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Hypertension and diabetes improvement during osilodrostat therapy in patients with Cushing's disease: Analyses from the Phase III LINC 3 study

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Introduction

- Hypertension and diabetes mellitus are common, serious complications that underlie cardiovascular risk in patients with Cushing's syndrome
- Alongside cortisol normalization, alleviating the burden, and risk for development, of comorbidities is a key treatment goal in patients with Cushing's disease[1]
- Osilodrostat, a potent oral 11β-hydroxylase inhibitor, normalized UFC and improved clinical signs of hypercortisolism in most patients with Cushing's disease during the 48-week Phase III LINC 3 core study (NCT02180217)[2]
- **We describe changes in blood pressure and glucose homeostasis during LINC 3 according to hypertensive and diabetic status at baseline**

CONCLUSIONS

- Comorbid hypertension or diabetes consistently improved in many patients during 48 weeks of osilodrostat therapy, with many patients able to stop or reduce the dose of antihypertensive or antidiabetic medications
- Comorbidities should be closely monitored as adjustments in concomitant medications are required for some patients taking osilodrostat as cortisol levels decline, including those with improving hypertension or diabetes
- Osilodrostat is effective at improving clinical signs of hypercortisolism and may alleviate treatment burden in patients with Cushing's disease

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Disclosures

This study was sponsored by Novartis Pharma AG; however, as of July 12, 2019, osilodrostat is an asset of Recordati AG.

References

1. Fleseriu M *et al. Lancet Diabetes Endocrinol* 2021;9:847–75
2. Pivonello R *et al. Lancet Diabetes Endocrinol* 2020;8:748–61

Abbreviations

DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; mUFC, mean urinary free cortisol; SBP, systolic blood pressure; SD, standard deviation; UFC, urinary free cortisol; ULN, upper limit of normal

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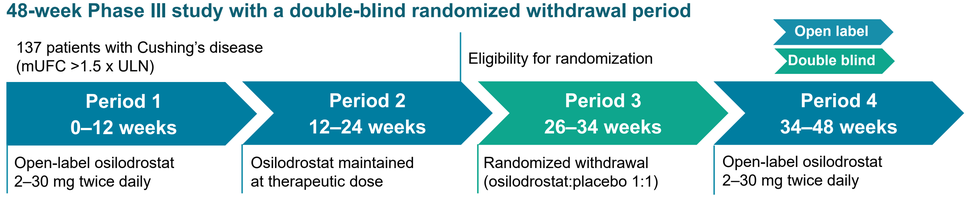
Methods

- Definition of terms:
  - **Baseline hypertension** (≥1 of the following at baseline): Taking antihypertensive medication, prior diagnosis of hypertension, SBP >130 mmHg, DBP >90 mmHg
  - **Baseline diabetes** (≥1 of the following at baseline): Taking antidiabetic medication, prior diagnosis of diabetes mellitus, HbA_{1c} ≥6.5%, FPG ≥126 mg/dL
- **Blood pressure and glycemic parameters:** Evaluated by the investigator at baseline, every 2, 4 or 12 weeks (depending on study period), and at week 48
- Exploratory data and correlative analyses are presented for all patients with data at baseline and specified visit, unless otherwise stated
  - Correlations were evaluated using the Pearson's correlation coefficient

48-week Phase III study with a double-blind randomized withdrawal period

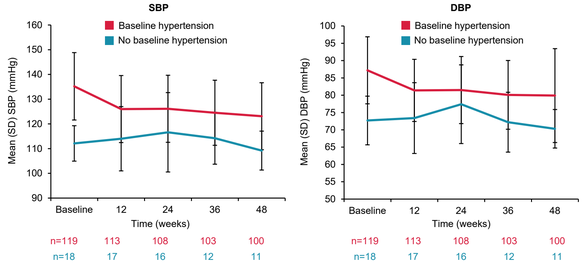


Results

1. Many patients were classed as hypertensive or diabetic at baseline

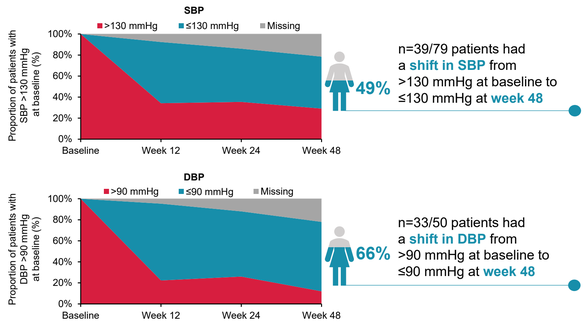
- Scan QR code for baseline characteristics of the study population, which was a typical Cushing's disease cohort

2. Mean SBP and DBP decreased from baseline in hypertensive patients during the study



- Mean 11-deoxycorticosterone increased during the study; mean potassium levels remained largely unchanged and within the normal range
  - There was no significant correlation between change in potassium and change in 11-deoxycorticosterone from baseline at week 24 (r=0.43; P=0.1882) or week 48 (r=0.66; P=0.0526)

