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# Effects of osilodrostat (LCI699) on cytochrome P450 enzymes in healthy volunteers indicates a low drug-drug interaction potential

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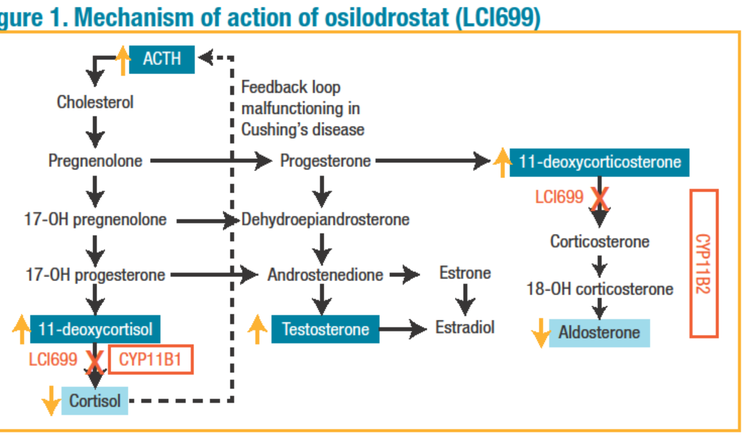
## BACKGROUND

- Osilodrostat (LCI699) is a potent inhibitor of 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) (**Figure 1**)
  - Three times more potent than metyrapone *in vitro* (IC50 2.5 nM vs. 7.5 nM for CYP11B1)
  - Blocks last step of cortisol and aldosterone production
  - Orally administered, twice-daily regimen ($T_{1/2}$ ~4h)

**Figure 1. Mechanism of action of osilodrostat (LCI699)**




- Osilodrostat is currently in development for Cushing's disease
  - Dose titration from 2 mg b.i.d. to 30 mg b.i.d.
  - 79% of patients in Ph II (LINC-2) study had normalized urinary free cortisol (UFC) at week 22 (**Figure 2**)
  - Therapeutic dose of osilodrostat was ≤10 mg b.i.d. for 80% of patients in PhII (**Figure 3**)
  - PhIII study (LINC-3) ongoing

**Figure 2. Change of UFC over time after osilodrostat treatment in LINC 2 study**

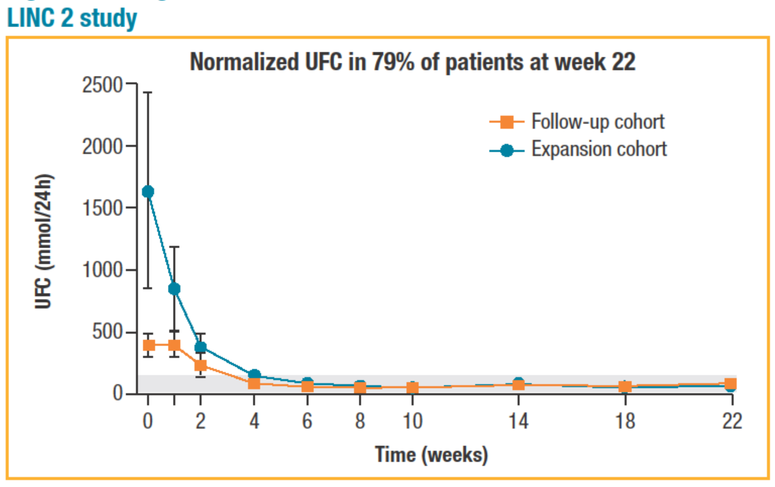
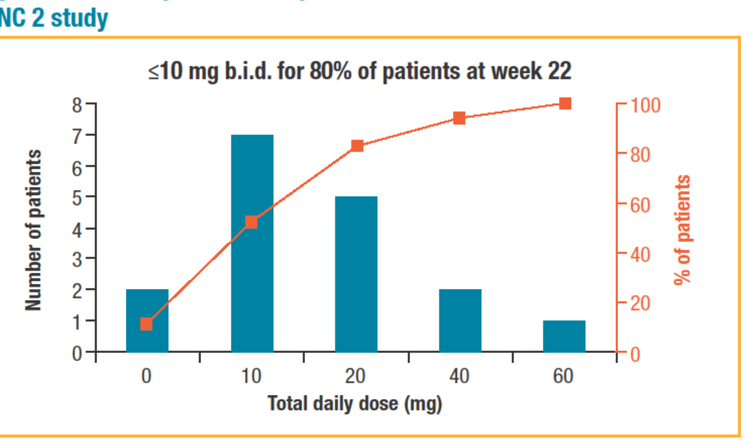
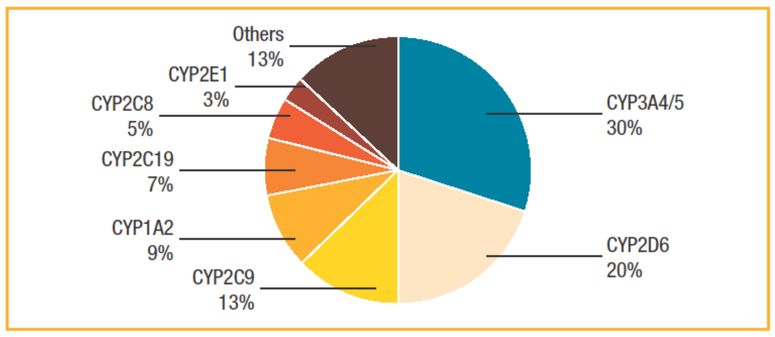



