Poster GP166

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

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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, an orally administered 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 levOketocoNazole 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)
- There were 3 study phases: 2- to 21-week dose-titration phase (150–600 mg twice daily, as needed, to target mUFC normalization), 6-month maintenance phase, and 6-month extended evaluation phase (**Figure 1**)
- Exclusion: patients with repeated hospitalization for hyperglycemia or DM complications within the last 12 months

Outcomes

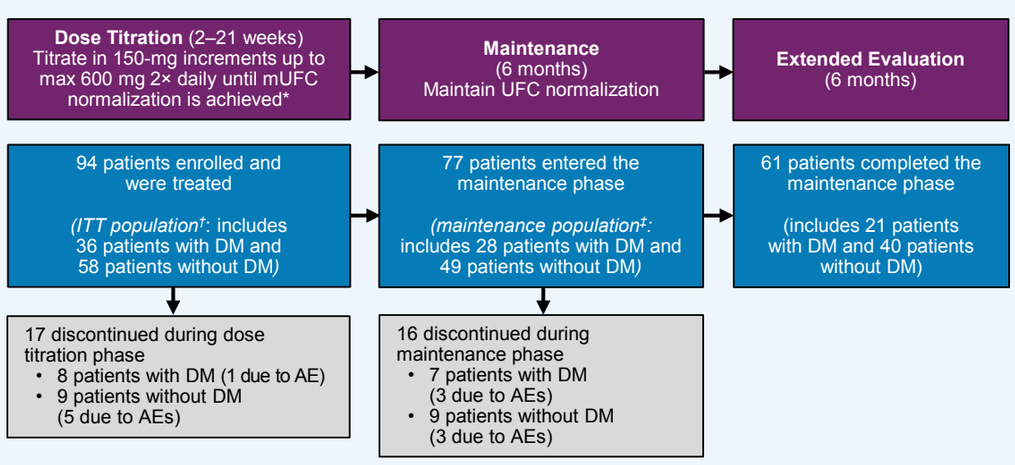
- Primary endpoint: mUFC normalization (mUFC ≤ULN) at end of maintenance phase (EOM) was presented previously[5]
- Key secondary endpoints reported here: changes from baseline in glycemic control (hemoglobin A_{1c} [HbA_{1c}] and fasting blood glucose [FBG]) and other cardiovascular (CV) risk biomarkers 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 1**)

Figure 1. Study Design and Patient Disposition



*All patients started at the protocol-mandated dose of 150 mg twice daily, but a reduction to 150 mg once daily to improve tolerability was allowed. †ITT population included all patients who received ≥1 dose of study medication. ‡Maintenance population consisted of all patients who entered the maintenance phase and received ≥1 dose of study medication during this phase.
AEs = adverse events; DM = diabetes mellitus; ITT = intent-to-treat; mUFC = mean 24-hour urinary free cortisol.

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 Other*	 34 (94.4) 2 (5.6)	 56 (96.6) 2 (3.4)	 90 (95.7) 4 (4.3)
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 mUFC Mean (SD), nmol/24 h Median, nmol/24 h Mean (SD), µg/24 h Median, µg/24 h	 579.6 (709.0)† 365.1; 3x ULN 210.0 (256.9)† 132.3	 725.2 (763.4) 420.3; 3x ULN 262.8 (276.6) 152.3	 671.4 (743.1) 407.9; 3x ULN 243.3 (269.3) 147.8

*Other includes black and unknown races. †Baseline mUFC based on 34 patients.
DM = diabetes mellitus; ITT = intent-to-treat; mUFC= mean 24-hour urinary free cortisol; SD = standard deviation; ULN = upper limit of normal.

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 versus null hypothesis of ≤20%); DM was not a significant factor in the statistical 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, n	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	16	1	1	0	9	5
Cholesterol lowering	5	0	0	0	4	1
Antihypertensive	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.

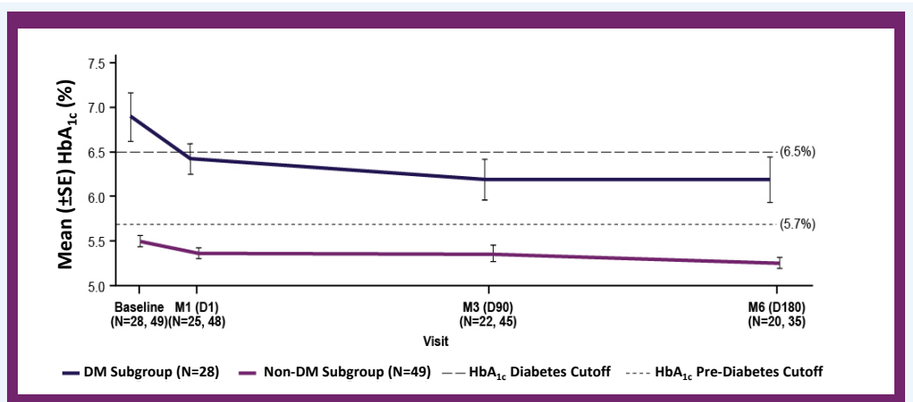
Table 3. Change From Baseline in Key Secondary Endpoints at EOM in Patients With and Without DM in the M Phase

