PMON165

Favorable liver safety profile of the selective glucocorticoid receptor modulator relacorilant in healthy and hepatically impaired adults and in patients with Cushing syndrome

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Disclosures

AGM, JMC, ICT: Employees, Corcept Therapeutics. This presentation describes an investigational use of relacorilant, which is being developed by Corcept Therapeutics.

Summary & Conclusions

- These results suggest that relacorilant has a favorable liver safety profile that includes a trend toward improved LFTs in healthy volunteers and patients with normal and impaired liver function
- The findings in adults with liver impairment support the use of relacorilant without dose adjustment in patients with moderate hepatic impairment
- Current clinical studies of relacorilant in patients with endogenous hypercortisolism will include LFT assessments to further confirm these findings

The authors want to thank all those who participated in the studies: The study participants and their families, the investigators, and the sponsor team.

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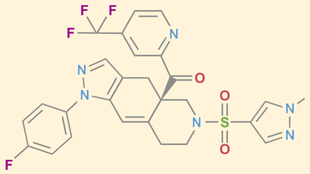
Introduction

Relacorilant (CORT125134, Corcept Therapeutics): A highly selective glucocorticoid receptor modulator (SGRM)

- In clinical development for the treatment of:
  - Endogenous hypercortisolism (Cushing syndrome, CS) of all etiologies (monotherapy)
  - Adrenocortical carcinoma and other solid tumors (with anticancer agents)
- Lacks affinity for the progesterone receptor (unlike the FDA-approved GR antagonist mifepristone)[1]

Relacorilant structure



Pharmacokinetics (PK)

- **Elimination:** Primarily hepatic (via CYP3A and carbonyl reductase)
- **Drug-drug interactions[2]:** Strong CYP3A4 inhibitor without inhibtion of CYP2C8 or CYP2C9

Phase 2 results in patients with CS

- Clinically meaningful improvement in hypertension and hyperglycemia, without antiprogesterone effects or drug-induced hypokalemia[3]
- Improvement in other cortisol-excess-related comorbidities, including hypercoagulopathy, cognitive function, mood, and quality of life

Objective

- To report safety results and changes in liver function tests (LFTs) from open-label phase 1 studies of relacorilant in healthy and hepatically impaired adults and from the open-label phase 2 study in adult patients with CS

1 Study Designs and Methods

Hepatic impairment study (CORT125134-128)

- A phase 1, open-label, multiple-dose study
- 18 subjects aged 18 to 70 years
  - 9 subjects with moderate hepatic impairment (Child-Pugh Class B)
  - 9 controls with normal hepatic function matched for age, sex, and body weight
- Relacorilant 300 mg administered once daily for 10 days under fasted conditions
- Blood samples for PK analysis collected before dosing on Day 1 and from before dosing on Day 10 through 144 hours after the last dose of study drug (Day 16)

Relacorilant-itraconazole drug-drug interaction study (NCT03512548)

- A phase 1, open-label, fixed-sequence crossover study
- 25 healthy subjects (18-65 years)
- Excluded subjects with AST and/or ALT levels >1.5x ULN
- Relacorilant 300 mg daily for 10 days, followed by 10 days of relacorilant 300 mg QD with itraconazole 200 mg QD

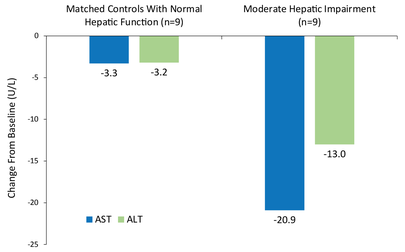
Phase 2 Cushing syndrome study (NCT02804750)[3]

- A multicenter, open-label study with two dose groups
- 34 patients (18-80 years) with endogenous CS and impaired glucose tolerance or type 2 diabetes mellitus and/or uncontrolled or untreated hypertension were treated with relacorilant
- Excluded patients with AST or ALT >3x ULN
- Each dose group underwent a 50-mg dose escalation every 4 weeks
  - Low-dose: relacorilant 100 mg/day to 200 mg/day (12-week treatment duration)
  - High-dose: relacorilant 250 mg/day to 400 mg/day (16-week treatment duration)

2 Results: Hepatic Impairment Study

- Subjects with moderate hepatic impairment were well matched for age, sex, and body weight
  - Mean total Child-Pugh score of 7.9 (range: 7-9) in subjects with moderate hepatic impairment
- Reductions in mean LFTs were observed in subjects with moderate hepatic impairment

Mean change in LFTs
From baseline to Day 16 (144 h after last dose of relacorilant)



ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFTs, liver function tests.

