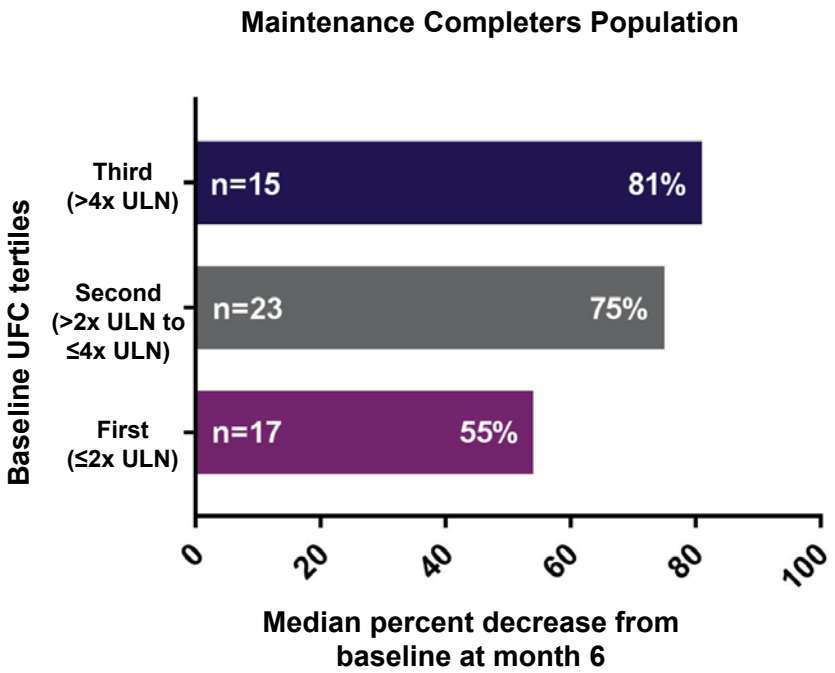
Efficacy: UFC Responder Analysis at End of Maintenance Phase

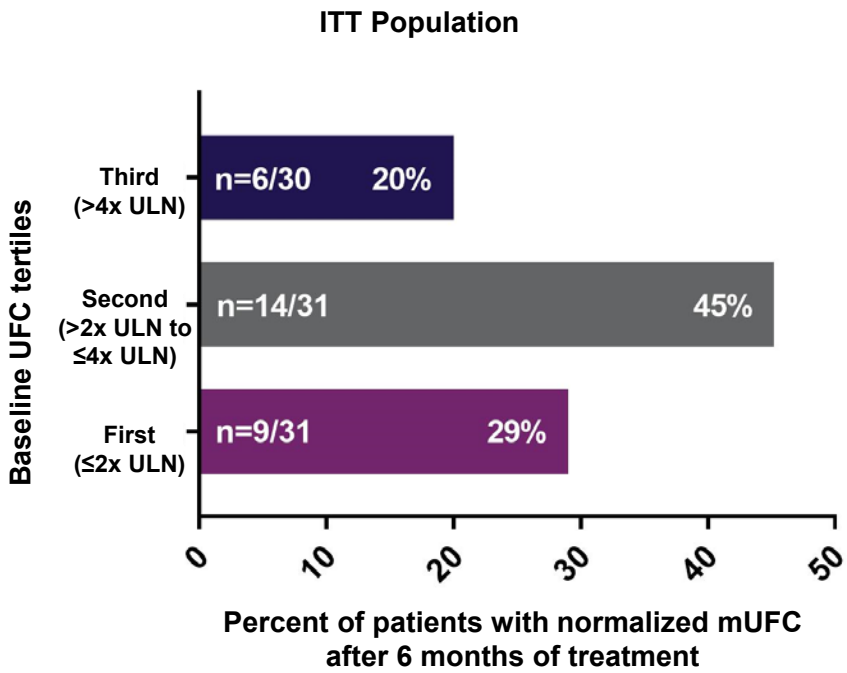
	N=94
Primary endpoint: mUFC normalization without a dose increase	**30% (29/94)* 95% CI, 21%-40%; *P*=0.0154**
mUFC normalization (regardless of dose increase)	38% (36/94)*† 95% CI, 28%-49%
Analysis of observed rate at month 6 with imputation for missing mUFC after month 3	42% (40/94)‡ 95% CI, 32%-53%
≥50% mUFC decrease or normalization (regardless of dose increase)	48% (45/94)*† 95% CI, 37%-58%
Maintenance Phase *completers* with mUFC data and mUFC normalization without a dose increase	53% (29/55)¥
Maintenance Phase *completers* with mUFC data and ≥50% UFC reduction from baseline	76% (42/55)¥

