Poster SAT-452

Results From the Phase 3 Multicenter SONICS Study of Levoketoconazole: Subgroup Analysis of Cushing's Syndrome Patients With Diabetes Mellitus

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*Potential conflicts of interest may exist. Refer to the Meeting App.

Introduction and Objective

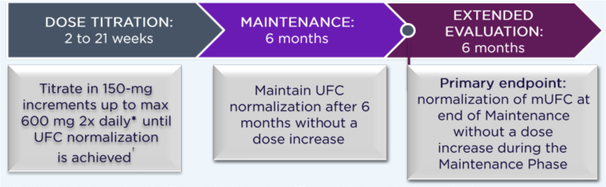
- Endogenous Cushing's Syndrome (CS) is characterized by chronic overproduction of cortisol[1,2] and is associated with numerous comorbidities, one of which is diabetes mellitus (DM)[3]
- Levoketoconazole, a ketoconazole stereoisomer, is a steroidogenesis inhibitor in development for the treatment of CS[4]
- This subgroup analysis assessed the efficacy and safety of levoketoconazole in the treatment of patients with CS and type 2 DM

Methods

Study Design and Patients

- The Study of levOketotocoNazole In Cushing's Syndrome (SONICS) is a phase 3, single-arm, open-label, dose-titration study of oral levoketoconazole in adults with confirmed diagnosis of CS and elevated mean 24-hour urinary free cortisol (mUFC) levels ≥1.5x 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 either: [a] mean UFC levels were ≤ULN or [b] a maximum allowed dose of 600 mg twice daily was reached or [c] a maximal tolerated dose was reached and there was a clinically meaningful partial response in the opinion of the investigator; mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal.

- Exclusion: patients with repeated hospitalization for hyperglycemia or DM complications within the last 12 months
- Hemoglobin A1c (HbA1c) and fasting blood glucose (FBG) were assessed at screening and at prespecified intervals throughout the study

Outcomes

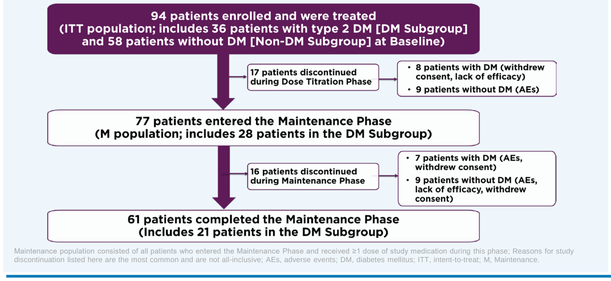
- Primary endpoint: mUFC normalization (mUFC ≤ULN) at End of Maintenance Phase (EOM) was presented previously[5]
- Key secondary endpoints reported here: changes from Baseline in glycemic control (HbA1c and FBG) and cardiovascular (CV) risk biomarkers at EOM
- Safety: treatment-emergent adverse events (TEAEs) and AEs of special interest (potential liver toxicity, QTc prolongation, and adrenal insufficiency)

Results

Patient Population

- Ninety-four patients received ≥1 dose of study medication (intent-to-treat [ITT] population; **Figure 2)**

Figure 2: Patient Disposition



Maintenance population consisted of all patients who entered the Maintenance Phase and received ≥1 dose of study medication during this phase; Reasons for study discontinuation listed here are the most common and are not all-inclusive; AEs, adverse events; DM, diabetes mellitus; ITT, intent-to-treat; M, Maintenance.

Table 1: Patient Demographics and Baseline Characteristics

	DM Subgroup (N=36)	Non-DM Subgroup (N=58)	ITT Population (N=94)
Age, y, mean (SD)	48.3 (12.21)	40.8 (13.46)	43.7 (13.43)
Female, n (%)	33 (91.7)	44 (75.9)	77 (81.9)
Race, n (%)			
White	34 (94.4)	56 (96.6)	90 (95.7)
Other^	2 (5.6)	2 (3.4)	4 (4.3)
Baseline weight, kg, mean (SD)	88.4 (22.45)	81.2 (23.79)	84 (23.43)
Baseline BMI,* kg/m^2, mean (SD)	34.01 (8.358)	28.79 (7.492)*	30.81 (8.202)*
Diagnosis of Cushing disease, n (%)	29 (80.6)	51 (87.9)	80 (85.1)
Diagnosis of hypertension, n (%)	32 (88.9)	35 (60.3)	67 (71.3)
Diagnosis of hypercholesterolemia, n (%)	21 (58.3)	13 (22.4)	34 (36 .2)
Baseline mean UFC, mcg/24 h			
Mean (SD)	210.0 (256.88)‡	262.8 (276.58)	243.3 (269.26)
Median	132.3; 3x	152.3; 3x	147.8; 3x

