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Trial Design of a Phase III, Multicentre, Randomized, Double-blind, Placebo-Controlled, 48-Week Study to Evaluate the Safety and Efficacy of Osilodrostat in Patients With Cushing's Disease

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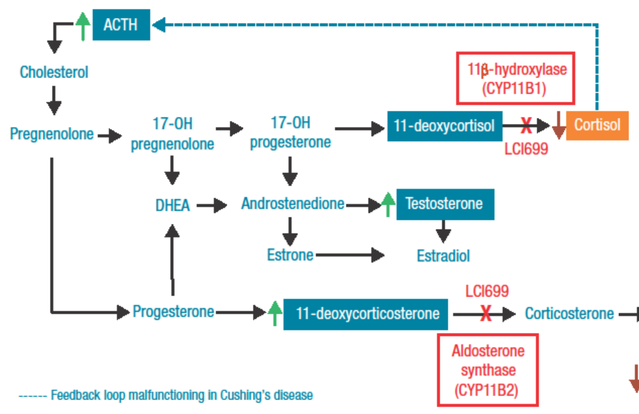
INTRODUCTION

- Cushing's disease is an endocrine disorder characterised by chronic hypercortisolism that results from excess adrenocorticotropic hormone (ACTH) secretion from a pituitary corticotroph adenoma.[1]
- The treatment options for Cushing's disease include transphenoidal surgery, radiation, medical therapy and bilateral adrenalectomy.[1]
- 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.[1]
- Osilodrostat (LCI699) is a potent oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyses the final step in cortisol biosynthesis (**Figure 1**), and also inhibits aldosterone synthase (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[2]: 92% (11/12) of patients had normalised mUFC at week 10. The most common AEs were gastrointestinal events i.e., nausea (n = 5) and diarrhea (n = 3).
  - LINC2 (amended LINC1) study[3]: 79% (15/19) of patients had normalised mUFC at week 22. The most common AEs were nausea, diarrhea, asthenia, adrenal insufficiency, (n = 6 for each) and nasopharyngitis (n = 5). The 19-month result from this trial is presented in poster number EP887.
- The planned phase III study **LINC4** is designed to confirm the safety and efficacy of osilodrostat in patients with Cushing's disease.

Figure 1. Mechanism of Action of Osilodrostat in Cushing's Disease



ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone.

OBJECTIVE

To demonstrate the superiority of osilodrostat compared to placebo in achieving a complete response (mUFC ≤ ULN) at week 12.

METHODS

Patients

- Patients with persistent or recurrent Cushing's disease as evidenced by
  - mUFC > 1.3 × ULN (mean of three 24-hour urine samples collected, with ≥ 2 of the individual UFC values being > 1.3 × ULN)
  - 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 (eg, poor surgical candidates, patients who refuse surgery, or surgical treatment is not available)

