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Phase III, Multicentre, Double-blind, Randomised Withdrawal Study of Osilodrostat (LCI699) in Patients With Cushing's Disease (CD): A Study Design

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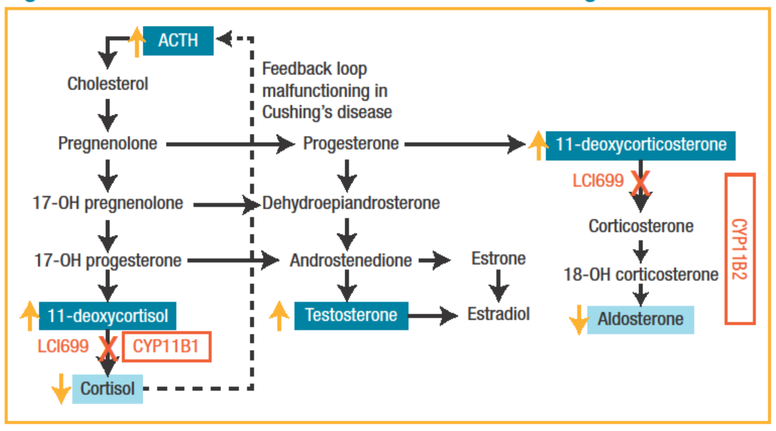
INTRODUCTION

- Cushing's disease (CD) is an endocrine disorder characterised by chronic hypercortisolism that results from excess adrenocorticotropic hormone (ACTH) secretion from a pituitary corticotroph adenoma. The treatment options for CD includes pituitary surgery, pituitary irradiation, medical therapy, and bilateral adrenalectomy.[1]
- Several medications are currently available for the treatment of CD. However, for most medications safety and efficacy is supported by a low level of evidence and/or are not widely approved for this indication except pasireotide and mifepristone.[2-5]
- Osilodrostat (LCI699) is a potent, oral inhibitor of the 11β-hydroxylase enzyme (CYP11B1) (**Figure 1**).

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



ACTH, adrenocorticotropic hormone.

STUDY RATIONALE

- There is a need for new medications to treat the patients with CD who may not achieve normalisation of mean urinary free cortisol (mUFC) or may not tolerate available medications.[6]
- Results from the phase II LINC1 and LINC2 study showed that osilodrostat normalised UFC in 92% (11/12) and 78.9% (15/19) of patients at week 10 and week 22, respectively. Osilodrostat treatment was generally well tolerated.[6,7]
- Thus, LINC3 (CLCI699C2301), a 48-week confirmatory phase III study with an 8-week randomised withdrawal period is designed to evaluate the long-term safety and efficacy of osilodrostat in a larger population of patients with CD (**Table 1**).
- A randomised withdrawal study is appropriate in rare and serious diseases because long-term placebo control in patients with CD might lead to chronic uncontrolled hypercortsolism.[8] The short (8-week) randomised withdrawal period and rescue treatment in this study design will allow a placebo-controlled comparison while minimising the duration of placebo exposure in patients with uncontrolled CD.

Table 1. Objective and Related Endpoints

OBJECTIVE	ENDPOINT
Primary	
To compare the complete response rate at the end of the randomised withdrawal period (week 34) between patients randomised to continue osilodrostat therapy vs placebo.	Proportion of randomised patients in each treatment group with normal mUFC (mUFC ≤ ULN) at week 34 who neither discontinued nor had dose increase above the level at week 24 during period 3.
Key Secondary	
To assess the complete response rate at the end of week 24.	Proportion of patients with normal mUFC at week 24 and with no dose increase above the level established at week 12 during period 2

mUFC, mean urinary free cortisol; ULN, upper limit of normal.