^Other includes black and unknown races; *BMI is based on 93 patients; One patient had a missing BMI due to missing height information; ‡Baseline mean UFC based on 34 patients; BMI, body mass index; DM, diabetes mellitus; ITT, intent-to-treat; UFC, urinary free cortisol

Efficacy

- At EOM, 34% in the DM Subgroup (*P*=0.035), 25% in the non-DM Subgroup (*P*=0.196), and 30% in the ITT population (*P*=0.015) had normalization of mUFC (one-sided P-value vs. null hypothesis of ≤20). DM was not a significant factor in the model of mUFC response among the ITT population (odds ratio 1.25; *P*=0.606)

Table 2: Number of Patients on Concomitant Medication at Baseline and Their Change in Usage at EOM*

Type of Medication	Patients Taking Medication Before the Start of Study Drug	Started New and Significant Medication	Dose Increased or Restarted After Gap	Dose Decreased	No Change From Baseline	Stopped Taking Medication
Antidiabetic, n	16	1	1	0	9	5
Cholesterol lowering, n	5	0	0	0	4	1
Antihypertensive, n	15	1	4	1	8	1

*These are patients in the DM Subgroup in the M Population (N=28); DM, diabetes mellitus; EOM, End of Maintenance; M, Maintenance.

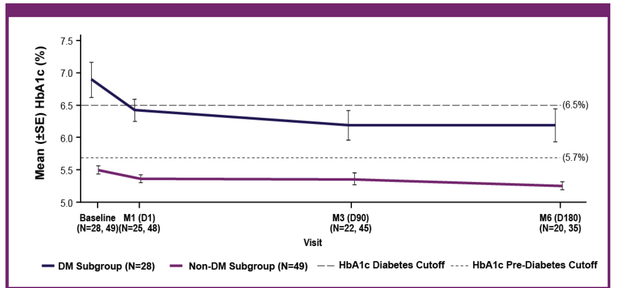
Table 3: Change from Baseline in Key Secondary Endpoints at EOM in Patients with and without DM in the M Phase

Outcome Measure at EOM Phase	DM Subgroup			Non-DM Subgroup		
	Baseline Mean (n)	EOM Mean (n)	Significance Level	Baseline Mean (n)	EOM Mean (n)	Significance Level
Fasting blood glucose, mg/dL	123.30 (28)	104.76 (18)	*P*=0.046	91.98 (48)	83.88 (33)	*P*=0.044
Hemoglobin A1c	6.90% (28)	6.20% (20)	*P*=0.031	5.51% (49)	5.27% (35)	*P*=0.003
Total cholesterol, mg/dL	98.08 (27)	83.07 (20)	*P*=0.004	103.68 (48)	83.41 (34)	*P*<0.0001
LDL cholesterol, mg/dL	55.46 (27)	41.90 (20)	*P*=0.002	61.56 (48)	44.96 (34)	*P*<0.0001
HDL cholesterol, mg/dL	26.66 (27)	25.16 (20)	*P*=0.107	30.96 (48)	27.38 (34)	*P*=0.001
Body weight, kg	86.6 (28)	81.3 (20)	*P*<0.0001	79.5 (49)	76.3 (34)	*P*=0.004
BMI, kg/m^2	33.50 (28)	31.15 (20)	*P*=0.0001	27.82 (48)	27.11 (34)	*P*=0.002
Abdominal girth, cm	111.81 (20)	99.72 (17)	*P*=0.038	100.86 (28)	95.16 (22)	*P*=0.268
Systolic blood pressure, mmHg	134.40 (28)	136.25 (20)	*P*=0.497	133.29 (49)	131.28 (34)	*P*=0.519
Diastolic blood pressure, mmHg	79.56 (28)	82.77 (20)	*P*=0.279	85.82 (49)	82.57 (34)	*P*=0.146
Triglycerides, mg/dL	36.22 (27)	38.12 (20)	*P*=0.398	24.34 (4 8)	24.14 (34)	*P*=0.520

The *P* values were from paired t-tests and are considered descriptive; BMI, body mass index; DM, diabetes mellitus; EOM, End of Maintenance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, Maintenance.

