GRADIENT: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Assess the Efficacy and Safety of a Selective Glucocorticoid Receptor Modulator, Relacorilant, in Patients With Autonomous Cortisol Secretion Due to Cortisol-Secreting Adrenal Adenoma(s)/Hyperplasia

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INTRODUCTION

HYPERCORTISOLISM (CUSHING SYNDROME)

- Endogenous hypercortisolism is a complex, multisystem endocrine disorder caused by adrenocorticotropic hormone (ACTH)-secreting pituitary or extra-pituitary tumors or by cortisol-secreting adrenal adenomas or adrenal hyperplasia.
- For patients with severe hypercortisolism, there is consensus about the need for treatment. However, there is lack of agreement regarding the management of patients with milder forms of hypercortisolism, especially those with adrenal adenomas or hyperplasia.[1]
- Autonomous cortisol secretion is common in patients with adrenal adenomas (up to 29%[1]). While these patients typically lack the classic stigmata of overt hypercortisolism, other comorbidities associated with elevated cortisol are frequently present (**Table 1**).
- Surgery is usually recommended in patients with post-dexamethasone suppression test (DST) serum cortisol >5 µg/dL and ≥2 comorbidities (at least one of which is poorly controlled).[1]
- For patients with post-DST serum cortisol between 1.9–5.0 µg/dL, there is no consensus on the optimal treatment approach.[1]
  - Published data show that some, but not all patients experience clinical improvement of their cortisol-related comorbidities after adrenalectomy.[4,5]
- If surgery is not considered the best option, medical therapy targeting cortisol activity can be used.
  - Treatment with the approved glucocorticoid receptor (GR) antagonist mifepristone (Corcept Therapeutics) has led to improvement in hyperglycemia[6,7] similar to that seen in patients treated with adrenal surgery.
  - However, due to its strong progesterone receptor affinity, mifepristone is associated with undesirable side effects, including endometrial hypertrophy, the potential for irregular vaginal bleeding, and termination of pregnancy.

Table 1. Common Comorbidities in Patients With Autonomous Cortisol-Secreting Adrenal Adenomas

Comorbidities	Prevalence
Hypertension	74%[2]
Glucose intolerance/type 2 diabetes mellitus	45%[2]
Obesity	43%[3]
Dyslipidemia	50%[3]
Osteoporosis	58%[2]

RELACORILANT

- Relacorilant (CORT125134, Corcept Therapeutics) is a highly selective GR modulator in clinical development for the treatment of all etiologies of endogenous hypercortisolism. **Figure 1** shows the chemical structures of mifepristone and relacorilant.
- Unlike mifepristone, relacorilant has no clinically relevant affinity for the progesterone receptor (**Table 2**) and does not cause antiprogesterone effects.

Figure 1. Structures of Mifepristone and Relacorilant

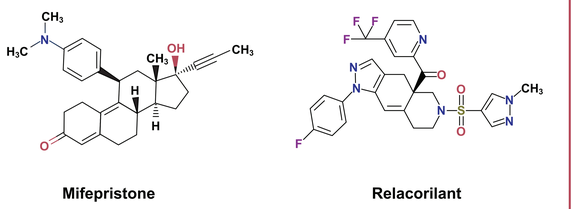


Table 2. Receptor Binding Affinity With Relacorilant and Mifepristone

	Inhibitory Constant (K_i)	
	Glucocorticoid Receptor (GR)	Progesterone Receptor (PR)
Relacorilant	<1 nM	>10 µM
Mifepristone	<1 nM	1.2 nM

Note: Smaller K_i values indicate greater binding affinity.

PHASE 2 RESULTS

EFFICACY

- A Phase 2 study (CORT125134-451, NCT02804750) of relacorilant in patients with overt endogenous hypercortisolism showed improvements in glycemic control, hypertension, and other comorbidities associated with cortisol excess, including hypercoagulopathy, insulin resistance, bone formation, and quality of life.[8,9]

SAFETY

- No drug-induced antiprogesterone effects were observed.[8]
- No drug-induced hypokalemia was observed.[9]
  - Unlike mifepristone, which induces a significant rise in cortisol levels that can stimulate the mineralocorticoid receptor, leading to hypokalemia and in some cases increased blood pressure, relacorilant had only a modest effect on cortisol levels.
  - As a result, relacorilant may potentially be more effective in immediately treating hypertension in this patient population.

PHASE 3 STUDIES

- Currently, two Phase 3 studies are ongoing to evaluate the efficacy and safety of relacorilant (**Table 3**).
  - GRACE (CORT125134-455, NCT03697109) focuses on overt cases of endogenous hypercortisolism of various etiologies.[10]
  - Here we introduce GRADIENT (CORT125134-456, NCT04308590), which focuses on patients with hypercortisolism secondary to adrenal adenoma(s) or hyperplasia.

GRADIENT STUDY DESIGN

- GRADIENT is a randomized, double-blind, placebo-controlled Phase 3 study conducted at approximately 60 North American and international sites (**Figure 2**).

Figure 2. Planned Regions Participating in the GRADIENT Study

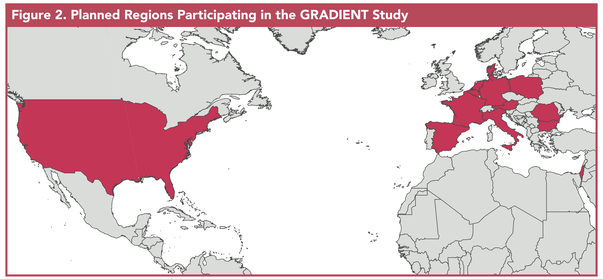
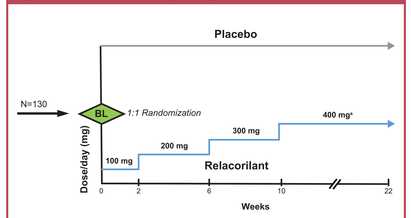


Figure 3. GRADIENT Study Design



*Or highest tolerated dose.
BL, baseline.