METHODS

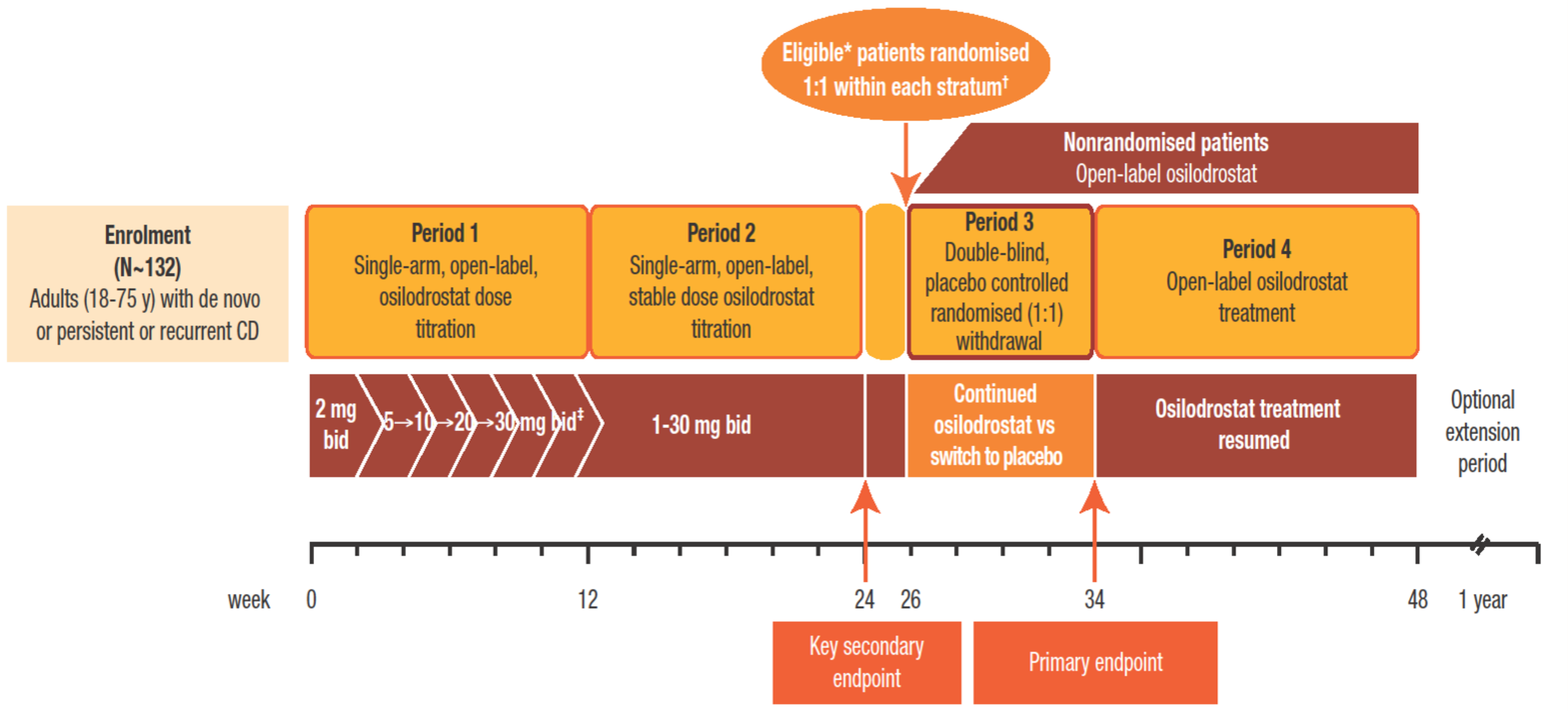
Patients

- Adults (aged 18-75 years) with
  - persistent or recurrent CD after primary pituitary surgery and/or irradiation as evidenced by the following
    - mUFC > 1.5 ULN
    - morning plasma ACTH > lower limit of normal (LLN)
    - confirmed pituitary source of excess ACTH
  - de novo CD who are not considered as surgical candidates or refuse to undergo surgery
- Patients receiving other medical treatment for CD are eligible after appropriate drug washout.
- Patients with tumour causing compression of the optic chiasm, uncontrolled diabetes (glycosylated haemoglobin [HbA_{1c}] > 9%), and/or hypertension (BP > 180/100) are excluded.

