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A Double-Blind, Randomized, Placebo-Controlled Phase 3 Study to Assess the Efficacy and Safety of Relacorilant, a Selective Glucocorticoid Receptor Modulator, in Patients With Hypercortisolism 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 pituitary tumors, extra-pituitary tumors, adrenal adenomas, or adrenal hyperplasia.
- Autonomous cortisol secretion is common in patients with adrenal adenomas, reported in up to 29% of patients[1].
  - While these patients typically lack the classic stigmata of overt hypercortisolism, other comorbidities associated with elevated cortisol are frequently present (**Table 1**).

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

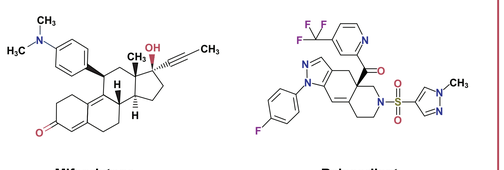
Comorbidities	Prevalence
Hypertension	74%[2]
Glucose intolerance/type 2 diabetes mellitus	45%[2]
Obesity	43%[3]
Dyslipidemia	50%[3]
Osteoporosis	58%[2]

- While there is consensus to treat severe hypercotisolism, agreement is lacking regarding the management of patients with less severe forms, especially adrenal adenomas or hyperplasia.[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]
  - Multiple studies have reported an increased risk of mortality due to cardiovascular events and infections in patients with post-DST serum cortisol >1.8 µg/dL.[4,5,6]
  - Published data show that some, but not all patients experience clinical improvement of their cortisol-related comorbidities after adrenalectomy.[7,8]
- 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[9,10] 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, irregular vaginal bleeding, and termination of pregnancy.

RELACORILANT

- Relacorilant (CORT125134, Corcept Therapeutics, **Figure 1**) is a highly selective GR modulator in clinical development for the treatment of all etiologies of endogenous hypercortisolism.
- Unlike mifepristone, relacorilant has no clinically relevant affinity for the progesterone receptor (**Table 2**) and does not cause antiprogesterone effects[11] or hypokalemia[12].

Figure 1. Chemical Structures of Mifepristone and Relacorilant



Mifepristone 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.[11,12]

SAFETY

- No drug-induced antiprogesterone effects were observed.[11]
- No drug-induced hypokalemia was observed.[12]
  - 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), a double-blind, placebo-controlled randomized-withdrawal study, focuses on overt cases of endogenous hypercortisolism of various etiologies.[13]
  - 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**).
- 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**.

Figure 2. Planned Regions Participating in the GRADIENT Study

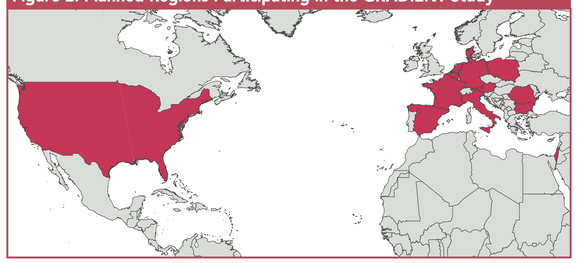
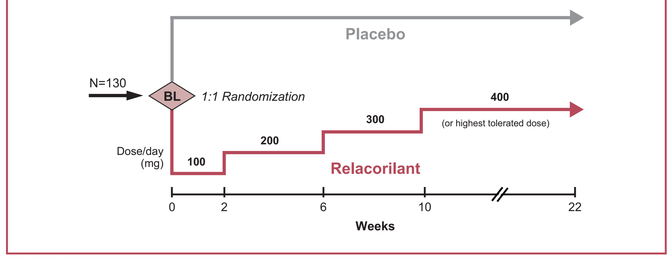


Figure 3. GRADIENT Study Design



BL, baseline.

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 • Low (≤15 pg/mL) early-morning ACTH levels on at least 2 occasions during screening	At least 2 of the following: • 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	At least 1 of the following: • **Glucose impairment** – *IGT*: Plasma glucose ≥140 and <200 mg/dL on 2-h oGTT or – *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	At least 1 of the following: • **Glucose impairment** – *IGT*: Plasma glucose ≥140 and <200 mg/dL on 2-h oGTT or – *DM:* Fasting plasma glucose ≥126 mg/dL, and/or plasma glucose ≥200 mg/dL on 2-h oGTT, or HbA1c ≥6.5% • **Uncontrolled hypertension** – Mean SBP ≥135 to ≤170 mmHg and/or mean DBP ≥85 to ≤110 mmHg based on 24-h ABPM And at least 2 of the following: • 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; DM, diabetes mellitus; DST, dexamethasone suppression test; DXA, dual-energy X-ray absorptiometry; IGT, impaired glucose tolerance; oGGT, oral glucose tolerance test; SBP, systolic blood pressure; ULN, upper limit of normal.

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

STUDY ENDPOINTS

- Primary efficacy endpoints (from baseline to week 22, 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 week 22, 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 is the first international, multicenter, randomized, double-blind, placebo-controlled Phase 3 study to test if patients with less severe forms of adrenal hypercortisolism benefit from medical treatment with relacorilant.
- Efficacy is being 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 are being 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 are being 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

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