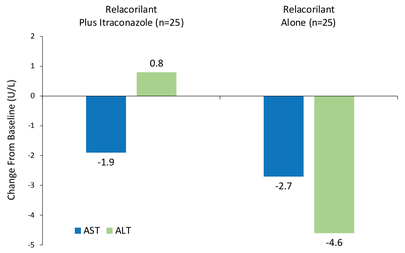
Relacorilant PK

- No apparent difference in subjects with moderate hepatic impairment vs matched controls observed, despite relacorilant's primary hepatic route of elimination
- Relacorilant exposures (measured by area under the curve and maximum plasma concentration) largely overlapped across both groups

3 Results: Drug-Drug Interaction Study (Relacorilant-Itraconazole)

- Addition of itraconazole (an agent with reported liver toxicity) had no relavent effect on the adverse event profile of relacorilant

Mean change in LFTs
From baseline to Day 11 of relacorilant plus itraconazole and from baseline to Day 10 of relacorilant alone



ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFTs, liver function tests.

References

1. Hunt HJ, et al. *J Med Chem*. 2017;60(8):3405-21.
2. Custodio JM, et al. *J Clin Pharmacol*. 2021;61(2):244-53.
3. Pivonello R, et al. *Front Endocrinol*. 2021;12:662865.

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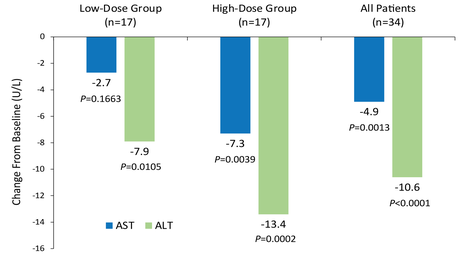
4 Results: Phase 2 Cushing Syndrome Study

- Reductions in LFTs were observed across both dose groups, with greater reductions in the high-dose group
  - Normalization of ALT occurred in 2 of 4 patients with abnormal ALT values at baseline

Mean change in LFTs
From baseline to last observation in the Efficacy Population (n=34)



P-values for mean change from baseline to last observation are from the Wilcoxon signed-rank test. The Efficacy Population included all patients treated with relacorilant who had postbaseline data.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFTs, liver function tests.

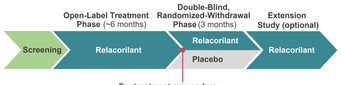
5 Ongoing Clinical Studies

4 clinical studies of relacorilant in patients with hypercortisolism are currently ongoing

Pituitary
Adrenal
Ectopic

GRACE STUDY

A phase 3, double-blind, randomized-withdrawal study to assess the efficacy and safety of relacorilant in patients with endogenous hypercortisolism of all etiologies (NCT03697109)



For treatment responders:
- Start of randomized-withdrawal phase
- Subjects receive either relacorilant or placebo (1:1 randomization)

GRADIENT STUDY

Cortisol-secreting adrenal adenoma(s) or hyperplasia

The first phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of relacorilant in patients with cortisol-secreting adrenal adenoma(s) or adrenal hyperplasia (NCT04308590)

Extension Study

A phase 2/3 long-term extension study of relacorilant in patients with endogenous hypercortisolism of all etiologies (NCT03604198)

Adrenocortical Cancer STUDY

Cortisol-secreting adrenocortical carcinoma

A phase 1b study to evaluate relacorilant in combination with pembrolizumab in patients with metastatic adrenocortical carcinoma associated with hypercortisolism (NCT04373265)