Levoketoconazole in the Treatment of Endogenous Cushing’s Syndrome: Secondary Endpoint Results From a Phase 3 Study (SONICS)

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Introduction

Cushing’s syndrome (CS) is a rare endocrine disorder characterized by overproduction of cortisol from the adrenal gland, which is associated with increased mortality and health-related quality of life burden.

Methods

The SONICS study (NCT03017568) is a phase 3, single-arm, open-label extension study of levoketoconazole in adults with Cushing’s disease (CD) designed to evaluate safety, tolerability, changes in markers of cortisol over time, and changes in markers of CS-related adverse events.

Outcome Measures

- Primary endpoint: mUFC normalization (mUFC ≤ ULN) at end of maintenance (EoM) through Month 6.
- Secondary endpoints: LNSC, ACTH levels, and other markers of cortisol over time.

Results

Patient Population

- Of 94 patients enrolled, 75 patients completed the maintenance phase (ITT population). Of the 19 patients who discontinued, 16 discontinued due to lack of efficacy (n=6), adverse events (n=4), physician decision (n=1), patient decision (n=1), 1 patient had a dose increase for lack of efficacy, and 1 patient had insufficient urine collection.

Efficacy

- mUFC levels decreased significantly from baseline to Month 1 visit (Day 30 of maintenance phase) and remained lower than baseline through Month 6 (Figure 2).

- ACTH levels in patients with CD increased less than 2-fold from baseline to EoM (n=36, 38.3).

- Ninety-four patients were enrolled and received ≥1 dose of study medication (ITT population; 80 (85.1)

- Percentage of mUFC complete responders (ie, mUFC normalizers without a dose increase during the maintenance phase) was presented previously (n=75).

- Levoketoconazole was generally well tolerated with 13% discontinuing at any time due to an AE; 1 patient with mUFC <1.5× ULN owing to inadequate urine collection.

Conclusions

- Levoketoconazole is a corticosteroid inhibitor, which is a dexamethasone inhibitor that is developed for the treatment of Cushing’s syndrome (CS), and is an adrenal enzyme characterized by overproduction of cortisol.

- The study was designed to evaluate the safety and efficacy of levoketoconazole in the treatment of endogenous CS, with a focus on selected secondary endpoints related to cortisol measurements.

- The study was conducted in a subset of patients with CD, where mean ACTH level at baseline was 1.5× ULN and at end of maintenance was 2.9× ULN, with 1 patient with mUFC <1.5× ULN owing to inadequate urine collection.

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- Select secondary endpoints reported here (through EoM) are presented in the following section.

- The most commonly reported AEs were nausea, headache, and hypokalemia (Table 2).

- More patients in the non-responder group had an initial response to treatment that fell in the IUHC (n=10/10) compared with the responder group, indicating that patients who achieve an initial response may have a better chance of achieving the EoM response (Figure 6).

- In the subset of patients with CD, mUFC ACTH level at baseline was 1.5× ULN, and at end of maintenance was 2.9× ULN. Percentage of patients with high ACTH at baseline that became normal (≤2.5 nmol/L [0.09 μg/dL]) over time ranged from 4% to 18% in the overall population and 5% to 11% in the subset of patients with CD.

- Figure 3. Percentage of Complete Responders From Baseline Through Month 6 (ITT Population)

- Figure 4. Change From Baseline in LNSC Levels Through Month 6 (Maintenance Population)

- Figure 5. Individual Plot of mUFC (IUHC) by Response

- Table 1. Demographic and Baseline Characteristics (ITT Population)

- Table 2. Summary of Adverse Events (Both Phases; ITT Population)

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- Figure 6. Change From Baseline in LNSC Levels Through Month 6 (Maintenance Population)

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