**Figure 3. Summary of total daily dose of osilodrostat at week 22 in LINC 2 study**




- CYP enzymes are important enzymes responsible for oxidative metabolism (Phase I metabolism) of most endogenous and exogenous compounds[1,2]
- CYP3A4/5 is the most clinically important drug metabolizing enzyme, as it metabolizes ~30% of drug that are cleared by CYP pathways[2] (**Figure 4**)

**Figure 4. Percentage of clinically used drugs metabolized by P450 (Adapted from Zanger UM and Schwab M. 2013)[2]**

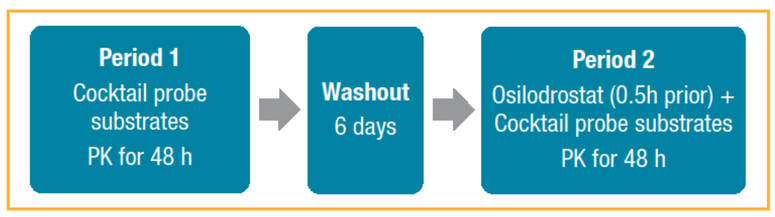



- *In vitro* assessment showed that osilodrostat inhibits various cytochrome P450 (CYP) enzymes via competitive and reversible inhibition, with potential clinical impact on drug metabolism
  - CYP1A2, 2C19, 2D6, 2E1 and 3A4/5
- Therefore a clinical drug-drug interaction study was conducted to evaluate the inhibitory effect of osilodrostat on the pharmacokinetics (PK) of CYP1A2, CYP2C19, CYP2D6, and CYP3A4/5 substrates using the modified Cooperstown cocktail.

## METHODS

- Subjects
  - Healthy male and female subjects
  - 18 to 55 years of age and in general good health
- Study design
  - Fixed sequence, single dose substrates, single dose osilodrostat (**Figure 5**)
- Cocktail substrates consisted of selective probe substrates for the respective enzyme
  - Caffeine (100 mg) as CYP1A2 substrate
  - Omeprazole (20 mg) as CYP2C19 substrate
  - Dextromethorphan (30 mg) as CYP2D6 substrate
  - Midazolam (2 mg) as CYP3A4/5 substrate
- Analysis
  - Primary endpoints were PK exposures (AUClast, AUCinf, Cmax) of cocktail substrates when administered alone and concomitantly with osilodrostat
  - The point estimate and 90% CI for the ratio of geometric means of the PK parameters of the test (osilodrostat + probe substrates) compared with the reference (probe substrates alone) were calculated

**Figure 5. Study design**




## RESULTS

- Subject population
  - 20 subjects dosed; 19 completed study (1 withdrew consent)
  - Subjects included 10 males and 10 females; mean(SD) age of 41.8±7.9 years, weight 73±13 kg, and BMI 24.4±2.9 kg/m²
- Safety and tolerability
  - Cocktail substrates and 50 mg osilodrostat were generally well tolerated and
  - Most common AEs were fatigue (15% of subjects) and dizziness (10% of subjects)
- Drug-drug interaction
  - Inhibitors are classified as strong, moderate or weak based on their impact on exposures of sensitive substrate (**Table 1**)

