1219

OPEN-LABEL PHASE 2 STUDY TO ASSESS SAFETY AND EFFICACY OF RELACORILANT (CORT125134), A SELECTIVE CORTISOL MODULATOR, IN THE TREATMENT OF ENDOGENOUS HYPERCORTISOLISM

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INTRODUCTION

- Cushing syndrome is a multisystem disorder resulting from prolonged hypercortisolism
- It is frequently associated with osteoporosis, hypertension, and impaired glucose tolerance/diabetes mellitus
- Relacorilant is a selective cortisol modulator being investigated by Corcept Therapeutics for the treatment of endogenous Cushing syndrome
- Its mechanism of action, competitive antagonism at the glucocorticoid receptor, is similar to that of mifepristone (Korlym®)
  - However, mifepristone can cause termination of pregnancy, as well as, in many women, endometrial thickening and irregular vaginal bleeding because of its high affinity for the progesterone receptor
- Relacorilant does not bind to the progesterone receptor, androgen receptor, or estrogen receptor[1]
- Relacorilant is being developed to provide patients with hypercortisolism with the treatment benefits of cortisol modulation, but without the disadvantages of progesterone receptor antagonism

METHODS

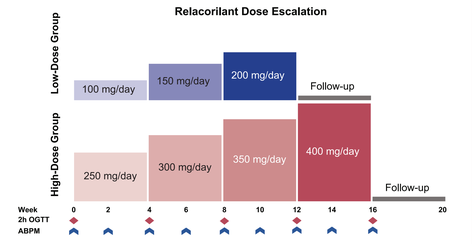
ELIGIBLE PATIENTS

- Patients aged 18-80 years with:
  - Confirmed endogenous hypercortisolism (adrenocorticotropic hormone [ACTH]-dependent or ACTH-independent), as evidenced by ≥2 of the following:
    - 24-hour urine free cortisol above the upper limit of normal
    - Late-night salivary cortisol above the upper limit of normal
    - Lack of cortisol suppression (>1.8 µg/dL serum cortisol) on either overnight 1-mg or 48-hour 2-mg dexamethasone suppression test
  - Impaired glucose tolerance or type 2 diabetes mellitus based on oral glucose tolerance test (OGTT) AND/OR uncontrolled or untreated hypertension (based on ambulatory blood pressure monitoring [ABPM]) defined as a mean systolic blood pressure (SBP) of ≥130 mmHg and/or a diastolic blood pressure (DBP) of ≥85 mmHg
  - At least two clinical signs and symptoms of Cushing syndrome (in addition to impaired glucose tolerance/diabetes mellitus and/or hypertension)
  - Requirement for medical treatment of hypercortisolism

STUDY DESIGN

- Phase 2, multicenter, open-label study with two dose groups of at least 15 patients each to assess the safety and efficacy of relacorilant
- Each group has a 50-mg dose escalation every 4 weeks (**Figure 1**)
  - Low-dose group: relacorilant 100 mg/day, followed by 150 mg/day, and then 200 mg/day
  - High-dose group: relacorilant 250 mg/day, followed by 300 mg/day, then 350 mg/day, and 400 mg/day
- Primary efficacy endpoints:
  - Patients with impaired glucose tolerance/diabetes mellitus: change in the area under the concentration-time curve for glucose ($AUC_{glucose}$) on the 2-hour OGTT from Baseline to Week 12/Early Termination
  - Patients with hypertension: change in SBP and DBP measured by 24-hour ABPM from Baseline to Week 12/Early Termination
- There were two analysis subgroups: patients with impaired glucose tolerance/diabetes mellitus and patients with uncontrolled hypertension. Some patients were members of both groups

Figure 1. Study Design: Phase 2, Open-Label, Relacorilant for Endogenous Hypercortisolism



ABPM=ambulatory blood pressure monitoring; OGTT=oral glucose tolerance test.

RESULTS

EXPOSURE

- Seventeen patients enrolled in the low-dose relacorilant group: 100 mg/day (n=17), 150 mg/day (n=17), and 200 mg/day (n=16)
- The planned total of 15 patients have been enrolled into the high-dose group and are receiving treatment

Table 1. Baseline Patient Characteristics

	Low-Dose Group (n=17)
Sex, n	
Male	8
Female	9
Age, years, mean (range: min-max)	47.8 (28-70)
Race, n	
White	17
Weight, kg	92.1±22.1
Body mass index, kg/m²	33.1±7.4
Etiology, n	
Adrenal	4
Pituitary/ectopic	13
Comorbidities, n	
Hypertension	12
Impaired glucose tolerance/type 2 diabetes mellitus	13
Both	8
Glucose parameters in impaired glucose tolerance/ type 2 diabetes mellitus subgroup, n=13	
HbA1c, %	6.4±0.9
Fasting plasma glucose, mg/dL	116.4±23.2
Fructosamine, µmol/L	225.7±18.9
Blood pressure parameters in hypertension subgroup (assessed by ABPM), n=12	
Mean systolic blood pressure, mmHg	138.0±6.2
Mean diastolic blood pressure, mmHg	87.2±6.3

Data presented as mean±standard deviation unless otherwise indicated.
ABPM=ambulatory blood pressure monitoring; HbA1c=glycated hemoglobin.
Normal laboratory ranges: HbA1c: ≤6.4%; fasting plasma glucose: 70-99 mg/dL; fructosamine: 190-270 µmol/L.