Study Design

- Phase III, multicentre study with 4 treatment periods and an optional extension period (**Figure 2**).

Figure 2. Study Design



*Patients with mUFC ≤ ULN at week 24 and did not require dose increase above dose level established at week 12
†Strata are determined by the combination of 2 stratification factors at randomisation: (1) LCI699 dose at week 24 (≤ 5 mg bid vs > 5 mg bid), and (2) history of pituitary irradiation (yes/no)
‡Dose will be increased every 2 week if mUFC > ULN in the dose titration sequence of 2 mg bid→5 mg bid→10 mg bid→20 mg bid→30 mg bid
Week 24-26: Patients will remain on open-label osilodrostat treatment until results from week 24 are available to allow determination of eligibility for randomisation.
bid, twice-daily; CD, Cushing's disease

Period 1 (Week 1-12)

- Single-arm, open-label **dose titration** period where individual therapeutic dose will be established.
- Patients will start receiving osilodrostat 2 mg bid.
- Dose will be increased if mUFC > ULN and maintained if mUFC ≤ ULN.
- Dose can be decreased (to 1 mg bid) or interrupted if mUFC < LLN or in lower part of normal range and/or if patient has symptomatic adrenal insufficiency.

Period 2 (Week 13-24)

- Single-arm, open-label, **stable treatment** period during which the efficacy and safety of continued treatment with osilodrostat will be assessed.
- Dose adjustments will be allowed based on the mUFC levels and safety.
  - A dose increase (above the week 12 level) during this period will render the patients ineligible for randomisation. However, a dose decrease or interruption will not affect the eligibility for randomisation.
- **Week 24-26:** Patients will continue osilodrostat treatment until mUFC (measured on week 24) results are available.

Period 3 (Week 26-34)

- Eight-week, double-blind, **placebo-controlled randomised withdrawal** period.
- Patients with mUFC ≤ ULN at week 24, who did not require dose increase above the level established at week 12, will be eligible for randomisation.
- Eligible patients will be randomised (1:1) at week 26 to continue osilodrostat treatment at the same dose as in period 2 or to receive matching placebo.
- Dose increases are not permitted.
  - Patients who are nonresponders (mUFC > 1.5 × ULN with UFC > 1.5 × ULN in ≥ 2 samples at a single visit) will discontinue from this randomised withdrawal study period, and resume open-label osilodrostat treatment until week 48
- Nonrandomised patients will continue to receive open-label osilodrostat.

Period 4 (Week 34-48)

- Single-arm period in which all patients will resume or continue open-label osilodrostat treatment.
- Osilodrostat dose may be adjusted or withheld depending on the mUFC levels and safety.

Optional Extension Period (1 Year)

- Patients may choose to enter the extension period without interruption of study drug or assessments.

Escape

- Escape is defined as loss of control of mUFC (ie, mUFC > 1.5 × ULN with UFC >1.5 × ULN in ≥ 2 samples), after prior normalisation of mUFC in period 1. Patients that are randomised to placebo, or have interruption of study drug for safety reasons are not included in this assessment.

CURRENT TRIAL STATUS

- This study is currently enrolling patients.
- Target enrolment is a total of 132 patients (**Figure 3**).
- Clinical trial.gov identifier: NCT02180217.

Figure 3. Location of Recruiting Countries

The recruiting countries listed below are shaded in dark blue color on the map

Argentina	Italy
Australia	Japan
Austria	Korea, Republic of
Bulgaria	Netherlands
Canada	Russia
China	Spain
Colombia	Thailand
France	Turkey
Germany	United Kingdom
India	United States

CONCLUSIONS

- **This study design with a short 8-week period of double-blind, placebo-controlled randomised withdrawal, after a 26-week run-in period of open-label osilodrostat treatment (dose titration and stable dose periods) allows assessment of efficacy vs placebo (8 weeks), long-term efficacy and safety (2 years) of osilodrostat in a larger group of patients with CD.**
- **This study design is well suited to patients with rare and serious diseases such as CD because long-term placebo-controlled studies would be difficult to conduct in this patient population.**

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