**Table 1. Classification of CYP inhibitors**

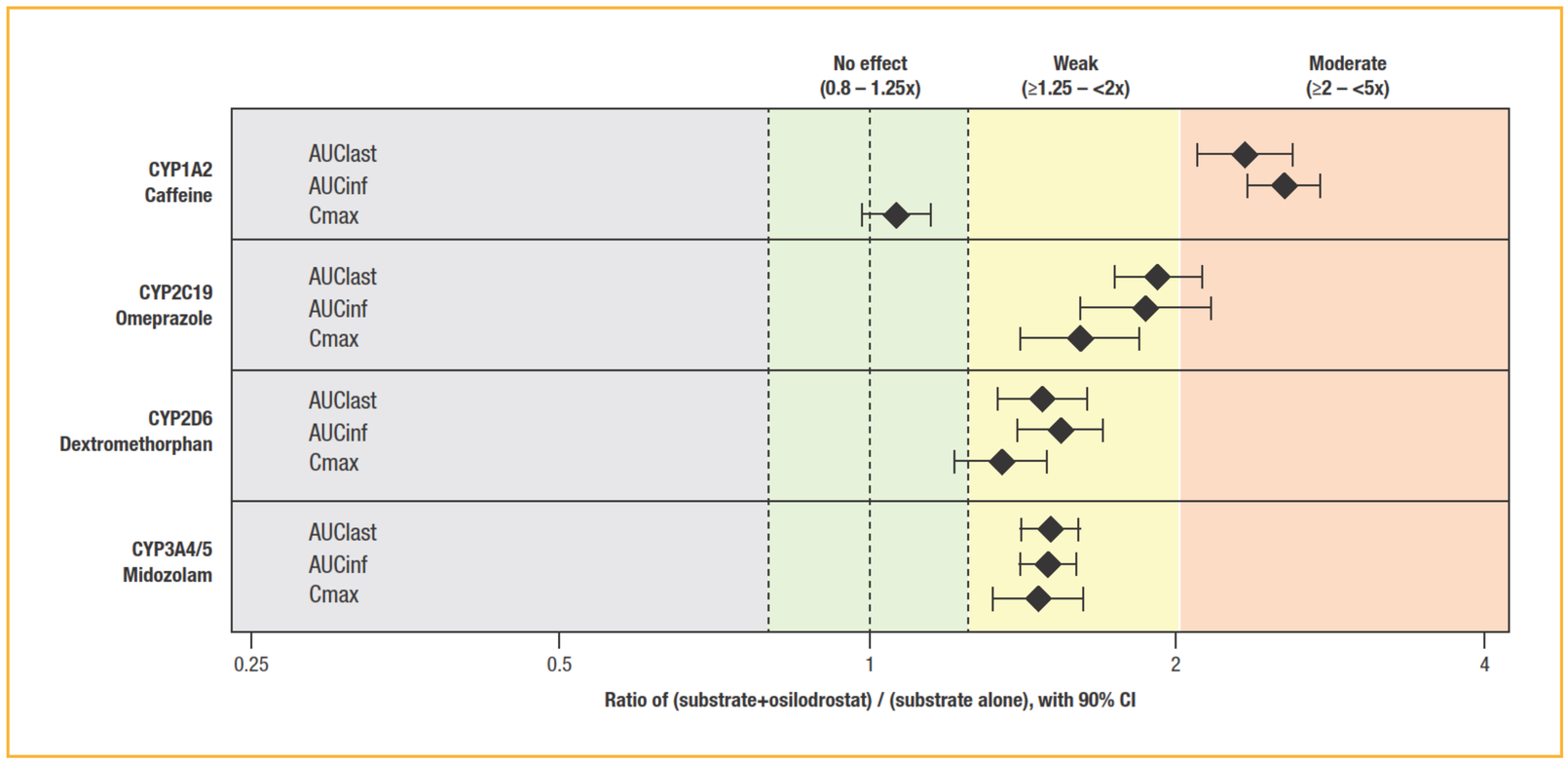
| Classification | Impact on sensitive substrate AUC |
|---|---|
| Strong inhibitor | ≥5 fold increase |
| Moderate inhibitor | ≥2 but <5 fold increase |
| Weak inhibitor | ≥1.25 but <2 fold increase |

FDA draft guidance 2012 - Drug interaction studies study design, data analysis, implications for dosing and labeling recommendations

EMA Guideline on the Investigation of Drug Interactions 2012

**Osilodrostat increases cocktail substrate exposure ~1.5–1.5-fold, and is considered a weak to moderate inhibitor of CYP enzymes (CYP1A2, 2C19, 2D6 and 3A4/5) (Figure 6)**

**Figure 6. Summary of cocktail substrate exposure change when co-administered with osilodrostat**




## DISCUSSION

- The single dose of 50 mg used in this study was selected to cover the osilodrostat exposures expected at the highest therapeutic dose of 30 mg b.i.d., and therefore the maximum extent of interaction
- Drug interaction potential is lower at lower therapeutic doses (≤10 mg b.i.d.)
  - Ph II study in patients with Cushing's disease (LINC-2) showed that the majority of patients (~80%) achieved normalized UFC at ≤10 mg b.i.d
- In comparison, other medical therapies ketoconazole and mifepristone are strong CYP3A4 inhibitors[3,4]
  - Coadministration of a number of CYP3A4 substrates is contraindicated with ketoconazole[3]
  - Mifepristone is contraindicated in patients taking simvastatin, lovastatin, and CYP3A substrates with narrow therapeutic ranges (such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) due to increased risk of adverse events[4]

## CONCLUSIONS

- **Osilodrostat is a weak to moderate inhibitor of CYP enzymes (CYP1A2, 2C19, 2D6 and 3A4/5)**
- **Osilodrostat is unlikely to have a clinically relevant impact on the exposure of other medications cleared by CYP3A4. This is a positive feature of osilodrostat as drug-drug interaction is an important consideration in the use of medical therapies for Cushing's disease patients**

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