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

Levoketoconazole (LCZ) is a synthetic analogue of ketoconazole, with a longer elimination half-life compared to ketoconazole and through direct glucocorticoid receptor (GR) interaction in the cytoplasm. Consistent with the findings of the recent phase 2 SONICS study in Cushing’s syndrome (CS) patients, the current analysis focuses on the subgroup of patients with diabetes mellitus (DM) to investigate the efficacy and safety of LCZ in the treatment of CS with and without DM.

Methods

Study Design and Patients

The Study of SONICS in Cushing’s Syndrome (SONICS) is a phase 3, single-arm, open-label, dose escalation study of LCZ and placebo in patients with cortisol hypersecretion due to CS. Patients were randomized to 1 of 2 groups: 190 mg/s/day (M Phase) or 380 mg/s/day (D Phase). Study treatment was a 12-week short-term induction phase (ITP) followed by a 12-week maintenance phase (M Phase). Patients were followed up to 24 weeks.

Outcomes

The primary endpoint was mUFC normalization (mUFC ≤ULN) at End of Maintenance Phase (EOM). The key secondary endpoints were changes from Baseline in glycemic control (HbA1c and fasting blood glucose [FBG]) and cardiovascular (CV) risk biomarkers at EOM.

Results

Patient Population

Ninety-four patients received ≥1 dose of study medication (intent-to-treat [ITT] population; n = 93 in both subgroups). Patient disposition is shown in Figure 1 (Study Design).

Table 1: Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M Phase</th>
<th>D Phase</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>56.8 (13.8)</td>
<td>57.6 (13.4)</td>
<td>0.436</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>29 (58.9)</td>
<td>59 (65.8)</td>
<td>0.191</td>
</tr>
<tr>
<td>White</td>
<td>67 (65.7)</td>
<td>101 (92.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Baseline weight, kg</td>
<td>86.0 (24)</td>
<td>85.2 (25)</td>
<td>0.573</td>
</tr>
<tr>
<td>EOM weight, kg</td>
<td>81.2 (22)</td>
<td>79.6 (23)</td>
<td>0.57</td>
</tr>
<tr>
<td>Antidiabetic, n</td>
<td>20 (40.8)</td>
<td>32 (36.8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Antihypertensive, n</td>
<td>32 (64.2)</td>
<td>57 (63.8)</td>
<td>0.98</td>
</tr>
<tr>
<td>Median glucose, mg/dL</td>
<td>113.8 (25)</td>
<td>115.8 (26)</td>
<td>0.52</td>
</tr>
<tr>
<td>Median sodium, mEq/L</td>
<td>144 (3)</td>
<td>144 (3)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Safety

Adverse events: 77 patients entered the Maintenance Phase (M Phase; includes 26 patients in the DM subgroup). Primary adverse events are listed in Table 2. Safety was similar in both subgroups throughout the study. The rate of discontinuation due to adverse events was low in both patients with and without DM; improvement in LDL-cholesterol occurred without any new use of statins or increases in statin dose.

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 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.

References


Figure 1: Study Design

Figure 2: Patient Disposition

Figure 3: Mean Hemoglobin A1c Levels During the Maintenance Phase

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

Table 1: Patient Demographics and Baseline Characteristics

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

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

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

Changes in glycemia over time

Improvements in HbA1c (Figure 3) and FBG (Figure 4) were more pronounced in the DM subgroup compared to the non-DM subgroup at EOM. Figure 3: Mean Hemoglobin A1c Levels During the Maintenance Phase

Changes in glycemia over time

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Reference