*Based on mixed-effects, repeated measures model with underlying binomial distribution and logit link function, adjusting for baseline covariates. For the primary analysis only, one-sided P-value vs null hypothesis of ≤20% response is presented.
†Imputed mUFC as normal for a missing value at EOM, if mUFC was normal at preceding and subsequent visits.
‡Imputed missing value at EOM as last non-missing mUFC from latest of month 3,4,or 5. CI is from the Clopper-Pearson two-sided 95% CI for the one-sample binomial proportion.
¥ Data based on 55 Maintenance Phase completers with both baseline and month 6 UFC data available.
EOM, End of Maintenance phase; mUFC, mean urinary free cortisol.

- At the end of the Dose Titration Phase, 81% (62/77) of M patients had achieved mUFC normalization
- A majority (66%) of the Maintenance Phase completers had received ≤600 mg/day

Influence of Baseline mUFC on mUFC Improvement at End of Maintenance Phase

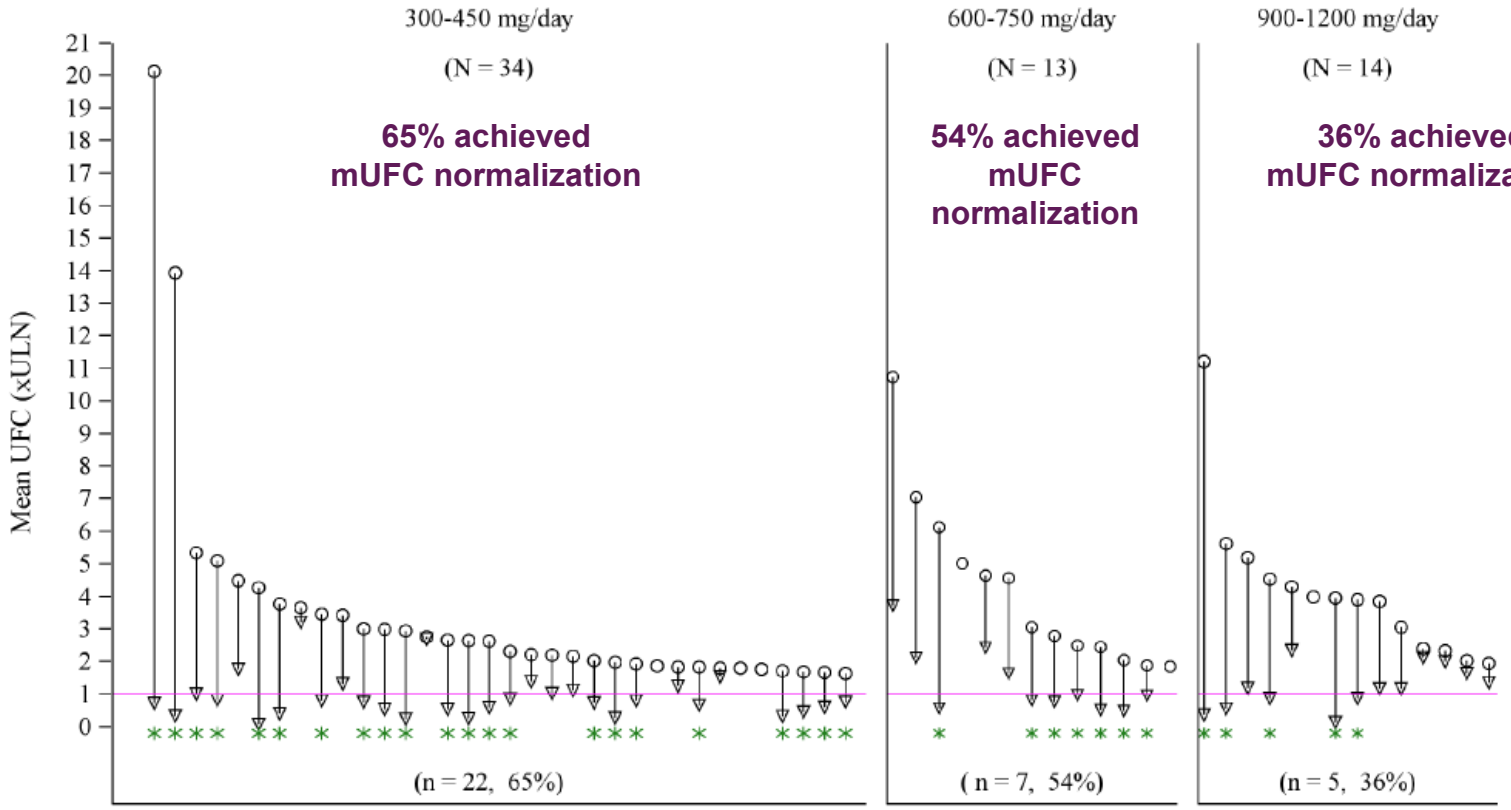




- Relative mUFC reductions from baseline were substantial and were not related to baseline UFC

EOM, End of Maintenance Phase; ITT, intention-to-treat; mUFC, mean urinary free cortisol.

Individual Patient mUFC* From Baseline to Month 6 by Combined Dose Groups in MC Population



*The patients within each dose group are plotted by decreasing baseline mUFC.
mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal.

Significant Changes From Baseline in Key Secondary Endpoints at Month 6*

Outcome Measure at EOM	Baseline Mean, (n)	Mean Change From Baseline, (n)
Fasting blood glucose	6 mmol/L (76)	-0.68‡ (50)
Hemoglobin A1c	6% (77)	-0.39‡ (55)
Total cholesterol	6 mmol/L (77)	-1.11‡ (53)
LDL-cholesterol	3 mmol/L (77)	-0.97‡ (53)
HDL-cholesterol	2 mmol/L (77)	-0.20‡ (53)
Body weight	82 kg (77)	-5.10‡ (54)
Body mass index	30 kg/m^2 (77)	-1.89 (54)

