**INTRODUCTION**

- Cushing’s disease is an endocrine disorder characterised by chronic hypercortisolism that results from excess adrenal/corticotrophin hormone (ACTH)-mediated adrenocortical hyperplasia.
- The treatment options for Cushing’s disease include transphenoidal surgery, radiation therapy, and bilateral adrenalectomy. 
- Medical therapy is preferred in patients with recurrent or persistent hypercortisolism after primary pituitary surgery (with or without radiation), who are not surgical candidates because of co-morbidities, or who refuse to undergo surgery, or who do not have access to a facility with expertise in pituitary surgery.

**Osilodrostat (LUP906) is a potent oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyzes the final step in cortisol biosynthesis (Figure 1), and also inhibits aldosterone synthesis (CYP11B2).**

- Results from prior analyses of an ongoing Phase II study (LINC1 and LINC2) in Cushing’s disease showed that osilodrostat treatment led to rapid and sustained suppression of mean urinary free cortisol (mUFC) and was well tolerated.
  - LINC1 (proof-of-concept study): 90% (11/12) of patients who had normal mUFC at week 10. The most common AEs were gastrointestinal events, i.e., nausea (n = 5) and diarrhea (n = 3). 
  - LINC2 ( amendment LINC1 study): 79% (10/13) of patients had normal mUFC at week 22. The most common AEs were nausea, diarrhea, asthenia, adrenal insufficiency, (n = 6 each) and hypochlorhydria (n = 5). The 19-month result from this trial is presented in poster number EP878.
  - The planned phase III study LINC4 is designed to confirm the safety and efficacy of osilodrostat in patients with Cushing’s disease.

**OBJECTIVE**

To demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC < 1 U/L) at week 12.

**METHODS**

**Patients**

- Patients with persistent or recurrent Cushing’s disease as evidenced by:
  - mUFC > 13 U/L (mean of three 24-hour urine samples collected, with ≥ 2 of the individual UFC values being > 13 U/L)
  - Morning plasma ACTH above lower limit of normal
  - Confirmation of pituitary source of excess ACTH
- Patients with de novo Cushing’s disease only if they are not surgical candidates (i.e., poor surgical candidates, patients who refuse surgery, or surgical treatment is not available)

**Study Design**

A pivotal, phase III, global, multicentre, randomized, all-week study with an initial 12-week, double-blind, placebo-controlled period. The study consists of 2 periods in core phase followed by an optional extension phase (Figure 2).

**Period 1 (week 1-12): double-blind, placebo-controlled:**

- Patients will be randomized to osilodrostat or matching placebo (2:1).
- Patients will receive an initial dose of 2 mg twice-daily (BID).
- The following dose adjustments will be allowed:
  - Dose can be up-titrated to a maximum of 20 mg bid to normalize UFC.
  - If necessary, dose reduction below 2 mg bid, by 1 mg bid, 1 mg once daily, or by every other day is permitted.
- Since investigator will be blinded to UFC, serum cortisol, and related lab results that may disclose treatment assignment, dose adjustments will be decided by an independent endocrinologist.

**Period 2 (week 13-48): single-arm, open-label:**

- At the beginning of this period, all patients will receive osilodrostat 2 mg bid.
- If patients were receiving osilodrostat dose ≥ 2 mg bid during period 1, they will continue with their most recent dose.
- Dose adjustments similar to period 1 will be permitted with dose escalation up to 30 mg bid.
- Investigators will monitor all lab tests results, including UFC, cortisol, and related tests that were blinded during Period 1 and are responsible for all dose adjustments through the rest of the study (period 2 and extension).

**Extension phase (week 48-96):**

- At week 48, patients have the option to enter an open-label extension phase.

**Endpoints**

**Primary endpoint**

- Proportion of randomized patients with a complete response (mUFC < 1 U/L) at week 12.

**Key secondary endpoint**

- Proportion of patients with complete response at week 36 for combined randomized patients who receive osilodrostat treatment.

**Other secondary endpoints**

- Proportion of patients with a complete response or a partial response (mUFC decrease ≥ 50% from baseline and > 1 U/L).
- Change from baseline to mUFC levels.
- Time-to-first control of mUFC, defined as the time (in days) from randomization to the first mUFC collection with ≤ 1 U/L before completion or discontinuation of placebo-controlled period.
- Time-to-scores, defined as time (in weeks) from the first collection of normal mUFC to the first mUFC > 13 U/L on two consecutive visits on the highest tolerated dose of osilodrostat.
- Change in cardiovascular and metabolic parameters and change in physical features of Cushing’s disease.
- Change from baseline in bone mineral density.
- Safety and tolerability.

- Changes in weight, height, and BMI.

**REFERENCES**


**ACKNOWLEDGEMENT**

We thank Svetaa Sinramia, Novartis Healthcare Pvt. Ltd. for providing medical editorial assistance with this poster.

This study was sponsored by Novartis.