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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