

Pivonello R et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. *Lancet Diabetes Endocrinol.* 2020;8(9):748-761. doi: 10.1016/S2213-8587(20)30240-0.

BACKGROUND: Cushing's disease is a rare endocrine disorder characterised by cortisol overproduction with severe complications. Therapies for cortisol reduction are often necessary. Here we report the outcomes from the pivotal phase III study of osilodrostat (a potent oral inhibitor of cytochrome P450 11B1, mitochondrial [11 β -hydroxylase]; Novartis Pharma AG, Basel, Switzerland) in patients with Cushing's disease.

METHODS: LINC 3 was a prospective, multicentre, open-label, phase III study with a double-blind randomised withdrawal period, that comprised four periods. Patients aged 18-75 years, with confirmed persistent or recurrent Cushing's disease (defined as mean 24-h urinary free cortisol [UFC] concentration >1.5 times the upper limit of normal [ULN] and morning plasma adrenocorticotrophic hormone above the lower limit of normal) who had previously had pituitary

surgery or irradiation, or were newly diagnosed and who refused surgery or were not surgical candidates, were recruited from 66 hospital sites and private clinical practices in 19 countries. In period 1, open-label osilodrostat was initiated in all participants and adjusted every 2 weeks (1-30 mg twice daily; film-coated tablets for oral administration) on the basis of mean 24-h UFC concentration and safety until week 12. In period 2, weeks 13-24, osilodrostat was continued at the therapeutic dose determined during period 1. In period 3, beginning at week 26, participants who had a mean 24-h UFC concentration of less than or equal to the ULN at week 24, without up-titration after week 12, were randomly assigned (1:1), via an interactive-response technology, stratified by osilodrostat dose at week 24 and history of pituitary irradiation, to continue osilodrostat or switch to placebo for 8 weeks. Participants and investigators were masked to treatment assignment. Ineligible participants continued open-label osilodrostat. In period 4, weeks 35-48, all participants were given open-label osilodrostat until core-study end. The primary objective was to compare the efficacy of osilodrostat versus placebo at the end of period 3. The

primary endpoint was the proportion of participants who had been randomly assigned to treatment or placebo with a complete response (ie, mean 24-h UFC concentration of \leq ULN) at the end of the randomised withdrawal period (week 34), without up-titration during this period. The key secondary endpoint was the proportion of participants with a complete response at the end of the single-arm, open-label period (ie, period 2, week 24) without up-titration during weeks 13-24. Analysis was by intention-to-treat for all patients who received at least one dose of osilodrostat (full analysis set; key secondary

endpoint) or randomised treatment (randomised analysis set; primary endpoint) and safety was assessed in all enrolled patients who received at least one dose of osilodrostat and had at least one post-baseline safety assessment. LINC 3 is registered with ClinicalTrials.gov, NCT02180217, and is now complete.

FINDINGS: Between Nov 12, 2014, and March 22, 2017, 202 patients were screened and 137 were enrolled. The median age was 40·0 years (31·0-49·0) and 106 (77%) participants were female. 72 (53%) participants were eligible for randomisation during the withdrawal phase, of whom 36 were assigned to continue osilodrostat and 35 were assigned to placebo; one patient was not randomly assigned due to investigator decision and continued open-label osilodrostat. More patients maintained a complete response with osilodrostat versus with placebo at week 34 (31 [86%] vs ten [29%]; odds ratio 13·7 [95% CI 3·7-53·4]; $p < 0·0001$). At week 24, 72 (53%; 95% CI 43·9-61·1) of 137 patients maintained a complete response without up-titration after week 12. Most common adverse events (ie, occurred in >25% of participants) were nausea (57 [42%]), headache (46 [34%]), fatigue (39 [28%]), and adrenal insufficiency (38 [28%]). Hypocortisolism occurred in 70 (51%) patients and adverse events related to adrenal hormone precursors occurred in 58 (42%) patients. One patient died, unrelated to study drug, after the core study phase.

INTERPRETATION: Twice-daily osilodrostat rapidly reduced mean 24-h UFC and sustained this reduction alongside improvements in clinical signs of hypercortisolism; it was also generally well tolerated. Osilodrostat is an effective new treatment option that is approved in Europe for the treatment of endogenous Cushing's syndrome and in the USA for Cushing's disease.

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