was higher in patients with primary polydipsia versus controls and lower on dulaglutide versus placebo, but functional neuronal activity was similar between groups and treatments. **Conclusion:** GLP-1 receptor agonists reduce fluid intake and thirst perception in patients with primary polydipsia and could therefore be a novel treatment option for these patients.

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Metyrapone Treatment in Endogenous Cushing's Syndrome: Results at Week 12 From PROMPT, a Prospective International Multicenter, Open-Label, Phase III/IV Study

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Background: Metyrapone is a steroidogenesis inhibitor approved in Europe for the treatment of endogenous Cushing's syndrome (CS) based on observational retrospective studies published over more than 50 years. We present data from the first prospective study designed to confirm metyrapone efficacy and good tolerance in patients with CS.
Methods: This single arm, open-label, multicenter, international trial enrolled 50 patients with CS who had three baseline 24 hours urine free cortisol (UFC) values at least 50% above the upper limit of normal (ULN=165 nmol/24h). Metyrapone was titrated over 12 weeks (W12) to achieve normal urine (mean of 3 values, mUFC) and serum cortisol levels. Patients whose mUFC did not exceed 2-fold the ULN could enter a 6-month extension period. The primary efficacy endpoint was the proportion of patients with mUFC ≤ ULN at W12 assessed in a central laboratory using LC-MS/MS. The most important secondary endpoint was mUFC decrease of ≥ 50% at W12.
Results: At baseline: mean age was 47 years, median mUFC (range) was 570 (291 - 8476) nmol/24h (3.5 x ULN). Hypercortisolism was in 96% of patients either moderate (mUFC ≥ 2xULN; < 5x ULN) in 63% or severe (≥5 x ULN) in 33%. Hypertension (69%) and diabetes mellitus (47%) were the most common comorbidities. At W12: 47% (23/ 49) met primary endpoint. Another 40% (19 / 49) had mUFC ≤ 2xULN. Median percentage decrease in mUFC from baseline to W12 was -74%. Secondary endpoint was met by 80% of patients who had a mUFC decrease of 50%. Final median metyrapone dose was 1500 (250; 5500) mg/day. Physical signs and symptoms were normalized or improved in 66% of patients. Circulating cholesterol, HbA1C and fasting glucose and insulin improved with median decrease of 12%, 3%, 5% and 9% respectively and median systolic and diastolic blood pressure also decreased by 4 and 5mmHg respectively. Among patients with antihypertensive treatments, 10 (31%) had a decrease in number of drugs and 5 (16%) had an increase in number of drugs during the study. Median ACTH increased by 11 % from baseline.
Twenty six (52%) patients experienced mild to moderate study drug related adverse events (AEs). One patient discontinued before W12 because of an unrelated SAE on day 2 (pneumonia with septic shock). The most common AEs were nausea (24%), decreased appetite (18%), fatigue (14%), headache (10%), peripheral edema (6.0%), hypokalemia (6.0%) and hypertension (6.0%). Reversible adrenal insufficiency occurred in 6 (12%) patients. Few patients 14% (7/50) experienced at least one AE that led to a dose interruption or dose adjustment. Cushing Quality of Life Questionnaire increased of 10 points from baseline which is close to minimal clinically important difference = 10.1. **Conclusions:** This prospective study in patients with CS confirms that metyrapone effectively lowers UFC levels with a tolerability profile similar to the previously reported safety profile and improves QoL, at Week 12.

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One-Year Outcomes of the Open-Label Extension of CHIASMA OPTIMAL, a Phase 3 Study of Oral Octreotide Capsules in Acromegaly

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Background: Based on the CHIASMA OPTIMAL study, oral octreotide capsules (OOC) were recently approved in the US as a long-term maintenance therapy for patients with acromegaly previously responding to injectable octreotide or lanreotide, somatostatin receptor ligands (SRLs). Results on longer-term efficacy and safety of OOC from the first 48 weeks of the open-label extension (OLE) of this study are presented here. **Methods:** Eligible patients had the option to enroll in the OLE of CHIASMA OPTIMAL following the double-blind placebo-controlled (DPC) period; 90% of patients who received OOC in the DPC period enrolled. All patients entering the OLE were initiated on a 60 mg/day dose of OOC and titrated up or down based on insulin-like growth factor I (IGF-I) level and/or acromegaly signs or symptoms. End points in the OLE were exploratory and included the proportion of patients who completed week 48 of the OLE, the proportion who completed as responders (defined as average IGF-I ≤1.0 × upper limit of normal [ULN] at weeks 46/48), and changes in IGF-I from baseline of DPC and OLE until week 48 of the OLE; multiple imputation (MI) was used for missing data. **Results:** Forty patients entered the OLE (n=20 each; OOC and placebo). Median exposure to OOC in the OLE was > 1 year for those who had been on placebo in the DPC and ≤ 21 months for those who had been on OOC. Dosing of OOC at the end of their participation in the OLE was 40 mg, n=3; 60 mg, n=10; and 80 mg, n=27. In those who received OOC during the DPC, 90% (n=18) completed 48 weeks of the OLE. Of responders at the end of the DPC period (n=14), 92.6% maintained response at OLE week 48. In patients from the OOC group who completed the DPC on study drug, average IGF-I using MI was 0.91 and 0.90 × ULN at OLE baseline and week 48, respectively. The mean change in IGF-I from the baseline of the DPC to OLE week 48 was 0.06 × ULN in patients who completed the DPC on OOC (n=19). In those who received placebo during the DPC, 70% (n=14) completed 48 weeks of the OLE. Of responders at the end of the DPC (n=5), 100% maintained response at OLE week 48. In patients from the placebo group who completed the DPC and did not revert to prior injectable therapy (n=9), the average IGF-I values were 1.09 and 0.87 × ULN at OLE baseline and week 48 respectively, using MI. The mean change in IGF-I from the baseline of the DPC to OLE week 48 was 0.08 × ULN in patients who completed the DPC on placebo (n=9). The most common treatment-emergent adverse events (TEAEs) were gastrointestinal; most were mild or moderate. The incidence of TEAEs was similar between patients who were on OOC or placebo during the DPC. The safety profile during the OLE did not show new concerns with increased duration of drug exposure. **Conclusion:** Long term maintenance of biochemical response to OOC is durable as assessed following ≤ 21 months of treatment. The OOC safety profile in the extension study is consistent with that of injectable SRLs but without injection-related AEs.

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Osilodrostat Is an Effective and Well-Tolerated Treatment for Cushing's Disease (CD): Results From a Phase III Study With an Upfront, Randomized, Double-Blind, Placebo-Controlled Phase (LINC 4)

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Background: In a prior Phase III, randomized-withdrawal study, osilodrostat, a potent oral 11β-hydroxylase inhibitor, provided rapid and sustained normalization of mean urinary free cortisol (mUFC) in most patients (pts) with CD. Now, we report efficacy and safety results from another Phase III study of osilodrostat in pts with CD that included an upfront, double-blind, randomized, placebo-controlled phase (LINC 4: NCT02697734). **Methods:** Adults with CD with mUFC >1.3 x ULN were randomized 2:1 to osilodrostat 2 mg bid or matching placebo for a 12-week (W) double-blind period, with dose adjustments at W2, 5 and 8 (range 1-20 mg bid) based on efficacy and tolerability; dose matching and adjustments were managed by independent endocrinologists. From W12 to W48, all pts received open-label osilodrostat, with dose adjustments permitted (range 1-30 mg bid). At W48, pts could enter an optional extension.