3. Many patients with SBP >130 mmHg or DBP >90 mmHg at baseline had SBP ≤130 mmHg or DBP ≤90 mmHg from as early as week 12 of treatment

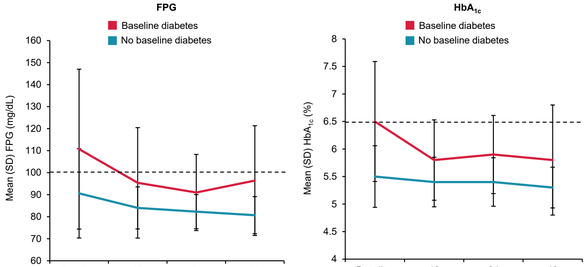


Analysis conducted in patients with SBP >130 mmHg (n=79) or DBP >90 mmHg (n=50) at baseline (not according to baseline hypertensive status as described above)

4. SBP >130 mmHg and DBP >90 mmHg at baseline correlated with greater reductions in these parameters at weeks 24 and 48

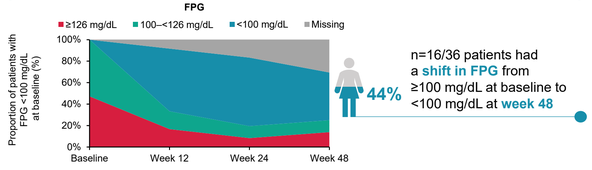
- Week 24: SBP, r=−0.57; DBP, r=−0.57 (both P<0.0001)
- Week 48: SBP, r=−0.58; DBP, r=−0.57 (both P<0.0001)

5. Mean FPG and HbA_{1c} decreased from baseline in diabetic patients during the study



Dashed lines indicate: FPG <100 mg/dL indicates normoglycemia (impaired glucose tolerance: FPG 100–<126 mg/dL; diabetic: FPG ≥126 mg/dL); HbA_{1c}, ≥6.5% indicates diabetes

6. Many patients with FPG ≥100 mg/dL at baseline had FPG <100 mg/dL from as early as week 12 of treatment, suggesting improved control of blood glucose

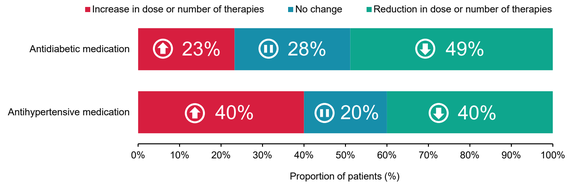


Analysis conducted in patients with FPG ≥100 mg/dL (n=36) at baseline (not according to baseline diabetic status as described above)

7. FPG ≥100 mg/dL and HbA_{1c} ≥6.5% at baseline correlated with greater reductions in these parameters at weeks 24 and 48

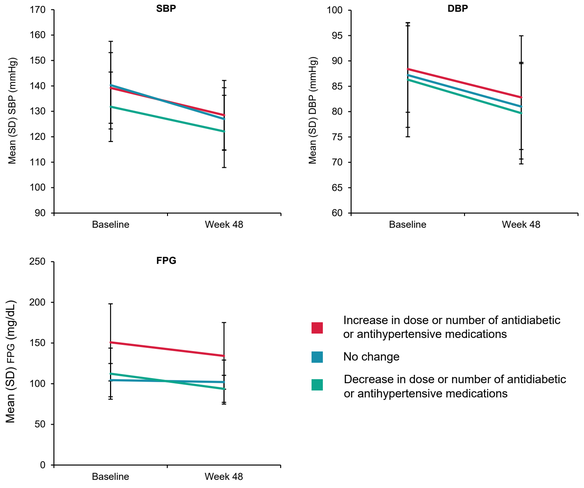
- Week 24: FPG, r=−0.92; HbA_{1c}, r=−0.76 (both P<0.0001)
- Week 48: FPG, r=−0.75; HbA_{1c}, r=−0.60 (both P<0.0001)

8. Many patients were able to stop or reduce the dose of concomitant antihypertensive or antidiabetic medication during the study



Analysis conducted in patients with hypertension at baseline who were receiving antihypertensive medication (n=85) and in patients with diabetes at baseline who were receiving antidiabetic medication (n=43)

- Dose or number of antihypertensive/antidiabetic medications were reduced or stopped in a numerically greater proportion of patients with mUFC ≤ULN than those with mUFC >ULN at week 48 (scan QR code)
- Improvements in blood pressure were seen in all subgroups regardless of change in antihypertensive medication
- Improvements in FPG were seen in patients whose dose or number of antidiabetic medications increased or decreased



9. No moderate or strong correlations between change in blood pressure or blood glucose parameters and change in mUFC from baseline were observed (scan QR code)