Note: All least squares mean changes from baseline for outcome measures at EOM were statistically significant; *P*<0.0001

‡Hochberg adjustment applied to *P* values to control type 1 error at 0.05 (except BMI); reductions from baseline based on least squares mean changes from baseline from mixed-effects, repeated measures models adjusting for baseline covariates.
*Analysis based on the N=77 patients who entered the Maintenance Phase. There was no imputation for missing data, so only those patients with both baseline and month 6 data were included in the analysis of each outcome measure.

No statistically significant mean changes observed in blood pressure or C-reactive protein.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TEAEs Summary

- 92 patients (98%) had at least 1 treatment-emergent adverse event (TEAE)
- 40 patients (43%) had at least 1 TEAEs *probably* or *definitely* related to study drug
- 12 patients (13%) discontinued study drug due to TEAEs
- 14 patients (15%) had at least 1 treatment-emergent serious AE
  - In 4 patients, the treatment-emergent serious AE was considered probably or definitely related to study drug
    - 1 case of elevated liver function tests, 2 cases of prolonged QTc, and 1 case of adrenal insufficiency
- 15 patients (16%) had at least 1 TEAE that was graded as severe (worst toxicity grade reported)

Most Commonly Reported TEAEs

TEAE	Number of Patients	% of Enrolled (N=94)
Nausea	30	32%
Headache	26	28%
Peripheral edema	18	19%
Hypertension	16	17%
Fatigue	15	16%
Diarrhea	14	15%
ALT increased*	**14**	**15%**
GGT increased*	**12**	**13%**

*Includes all ALT/GGT increases reported as an adverse event regardless of level or relationship to drug. *A subset of these ALT/GGT increased events was also reported as adverse events of special interest. Patients rarely discontinued from common AEs.*

ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; TEAEs, treatment-emergent adverse events.

