Programme code: P410

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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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

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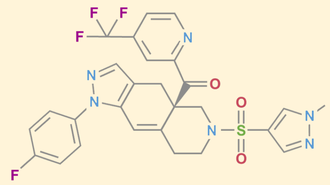
Introduction

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 interations**[2]: Strong CYP3A4 inhibitor without inhibition of CYP2C8 or CYP2C9

Phase 2 results in patients with CS

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

1 Study Designs and Methods

Hepatic impairment study (CORT125134-128)

- A phase 1, open-label, multiple-dose study
- 18 subjects (18-70 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 QD 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)
- Relacorilant 300 mg QD for 10 days, followed by 10 days of relacorilant 300 mg QD with itraconazole 200 mg QD
- Excluded subjects with AST and/or ALT levels >1.5x ULN

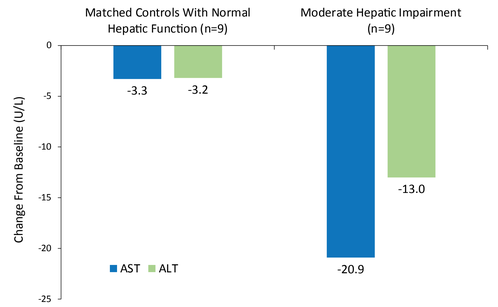
Phase 2 Cushing syndrome study (NCT02804750)[3]

- 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 elevated AST or ALT >3x ULN
- 50-mg dose escalation every 4 weeks
  - Low-dose group: relacorilant 100 mg/day to 200 mg/day (12-week treatment duration)
  - High-dose group: 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.

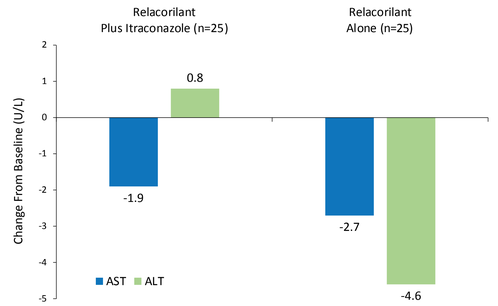
Relacorilant PK

- No apparent difference in subjects with moderate hepatic impairment vs matched controls, 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 relevant 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

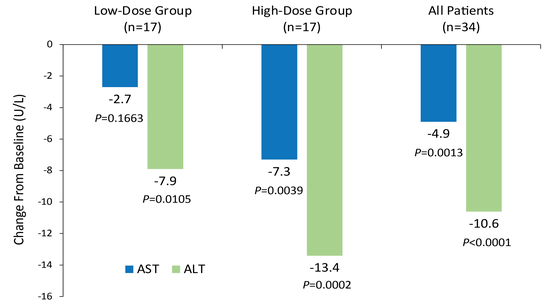


ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFTs, liver function tests.

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 includes all patients treated with relacorilant who had postbaseline data.

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

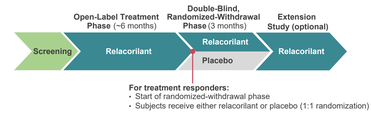
5 Ongoing Clinical Studies

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)



Cortisol-secreting adrenal adenoma(s) or hyperplasia

GRADIENT STUDY

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)

Cortisol-secreting adrenocortical carcinoma

Adrenocortical Cancer STUDY

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

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.

Disclosures

AGM, JMC, ICT: Employees, Corcept Therapeutics.

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