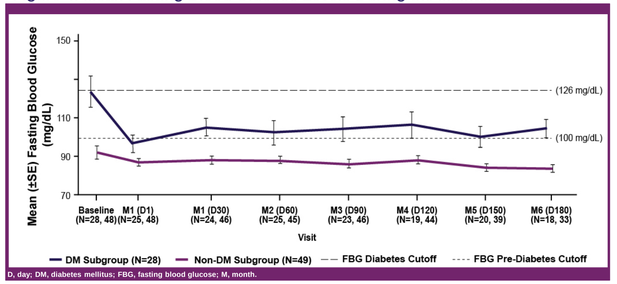
- Changes in glycemia over time
  - Improvements in HbA1c (**Figure 3**) and FBG (**Figure 4**) were more pronounced in the DM subgroup compared with the non-DM subgroup at EOM

Figure 3: Mean Hemoglobin A1c Levels During the Maintenance Phase



D, day; DM, diabetes mellitus; HbA1c, hemoglobin A1c; M, month.

Figure 4: Mean Fasting Blood Glucose Levels During the Maintenance Phase



D, day; DM, diabetes mellitus; FBG, fasting blood glucose; M, month.

Safety

- The most common TEAEs in the DM subgroup were nausea (58%), vomiting (19%), and urinary tract infection (17%) and in the non-DM subgroup were headache (36%), peripheral edema (22%), and hypertension (19%)

Table 4: Summary of Safety Information During the Dose Titration and Maintenance Phases

	DM Subgroup (N=36)	Non-DM Subgroup (N=58)
Patients reporting at least 1 TEAE, n (%)	35 (97)	57 (98)
Patients with TEAEs probably or definitely related to the study drug, n (%)	15 (42)	25 (43)
Patients discontinued due to TEAEs, n (%)	4 (11)	8 (14)
Patients with treatment-emergent SAEs, n (%)	7 (19)	7 (12)
Patients with treatment-emergent SAEs probably or definitely related to the study drug, n (%)	3 (8)	1 (2)
Patients with post-baseline QTc, n	35	53
Patients with post-baseline QTc who had at least 1 QTc value representing >60 msec increase from baseline, n (%)	3 (9)	6 (11)
Patients reporting adrenal insufficiency, n (%)	1 (3)	2 (3)

DM, diabetes mellitus; QTc, corrected QT interval; SAEs, serious adverse events; TEAE, treatment-emergent adverse event.

- Alanine aminotransferase (ALT) levels were similar between the DM and non-DM subgroups throughout the study (data not shown)
- At Baseline, urine glucose was present in 10.8% (10/93) of the ITT population; 7 of these 10 were patients with DM. At EOM, no urine glucose was present in the DM and non-DM subgroups

Conclusions

- In this prospective trial, maintenance of mUFC normalization with levoketoconazole was similar in patients with and without DM
- Improvements in HbA1c and FBG in the Maintenance population were more pronounced among patients with DM, while anti-diabetic medications were more often decreased than increased
- Significant improvements in CV risk markers of LDL-cholesterol, weight, BMI, and waist circumference were seen in patients with and without DM; improvement in LDL-cholesterol occurred without any new use of statins or increases in statin dose
- The improvement in LDL-cholesterol was partially counterbalanced by a relatively smaller increase in triglycerides and a decrease in HDL-cholesterol that was not apparently different in DM patients
- The rate of discontinuation due to TEAEs was low in both patients with DM and without DM; however, patients with DM reported nausea, vomiting, and urinary tract infection more frequently. The differing TEAE profile may be related to diabetes itself or to concomitant medications used to treat it, especially metformin

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