Liver-Related Laboratory Values

	N=94
Liver-related AEs defined in protocol as AE of special interest	7 (7%)*
ALT >1x ULN to 3x ULN	29 (31%)
ALT >3x ULN to 5x ULN	7 (7%)
ALT >5x ULN	3 (3%)
Total bilirubin values >1.5x ULN	0%

*No severe drug-induced liver injury; no Hy's law; no transaminases >20x ULN; no obvious dose relationship.

- All ALT >3X ULN occurred at Day 60 of Maintenance or earlier
- In all 10 (11%) patients with ALT >3x ULN (including 3 with ALT >5x ULN), the ALT elevation was reversible after discontinuing drug without any clinical sequelae

AE, adverse event; ALT, alanine aminotransferase; ULN, upper limit of normal.

QTc Data Summary (ECG)

- Normal QTc: <450 msec in men and <460 msec in women
  - Allowed up to 470 msec into study
- Baseline QTcF: mean 404 msec; median 402 msec
- 9 patients (10%) had at least 1 QTc value representing >60 msec increase from baseline value
- 2 patients (2%) had at least 1 confirmed QTc interval of >500 msec at any time
  - Both represented an increase of more than 60 msec above baseline and were during the Maintenance Phase
- All QTc prolongations reversed with temporary drug interruption and all patients affected were able to resume study drug at the same or lower dose following the prolongation event
- No arrhythmias, associated or unassociated with QTc prolongation, were reported during the study

SONICS Conclusions

- In this large, international, prospective trial, levoketoconazole* monotherapy normalized mUFC initially in 62 (of 77) patients with CS who advanced into the Maintenance Phase
- Of the 62 patients with normalized mUFC at entry into Maintenance, 27 had normalized mUFC at Month 6, *without a preceding dose increase* (using rigorous criteria for primary endpoint analysis); 2 patients with non-normal mUFC at entry also normalized at Month 6
- Markers of cardiovascular risk also improved significantly coincident with mUFC improvement
- No unexpected safety signals observed from AE data and there was a low discontinuation rate due to TEAEs (13%)
- Liver enzyme elevation >3x ULN, which occurred among 10 (11%) patients, on or before D60 of M, was fully reversible upon drug discontinuation without clinical sequelae

**The safety and efficacy of levoketoconazole (COR-003) for treatment of endogenous Cushing syndrome have not been established.*

Acknowledgements

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- This trial was sponsored by Cortendo AB, a subsidiary of Strongbridge Biopharma, Trevose, PA, USA and funding for this support was provided by Strongbridge Biopharma

Shift Table From Baseline for LFT: ALT

	Worst Post-baseline Alanine Aminotransferase (ALT), n (%)					
Baseline ALT*	**Normal**	**>1x ULN to 3x ULN**	**>3x ULN to 5x ULN**	**>5x ULN to 10x ULN**	**>10x ULN**	**Total**
Normal	54 (57)	27 (29)	6 (6)	1 (1)	2 (2)	90 (96)
>1x ULN to 3x ULN	1 (1)	2 (2)	1 (1)	0	0	4 (4)
Total	55 (59)	29 (31)	7 (7)	1 (1)	2 (2)	94

- Nearly all ALT values that became ULN during the study were within normal limits at the Screening/Baseline visits

*Patients were excluded for Screening/Baseline ALT levels greater than 3-fold ULN.
ALT, alanine aminotransferase; LFT, liver function test; ULN, upper limit of normal.