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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.

Neuroendocrinology and Pituitary

CLINICAL ADVANCES IN PITUITARY DISEASES

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.

Primary endpoint: proportion of randomized pts in each arm who received ≥1 treatment dose with mUFC ≤ULN at W12. **Results:** 73 pts were randomized and received osilodrostat (n=48) or matching placebo (n=25; baseline median [range] mUFC 2.5 x ULN [0.7-12.5] vs 2.2 x ULN [0.2-18.9]). 77% of osilodrostat recipients achieved mUFC ≤ULN at W12 vs 8% of placebo recipients (OR 43.4; 95% CI 7.1-343.2; P<0.0001). At W36, 81% (95% CI 69.9-89.1) of osilodrostat recipients had mUFC ≤ULN (key secondary endpoint). Median time to first controlled mUFC response was 35 days (95% CI 34–52) for pts randomized to osilodrostat. Median duration of osilodrostat exposure at data cut-off (Feb 25, 2020) was 71.7 vs 62.3 weeks for pts randomized to osilodrostat and placebo (median [IQR] dose 4.7 [3.8-9.0] vs 6.0 mg/day [3.7-9.7]). Up to W12, 3 osilodrostat pts discontinued, 1 because of an AE (arthralgia), vs 0 with placebo. The most common (≥30%) AEs occurring by W12 were decreased appetite (38% osilodrostat vs 16% placebo), arthralgia (35% vs 8%) and nausea (31% vs 12%). AEs related to hypocortisolism and adrenal-hormone-precursor accumulation occurred in 15% vs 0% and 44% vs 36% of osilodrostat and placebo pts; most were grade 1/2 and resolved with dose reduction/interruption and/or concomitant medication. During the overall study period, the most common (≥30%) AEs occurring on osilodrostat treatment were arthralgia (45%), decreased appetite (45%), fatigue (38%), nausea (37%) and headache (33%). Improvements in cardiovascular- and metabolic-related parameters, including systolic and diastolic blood pressure and HbA_{1c}, were observed with osilodrostat treatment at W12 and W48.
Conclusion: Osilodrostat was superior to placebo at normalizing mUFC levels at W12 (77% vs 8%). Improvements in mUFC levels were sustained at W36. Few pts discontinued because of AEs; hypocortisolism-related AEs were infrequent and manageable. We conclude that osilodrostat is a highly effective and well-tolerated treatment for pts with CD.

Neuroendocrinology and Pituitary

CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY

A Phase 3 Large International Noninferiority Trial (MPOWERED): Assessing Maintenance of Response to Oral Octreotide Capsules in Comparison to Injectable Somatostatin Receptor Ligands

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Background: MPOWERED, a large phase 3 trial, assessed maintenance of response to oral octreotide capsules (OOC; MYCAPSSA®) compared to injectable somatostatin receptor ligands (iSRLs) in patients with acromegaly who responded to OOC and iSRLs (octreotide or lanreotide). OOC were recently approved in the US for patients with acromegaly who responded to and tolerated iSRLs.
Methods: Eligibility criteria included age 18-75 years at screening, acromegaly diagnosis, disease evidence, biochemical control (insulin-like growth factor I [IGF-I] <1.3 × upper limit of normal [ULN] and mean integrated growth hormone [GH] <2.5 ng/mL) at screening, and ≥6 months' iSRL treatment. Effective OOC dose was determined in a 26-week Run-in phase. Eligible patients (IGF-I <1.3 × ULN and mean integrated GH <2.5 ng/mL, week 24) were randomized to a 36-week controlled treatment phase (RCT), receiving OOC or iSRLs starting at week 26. The primary end point was a noninferiority assessment of proportion of patients biochemically controlled in the RCT (IGF-I <1.3 × ULN using time-weighted average). Other end points included nonresponse imputation of the primary end point, landmark analysis using proportion of responders based on average of last 2 IGF-I values at end of RCT, and change from baseline RCT (week 26) IGF-I and GH levels.
Results: Of 146 enrolled patients, 92 entered the RCT (OOC, n=55; iSRLs, n=37). Both arms were well balanced for age, sex, and acromegaly duration. OOC demonstrated noninferiority to iSRLs in maintaining biochemical response, with 91% (CI, 80%-97%) of OOC and 100% (CI, 91%-100%) of iSRL groups maintaining control during the RCT. Of those responding at end of Run-in, 96% of patients on OOC maintained response during RCT. Using nonresponse imputation, 89% of OOC and 95% of iSRL groups were biochemically controlled in RCT. Landmark analysis of those respnding at end of Run-in showed that 94% of patients in each group maintained response at RCT end. In both groups, IGF-I levels were stable in the RCT, average IGF-I at baseline and RCT end being 0.9 × ULN (OOC) and 0.8 × ULN (iSRL). Mean change in GH from RCT start to RCT end was -0.03 ng/mL (OOC) and +0.29 ng/mL (iSRL). Safety data were mostly similar between groups; the OOC group did not experience injection site reactions.
Conclusion: In this noninferiority trial in patients with acromegaly, OOC demonstrated maintenance of biochemical response compared to iSRLs. Results support the efficacy of OOC as a possible iSRL alternative.

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CLINICAL TRIALS AND STUDY UPDATES IN NEUROENDOCRINOLOGY AND PITUITARY