An Open-Label Study to Assess the Safety and Efficacy of COR-003 (Levoketoconazole) in the Treatment of Endogenous Cushing’s Syndrome

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BACKGROUND
- Endogenous Cushing’s syndrome (CS) is a rare disorder.
- Approved medical therapy options for the management of hypercortisolism in CS are limited, and no US Food and Drug Administration-approved treatment reduces cortisol levels by acting directly on the adrenal gland.
- Ketoconazole, a racemic mixture of 2 enantiomers (2R,4S and 2S,4R) and an inhibitor of cortisol synthesis, has been used off-label for many years as an effective treatment for CS (Figure 1).

STUDY DESIGN
- Single-arm, open-label study to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of COR-003.
- Following screening, there are 3 treatment phases: dose titration, maintenance (6 months at therapeutic dose), and extended evaluation for onsets of continued treatment after maintenance.

STUDY ELIGIBILITY
- Selected inclusion criteria:
  - Patients aged ≥18 years with a confirmed diagnosis of persistent or recurrent CS (with or without previous therapy) or newly diagnosed disease (excluding adrenal carcinomas) who are not candidates for surgery.
  - Selected exclusion criteria:
    - Nonendogenous source of hypercortisolism (eg, exposure to exogenous glucocorticoids).
    - Pseudo-Cushing’s syndrome (based on investigator assessment).

Primary Endpoint
- Reduction in mean 24-hour UFC levels to ≤ULN following 6 months of maintenance phase therapy without additional dose increase.

Statistical Considerations
- Proportion of responders in the ITT and PP populations will be estimated along with corresponding 95% confidence intervals (CI).

Safety Summary Analyses
- Safety evaluations (clinical observations and adverse events reporting).
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Efficacy (24-hour urine and midnight salivary cortisol measurements), and for clinical, safety, metabolic, and PK assessments.

PK Sample Collection
- Assessment of clinical signs and symptoms of CS.

Study Assessments
- Study exposures: average daily and cumulative dose, and total days on study drug.
- Averse events: all, most, common, drug-related, serious, and those leading to discontinuation and withdrawal from study.

STUDY METHODOLOGY

Dose Titration Phase
- 2-16 weeks

Maintenance Phase
- 4 weeks

Extended Evaluation Phase
- 6 months

Enrollment

Visit Months
- Screwing/Baseline
- 1 month
- 3 months
- 6 months
- 9 months
- 12 months

Extended Evaluation Phase
- 6 months

Visit Months
- 18 months

Primary Endpoint
- Reduction in mean 24-hour UFC levels to ≤ULN following 6 months of maintenance phase therapy without additional dose increase.

Selected Secondary Endpoints
- Monthly assessments of mean UFC levels, mean plasma and late-night salivary cortisol levels.
- Clinical signs and symptoms, HbA1c and glucose levels, blood pressure values, lipid profile results, C-reactive protein level, weight, and quality of life.
- Safety evaluations (clinical observations and adverse events reporting).

DISCUSSION
- There is a need for new medical therapy options to manage hypercortisolism in CS.
- Ketoconazole has a long history of effective off-label use in the treatment of CS but is associated with potential hepatic toxicity.
- The SONICS trial investigating the efficacy and safety of COR-003, the 2S,4R enantiomer of ketoconazole, is currently enrolling patients with endogenous CS in vitro. COR-003 has a higher potency for the inhibition of cortisol biosynthesis enzymes and a considerably lower potential to inhibit CYP3A4, a key enzyme for bile acid synthesis, compared with ketoconazole and may therefore have a higher therapeutic index.
- As observed with the off-label use of ketoconazole in CS, COR-003, the single enantiomer of ketoconazole, may have beneficial effects in secondary endpoints contributing to morbidity and mortality in patients with CS, including hyperglycemia, dyslipidemia, obesity, and hypertension.

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References