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Osilodrostat provides clinical benefit over 48 weeks in patients with Cushing disease: Results from the LINC 3 study

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Introduction

Osilodrosat is a potent oral 11b-hydroxylase inhibitor. During the 24-week, single-arm, open-label period of the Phase III LINC 3 study (NCT02180217), osilodrostat treatment demonstrated rapid, sustained reduction in mean urinary free cortisol (mUFC) in most Cushing disease (CD) patients. In the subsequent 8-week, double-blind, randomized-withdrawal phase, a significantly higher proportion of patients receiving osilodrostat maintained normal mUFC at week (W)34 without a dose increase versus placebo (86.1% vs 29.4%; OR: 13.7, P!0.001 [primary efficacy endpoint]; Pivonello R et al. ICE 2018;abstract 1025). The effects of osilodrostat on CD signs/symptoms/biochemistry parameters are reported here for the first time.

Methods

137 adults with CD and mUFCO1.5xULN (ULNZ138 nmol/24h; baseline

median mUFCZ3.5!ULN) initiated open-label osilodrostat 2mg bid with dose adjustments every 2 weeks (maximum 30 mg bid) until W12 based on mUFC and safety. At W26, 71 eligible patients (mUFC%ULN at W24 without up-titration after W12) were randomized to continue osilodrostat (nZ36) or matching placebo (nZ35) in an 8-week double-blind phase (ineligible patients continued open-label osilodrostat; nZ47), followed by open-label osilodrostat until W48. Cardiovascular-related metabolic parameters and CushingQoL and Beck Depression Inventory (BDI) scores were evaluated at baseline, every 2, 4 or 12 weeks (depending on study phase), and at end of treatment (W48).

Results

By W48, in all patients (NZ137), mean absolute changeGSD from baseline in signs/symptoms/biochemistry parameters were: weight, K3.8G5.7 kg; BMI, –1.4G2.2 kg/m_2; waist circumference, –4.6G7.8 cm; fasting plasma glucose, –0.5G1.3 mmol/L; HbA_{1c}, –0.4G0.7%; total cholesterol, –0.5G0.9 mmol/L; LDL cholesterol, –0.2G0.8 mmol/L; HDL cholesterol, –0.3G0.3 mmol/L; triglycerides, –0.1G0.9 mmol/L; systolic blood pressure (BP), –9.8G15.5 mmHg; diastolic BP, –6.3G11.1 mmHg. MeanGSD CushingQoL score (including physical problems and psychological issues subscores) improved by 52.4G107.4% and BDI score by –31.8G65.0%. Osilodrostat was generally well tolerated; most common AEs were nausea (42%), headache (34%), fatigue (29%). Hypocortisolism-related AEs were experienced by 51% of patients, occurring mainly during dose titration (W0–12) as a single episode. Anticipated AEs of interest (based on osilodrostat mechanism of action) were manageable; those leading to discontinuation were adrenal insufficiency (nZ4 [2.9%]), hypokalaemia, increased diastolic or systolic BP, and electrocardiogram QT prolonged (nZ1 [0.7%] each).

Conclusion

Reductions in mUFC during 48 weeks of osilodrostat treatment were accompanied by weight, waist circumference, glucose, and systolic/diastolic BP improvements, as well as improved CushingQoL and BDI scores. Osilodrostat was effective and generally well tolerated, showing promise for the treatment of patients with CD.

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