Table 2. Baseline Biochemistry by Etiology for the Low-Dose Group

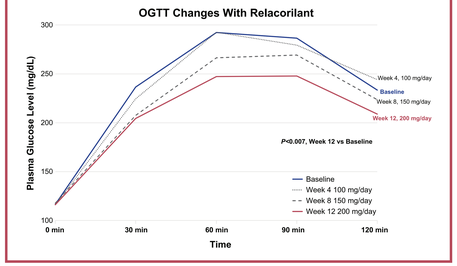
Laboratory Test	Adrenal (n=4)	Pituitary/Ectopic (n=13)
ACTH, pg/mL	5.4±1.3	63.9±30.1
UFC, nmol/24h	311.3±366.9	591.3±517.0
Late-night salivary cortisol, nmol/L	5.9±5.4	8.8±5.4

Data presented as mean±standard deviation unless otherwise indicated.
ACTH=adrenocorticotropic hormone; UFC=urine free cortisol.
Normal laboratory ranges: ACTH: 6-50 pg/mL; UFC: <138 nmol/24h; late-night salivary cortisol: ≤2.5 nmol/L.

CHANGES IN $AUC_{GLUCOSE}$

- Patients with impaired glucose tolerance/type 2 diabetes mellitus exhibited dose-dependent improvement in glycemic control as measured by change from Baseline in $AUC_{glucose}$ ($P<0.007$, two-sided Wilcoxon signed rank test; **Figure 2**)
  - Of the 11 patients who provided a Week 12 OGTT, nine (81.8%) had a decrease in $AUC_{glucose}$ from Baseline, with three patients normalizing their OGTT based on the 2-hour glucose value
  - At Week 12, mean glucose levels at all post-dose timepoints following the OGTT were numerically lower compared with Baseline

Figure 2. Changes in OGTT in the Low-Dose Group



OGTT=oral glucose tolerance test.

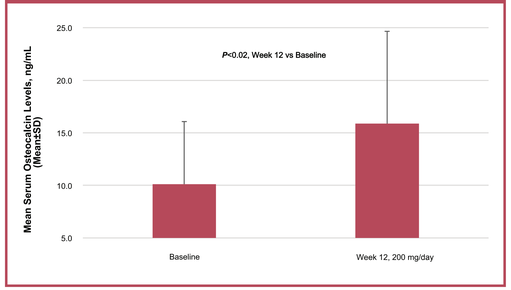
CHANGES IN AMBULATORY BLOOD PRESSURE

- Of the 11 patients in the hypertensive subgroup who completed 12 weeks of dosing, five (45.5%) met the primary efficacy endpoint (decrease in mean SBP or DBP by ≥5 mmHg)

CHANGES IN OSTEOCALCIN LEVELS

- The prevalence of osteoporosis in patients with hypercortisolism is estimated to be between 30% to 65%[2]
- Excess glucocorticoids increase bone resorption and decrease bone formation
- Osteocalcin is a marker of bone formation that is sensitive to glucocorticoid activity; it is suppressed in patients with hypercortisolism
- Treatment with relacorilant resulted in a significant increase in the mean serum osteocalcin level at Week 12 from Baseline (6.3 ng/mL, $P<0.02$; two-sided Wilcoxon signed rank test)

Figure 3. Changes in Serum Osteocalcin Levels in the Low-Dose Group



SD=standard deviation.

CHANGES IN ACTH AND UFC

- Treatment with relacorilant up to 200 mg daily caused only small changes in the ACTH and did not significantly increase UFC

Table 3. ACTH and UFC in All Patients (Baseline and Week 12)

	Baseline, Mean (SD)	Week 12, Mean (SD)	Fold Change Over Baseline
ACTH, pg/mL	50.1±6.4	71.8±48.7	1.4
UFC, nmol/24h	525.6±490.6	549.8±767.3	1.1

ACTH=adrenocorticotropic hormone; UFC=urine free cortisol.
Normal laboratory ranges: ACTH: 6-50 pg/mL; UFC: <138 nmol/24h.

ADVERSE EVENTS

- Treatment with relacorilant (up to 200 mg/day) for up to 84 days was well tolerated
  - Fifteen of 17 (88.2%) patients reported one or more treatment-emergent adverse events (TEAEs) across the 12-week treatment period
  - The most commonly reported TEAEs were musculoskeletal and gastrointestinal in nature (25% and 19% of all TEAEs, respectively)
  - Frequency of TEAEs did not increase with increasing dose
  - There were no serious adverse events
  - There were no discontinuations attributed to relacorilant

CURRENT STUDY STATUS

- Enrollment is complete
- Patients in the high-dose group continue to be treated and results are expected in third quarter 2018
- A Phase 3 study is planned to begin this year

DISCUSSION/CONCLUSION

- Improvement in glucose control was achieved with short duration of treatment at low doses
- Relacorilant demonstrated clinically significant improvements in mean SBP and/or DBP in 45.5% (5/11) of patients in the low-dose group who completed the 12-week treatment period
- Biochemical response to relacorilant treatment was evident, with significant increases in osteocalcin levels
- Relacorilant was well tolerated, with no evidence of progesterone receptor affinity[1]
- Based on the unexpectedly small changes in ACTH and UFC, relacorilant could potentially have an important safety advantage over mifepristone in terms of lower risk of hypokalemia
  - With mifepristone, hypokalemia occurred in 44% of treated patients[3]
- Relacorilant may offer the benefit of potent cortisol modulation without undesirable progesterone receptor-related effects

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DISCLOSURES

AGM is an employee of Corcept Therapeutics.

NA, **IB**, **FSC**, **MBG**, **AYK**, **SL**, **CNM**, **JMS**, and **MEW** served as investigators for this study.

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