Outcome Measure at EOM Phase	DM Subgroup Baseline Mean (n)	DM Subgroup EOM Mean (n)	DM Subgroup Significance Level	Non-DM Subgroup Baseline Mean (n)	Non-DM Subgroup EOM Mean (n)	Non-DM Subgroup Significance Level
Fasting blood glucose, mmol/L mg/dL	7 (28) 123	6 (18) 105	*P*=0.046	5 (48) 92	5 (33) 84	*P*=0.044
Hemoglobin A_{1c}	7% (28)	6% (20)	*P*=0.031	6% (49)	5% (35)	*P*=0.003
Total cholesterol, mmol/L mg/dL	5 (27) 210	5 (20) 178	*P*=0.004	6 (48) 222	5 (34) 179	*P*<0.0001
LDL cholesterol, mmol/L mg/dL	3 (27) 119	2 (20) 90	*P*=0.002	3 (48) 132	3 (34) 96	*P*<0.0001
HDL cholesterol, mmol/L mg/dL	1 (27) 57	1 (20) 54	*P*=0.107	2 (48) 66	2 (34) 59	*P*=0.001
Body weight, kg	87 (28)	81 (20)	*P*<0.0001	80 (49)	76 (34)	*P*=0.004
BMI, kg/m^2	34 (28)	31 (20)	*P*=0.0001	28 (48)	27 (34)	*P*=0.002
Abdominal girth, cm	112 (20)	100 (17)	*P*=0.038	101 (28)	95 (22)	*P*=0.268
Systolic blood pressure, mmHg	134 (28)	136 (20)	*P*=0.497	133 (49)	131 (34)	*P*=0.519
Diastolic blood pressure, mmHg	80 (28)	83 (20)	*P*=0.279	86 (49)	83 (34)	*P*=0.146
Triglycerides, mmol/L mg/dL	2 (27) 178	2 (20) 187	*P*=0.398	1 (48) 120	1 (34) 119	*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.

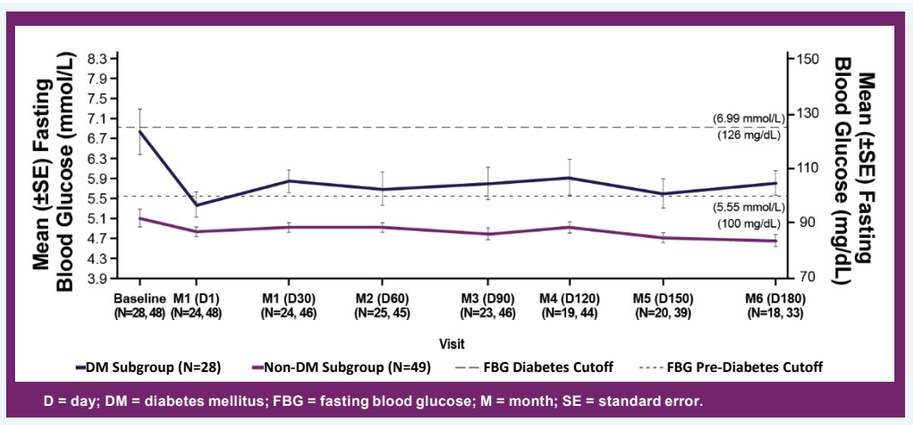
- Changes in glycemia over time
  - Improvements in HbA_{1c} (**Figure 2**) and FBG (**Figure 3**) were more pronounced in the DM subgroup compared with the non-DM subgroup at EOM

Figure 2. Mean Hemoglobin A_{1c} Levels During the Maintenance Phase



D = day; DM = diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}; M = month; SE = standard error.

Figure 3. Mean Fasting Blood Glucose Levels During the Maintenance Phase



D = day; DM = diabetes mellitus; FBG = fasting blood glucose; M = month; SE = standard error.

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 with 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 with adrenal insufficiency, n (%)	1 (3)	2 (3)
Patients with ALT >3x ULN, n (%)	2 (6)	8 (14)
Patients with ALT >5x ULN, n (%)	0 (0)	3 (5)

ALT = alanine aminotransferase; DM = diabetes mellitus; QTc = corrected QT interval; SAEs = serious adverse events; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

- 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 HbA_{1c} and FBG in the maintenance population were more pronounced among patients with DM, whereas anti-diabetic medications were more often decreased than increased
- Significant improvements in CV risk markers of low-density lipoprotein (LDL)-cholesterol, weight, body mass index, 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
  - A significant decrease in mean high-density lipoprotein-cholesterol level was observed only in patients without DM
- 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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Acknowledgements
The authors acknowledge all investigators, coinvestigators, and research nurses/study coordinators who performed the study and all patients who participated in the study. This study was funded by Cortendo AB (a subsidiary of Strongbridge Biopharma, Trevose, PA, USA). Medical writing assistance was provided by Michelle Uberti, PhD, and Amy Ross, PhD, of ETHOS Health Communications of Yardley, PA, and Pratibha Hebbar, PhD, of Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Strongbridge Biopharma.

Disclosures
Authors report serving as principal/clinical investigators and/or receiving research grants (to their institutions): Chiasma (YG), Corcept Therapeutics (RP), Ionis (EBG), Millendo Therapeutics (MF), Novartis (MF, RP, RS, RJA, EBG, YG, BMKB), and Strongbridge Biopharma (MF, RP, RS, RJA, EBG, YG, BMKB); serving as scientific consultants, receiving consulting honoraria, receiving clinical investigator/research/speakers' fees, and/or receiving travel grants: Corcept Therapeutics (EBG), HRA Pharma (RAF), Ipsen (PW), Medison (YG), Novartis (MF, RP, AE, RJA, RAF, EBG, YG, PW, BMKB), Novo Nordisk (PW), Pfizer (YG), and Strongbridge Biopharma (MF, RP, RJA, EBG, PW, BMKB); and being employed by Strongbridge Biopharma (FC).

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