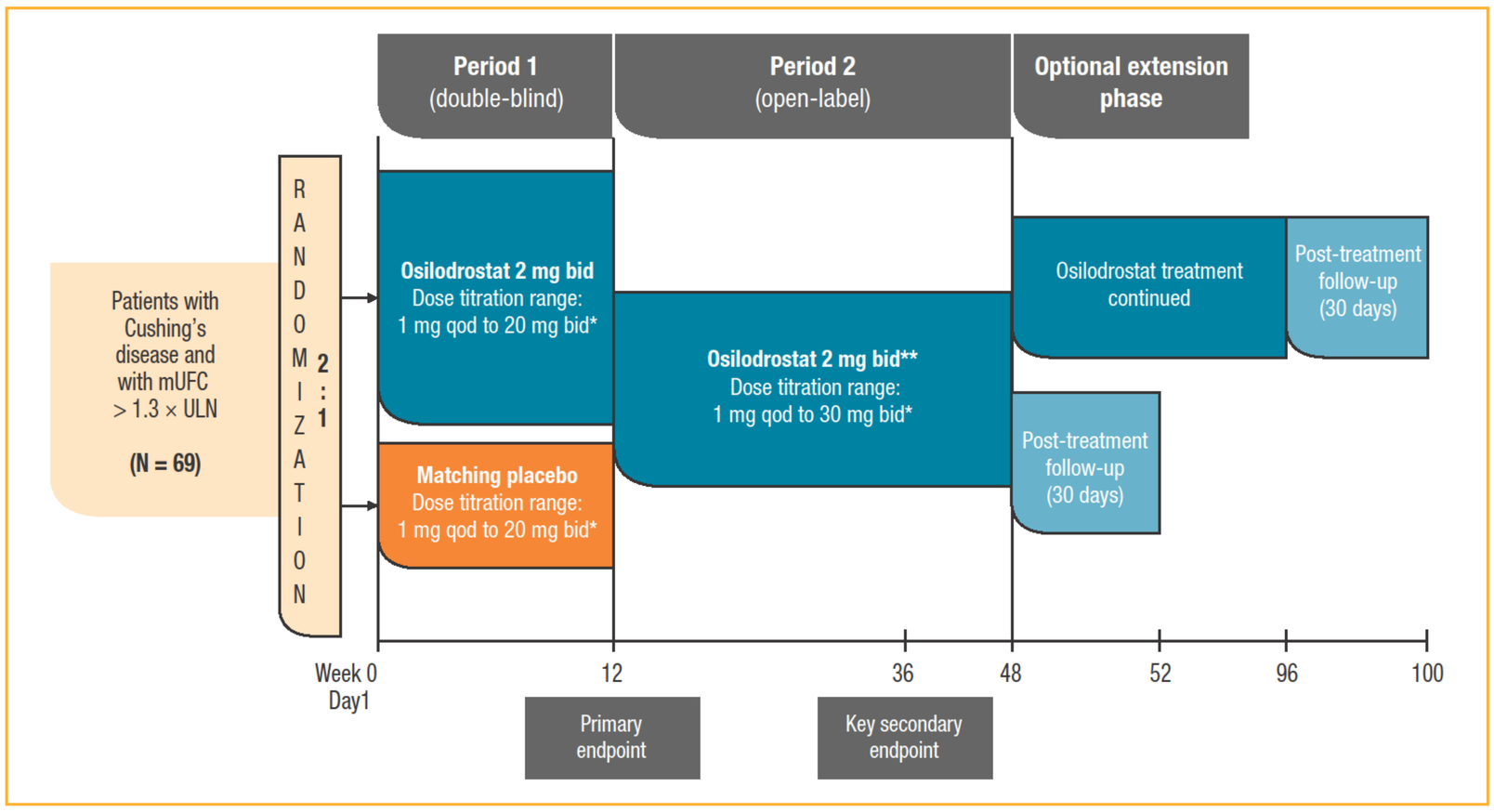
Study Design

- A pivotal, phase III, global, multicentre, randomized, 48-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 normalise UFC.
  - If necessary, dose reduction below 2 mg bid (ie, 1 mg bid, 1 mg once daily, or 1 mg 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.

Figure 2. Study Design



*Dose adjustments to normalise UFC or to address safety reasons are permitted. Dose titration sequence: 2 mg → 5 mg → 10 mg → 20 mg → 30 mg. Doses below 2 mg bid (1 mg bid, 1 mg qd, 1 mg qod) are allowed if necessary.

**All patients on doses of ≥ 2 mg bid will start open-label osilodrostat 2 mg bid at week 12, while patients on < 2 mg bid will continue their most recent dose.

bid, twice a day; mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal; qd, once a day; qod, every other day.

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 receive 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 ≤ ULN) 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 > ULN) at week 12, week 36, and week 48 by treatment arms and for all patients
- Actual and percentage change from baseline in mUFC levels
- Time-to-first control of mUFC, defined as the time (in days) from randomization to the first mUFC collection with ≤ ULN before completion or discontinuation of placebo-controlled period
- Time-to-escape, defined as time (in weeks) from the first collection of normal mUFC to the first mUFC > 1.3 × ULN on two consecutive visits on the highest tolerated dose of osilodrostat
- Actual and percentage 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
- Change in health related quality of life, as measured by standardised score of CushingQoL, Beck Depression Inventory-II, and EQ-5D-5L
- Plasma concentrations (pre-dose, 1-2 h post-dose) of osilodrostat

CushingQoL, Cushing quality of life; EQ-5D-5L, 5-level 5-dimensional EuroQoL; mUFC, mean urinary free cortisol; UFC, urinary free cortisol; ULN, upper limit of normal.

CURRENT TRIAL STATUS

- The study targets to enrol 69 patients.
  - Assuming a 10% drop-out this sample size enables detection of a 45% difference in the placebo and treatment arms using 1-sided CMH test at 0.025 level with adequate power.
- As per the current plan, enrolment to be initiated this year. The trial is registered at Clinicaltrials.gov (NCT02697734).

CONCLUSIONS

- **The present study design consists of a 12-week, double-blind, placebo-controlled period along with an open-label period, which enables blinded, placebo-controlled assessments and long-term evaluation of efficacy and safety of osilodrostat in patients with Cushing's disease.**

REFERENCES

1. Tritos NA, *et al. Nat Rev Endocrinol.* 2011;7(5):279-289
2. Bertagna X, *et al. J Clin Endocrinol Metab.* 2014;99(4):1375-1383.
3. Fleseriu M, *et al. Pituitary.* 2016;19(2):138-148.

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