- Approximately 130 patients 18–80 years old will be recruited and assigned to either the impaired glucose tolerance/diabetes mellitus (IGT/DM) or hypertension (HTN) subgroup.
- The GRADIENT study design is shown in **Figure 3**.

GRADIENT KEY EXCLUSION CRITERIA

- Severe, uncontrolled hypertension (mean SBP >170 mmHg or mean DBP >110 mmHg; based on 24-hour ABPM) or poorly controlled DM (HbA1c >12%)
- Adrenocortical carcinoma
- Autonomous co-secretion of aldosterone
- Uncontrolled, clinically significant hypo- or hyperthyroidism

KEY INCLUSION CRITERIA: GRADIENT VS GRACE

	GRADIENT (NCT04308590)	GRACE (NCT03697109)
Biochemical	• Lack of cortisol suppression (>1.8 µg/dL serum cortisol) on either 1-mg overnight DST or 2-mg 48-hour DST • Suppressed or low (≤15 pg/mL) early-morning ACTH levels on at least 2 occasions	<u>At least 2 of the following:</u> • Lack of cortisol suppression (>1.8 µg/dL serum cortisol) on either 1-mg overnight DST or 2-mg 48-hour DST • Urinary free cortisol >ULN • Late night salivary cortisol >ULN
Source/ Etiology	• Adrenal adenoma(s)/hyperplasia	• Pituitary, adrenal, ectopic
Comorbidities	<u>At least 1 of the following:</u> • **Glucose impairment** – *Impaired glucose tolerance (IGT):* Plasma glucose ≥140 and <200 mg/dL on 2-h oGTT or – *Diabetes mellitus (DM):* Fasting plasma glucose ≥126 mg/dL, and/or plasma glucose ≥200 mg/dL on 2-h oGTT, or HbA1c ≥6.5% • **Uncontrolled systolic hypertension** – Mean SBP ≥130 to ≤170 mmHg based on 24-h ABPM	<u>At least 1 of the following:</u> • **Glucose impairment** – *Impaired glucose tolerance (IGT):* Plasma glucose ≥140 and <200 mg/dL on 2-h oGTT or – *Diabetes mellitus (DM):* Fasting plasma glucose ≥126 mg/dL and/or plasma glucose ≥200 mg/dL on 2-h oGTT • **Uncontrolled hypertension** – Mean SBP ≥135 to ≤170 mmHg or mean DBP ≥85 to ≤110 mmHg based on 24-h ABPM <u>And at least 2 of the following:</u> • Cushingoid appearance (eg, facial rubor, moon facies, dorsocervical or supraclavicular fat pad) • Increased body weight or central obesity • Proximal muscle weakness • Low bone mass based on DXA scan • Psychiatric symptoms (including depression or psychosis) • Skin manifestations: violaceous striae, acne, and/or hirsutism • Easy bruisability

ABPM, ambulatory blood pressure monitoring; ACTH, adrenocorticotropic hormone; DBP, diastolic blood pressure; DST, dexamethasone suppression test; DXA, dual-energy X-ray absorptiometry; oGGT, oral glucose tolerance test; SBP, systolic blood pressure; ULN, upper limit of normal.

STUDY ENDPOINTS

- Primary efficacy endpoints (from baseline to 22 weeks, relacorilant vs placebo):
  - *IGT/DM group:* Mean change in $AUC_{glucose}$
  - *HTN group:* Mean change in mean systolic blood pressure based on 24-h ambulatory blood pressure monitoring
- Safety assessment based on treatment-emergent adverse events in all patients
- Other measures (from baseline to 22 weeks, relacorilant vs placebo):
  - Changes in the hypothalamic-pituitary-adrenal axis (changes in ACTH and dehydroepiandrosterone sulfate [DHEA-S])
  - Changes in cortisol excess-related comorbidities (body weight and waist circumference, dyslipidemia, and quality of life)
  - Changes in insulin resistance indices, coagulation markers, GR activity biomarkers, bone density, trabecular bone score, and bone markers

SUMMARY

- GRADIENT will be the first international, multicenter, randomized, double-blind, placebo-controlled Phase 3 study to test if patients with less severe forms of adrenal hypercortisolism and hyperglycemia (IGT/DM) and/or HTN benefit from medical treatment with relacorilant.
- Efficacy will be assessed by monitoring hyperglycemia and HTN, two clinical manifestations that are frequently associated with cortisol excess.
  - Two robust and validated clinical measures of blood glucose and blood pressure control will be used, $AUC_{glucose}$ after oGTT and ambulatory blood pressure monitoring.
  - Mean change in $AUC_{glucose}$, a primary endpoint of this study, reflects glucose control in patients with diabetes as well as those with IGT, for whom neither HbA1c nor fasting glucose are reliable measures of glucose control.
  - Adrenal adenomas are usually diagnosed in older patients for whom systolic HTN is most frequently observed. Thus, mean change in SBP was chosen as another primary endpoint.
- To examine the many manifestations of cortisol excess, several other efficacy measures will be used to assess clinical benefit, including quality of life, bone changes, weight, whole-body fat composition, coagulation markers, and lipid profile.
- These endpoints will help inform the potential of relacorilant to treat patients with less severe hypercortisolism secondary to cortisol-secreting adrenal adenomas or hyperplasia.

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DISCLOSURES

RJA: Consultant, Corcept Therapeutics; GRADIENT Investigator; **AG, AGM:** Employees, Corcept Therapeutics.