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Continued Improvements in Hypertension and Diabetes During Long-Term Osilodrostat Therapy in Patients with Cushing's Disease: A Pooled Analysis from the Phase III LINC 3 and LINC 4 Studies

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Introduction: Alleviating the burden of comorbidities such as hypertension (HTN) and diabetes mellitus (DM), through control of hypercortisolism, is an important treatment goal in the management of Cushing's syndrome. Osilodrostat, a potent oral 11β-hydroxylase inhibitor, provided rapid, sustained cortisol normalization in Cushing's disease (CD) patients (pts) in two Phase III studies (LINC 3, NCT02180217; LINC 4, NCT02697734), with improvements in clinical manifestations of hypercortisolism. Here, we report on the long-term changes in blood pressure (BP) and markers of glucose homeostasis in a large, pooled pt population from both trials at weeks (W) 48 and 72. **Methods:** LINC 3 comprised a 48W core phase, including an 8W randomized withdrawal phase for eligible pts. LINC 4 included an upfront 12W, double-blind, randomized, placebo-controlled period and 36W of open-label osilodrostat. Both studies had an optional extension. Baseline (BL) HTN was defined as prior diagnosis, taking

antihypertensive medication, and/or systolic/diastolic BP (SBP/DBP) >130/>90 mmHg. BL DM was defined as prior diagnosis, taking antidiabetic medication, HbA_{1c} ≥6.5%, and/or fasting plasma glucose (FPG) ≥126 mg/dL. Data from LINC 3 and LINC 4 were pooled in a secondary exploratory analysis for all pts with data at BL and the given visit, excluding periods where pts were randomized to placebo. No formal statistical hypothesis testing was performed; all analyses are descriptive. **Results:** In pts with BL HTN (n=174/210; 82.9%), mean (95% CI) change in SBP/DBP was -13.9 (-18.5, -9.4)/-9.1 (-12.4, -5.8) mmHg at W48 and -14.7 (-20.1, -9.4)/-9.4 (-13.0, -5.7) mmHg at W72 for those not receiving antihypertensive medication during the study, and -8.4 (-11.9, -4.9)/-5.3 (-7.5, -3.1) mmHg at W48 and -10.1 (-14.3, -5.8)/-5.7 (-8.1, -3.2) mmHg at W72 for those who received antihypertensives. Of pts with BL SBP >130 mmHg (n=110), 50.0% had SBP ≤130 mmHg at W48 and 49.1% at W72. Of pts with BL DBP >90 mmHg (n=65), 64.6% had DBP ≤90 mmHg at W48 and 58.5% at W72. The proportion of pts taking antihypertensive medication declined from 54.3% at BL to 47.3% at W72. Mean (95% CI) change in potassium levels was -0.1 (-0.1, 0.0) mmol/L at W48 and 0.0 (-0.1, 0.1) mmol/L at W72 in pts with BL HTN, and -0.1 (-0.3, 0.1) mmol/L at both W48 and W72 in pts without BL HTN. 40.0% (n=84/210) of pts had BL DM. Of pts with BL FPG ≥100 mg/dL (n=60), 43.3% and 33.3% had FPG <100 mg/dL at W48 and W72, respectively. The proportion of pts taking antidiabetic medication declined from 21.9% at BL to 17.1% at W72. **Conclusions:** Many pts with CD and HTN or DM showed improvements during osilodrostat therapy, which were maintained or further improved with long-term therapy. Cortisol normalization is associated with improvements in hypercortisolism-associated comorbidities in pts with CD.

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