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Effect of Osilodrostat on Androgens and Adrenal Hormones in Patients With Cushing's Disease: Long-Term Findings From the Phase III, Prospective LINC 3 Study

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Introduction: Osilodrostat decreases cortisol production by inhibiting 11β-hydroxylase, which increases adrenal hormones proximal to the blockade. Here, we describe these effects of osilodrostat and associated adverse events (AEs). The efficacy and safety of osilodrostat in patients with Cushing's disease (CD) were confirmed in the published Phase III, prospective LINC 3 study (NCT02180217).

Methods: 137 patients with CD and mUFC >1.5×upper limit of normal were enrolled into a 48-week (W) core phase that included an 8W double-blind, randomized-withdrawal period for eligible patients. Of 113 patients who completed W48, 106 opted to enter the extension, ending when all ongoing patients completed ≥72W of treatment or discontinued. Testosterone, 11-deoxycortisol, 11-deoxycorticosterone and aldosterone were assessed centrally at baseline and regular intervals by liquid chromatography-tandem mass spectrometry and dehydroepiandrosterone sulfate (DHEAS) by chemiluminescence immunoassay. Hirsutism (females; rated on a semi-quantitative scale: 0=absent; 1=mild; 2=moderate; 3=severe), blood pressure, edema and serum potassium were assessed at regular intervals.

Results: Median osilodrostat exposure was 130W (range, 1–245); median osilodrostat dose was 7.4 mg/day (range, 0.8–46.6). Following an initial increase during the core phase, mean (SD) testosterone levels stabilized in males and decreased towards baseline levels in females during long-term treatment. Of female patients with assessments at baseline and W48 (n=76) and W72 (n=64), hirsutism score improved from baseline in 26 and 22 patients at W48 and W72, respectively and remained unchanged in 37 and 33 patients, respectively. Mean (SD) DHEAS levels decreased during the core phase to within the normal range, then stabilized during the extension in females (1.6 [1.6] and 1.0 [0.9] μmol/L at W48 and W72, respectively) and

males (3.4 [3.3] and 3.0 [3.1] μmol/L at W48 and W72, respectively). Aldosterone levels also decreased and then stabilized during long-term treatment. Adrenal hormone precursor accumulation-related AEs were reported in 58.4% (n=80/137) of patients, regardless of study drug relationship and managed with additional therapy in 36.5% (n=50/137) of patients. They mostly occurred during the first 26W of treatment (35.5% and 49.1% in females and males, respectively) and at different osilodrostat doses (1–60 mg), with no discernable dose-related effect. Although mean potassium levels remained stable, AEs of hypertension, peripheral edema and hypokalemia were the most common adrenal hormone precursor accumulation-related AEs and were reported in 24 (17.5%), 22 (16.1%) and 18 (13.1%) patients, respectively; managed with concomitant medication in 17, 6 and 14 patients, respectively. Overall, few patients discontinued because of adrenal hormone precursor accumulation-related AEs (1.5%; n=2/137).

Conclusions: Adrenal hormone levels frequently change upon initiation of osilodrostat but stabilize during long-term treatment. AEs associated with these changes can occur and are manageable without osilodrostat discontinuation. These AEs should be closely monitored and treatment initiated as needed to achieve optimal patient outcomes.

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