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A Randomized-Withdrawal, Placebo-Controlled, Phase 3 Study to Assess the Efficacy and Safety of Selective Glucocorticoid Receptor Antagonist, Relacorilant, in Patients With Cushing Syndrome (GRACE Study)

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INTRODUCTION

- Relacorilant (CORT125134, Corcept Therapeutics, **Figure 1**)
  - A highly selective glucocorticoid receptor modulator in clinical development for the treatment of all etiologies of endogenous Cushing syndrome (CS)
  - Reduces effects of cortisol, but unlike mifepristone, does not bind to the progesterone receptor (**Table 1**)[1]
- Results from a phase 2, open-label study of relacorilant showed:
  - Improved glycemic control and reduced hypertension[2]
  - Significant improvement in other manifestations of hypercortisolism, including hypercoagulopathy, liver function, cognitive function, and mood
  - No instances of drug-related hypokalemia or progesterone receptor–mediated effects
  - Most commonly reported adverse events (AEs) were back pain, peripheral edema, headache, pain in extremities, and nausea

Figure 1. Relacorilant Structure

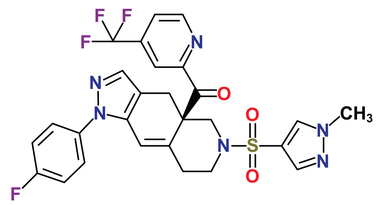


Table 1. Glucocorticoid Receptor and Progesterone Receptor Binding Affinity With Mifepristone and Relacorilant

GR Antagonist	Inhibitory Constant (Ki)	
	GR	PR
Mifepristone	1.0 nM	1.0 nM
Relacorilant	0.5 nM	>1000 nM

Note: Smaller Ki values indicate greater binding affinity.
GR, glucocorticoid receptor; PR, progesterone receptor.

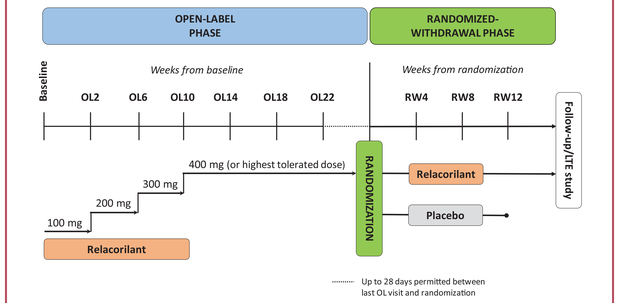
STUDY DESIGN

- GRACE is a phase 3, double-blind, placebo-controlled, randomized-withdrawal study (NCT 03697109) being conducted at 60 North American and international sites (**Figure 2**)
  - Randomized-withdrawal designs help establish longer-term effectiveness of an agent when use of placebo at the start of a trial is not acceptable[3]

Figure 2. Regions Participating in the GRACE Study

- Includes a screening phase, an open-label phase, and a randomized-withdrawal phase, followed by a long-term extension study (**Figure 3**)

Figure 3. GRACE Study Design



OL, open-label; LTE, long-term extension; RW, randomized-withdrawal.

OPEN-LABEL PHASE (UP TO 26 WEEKS DURATION)

- All qualified patients receive relacorilant (**Figure 3**)

RANDOMIZED-WITHDRAWAL PHASE (12 WEEKS DURATION)

- Patients who complete the open-label phase and meet response criteria for impaired glucose tolerance/diabetes mellitus (IGT/DM) or hypertension (HTN) are randomized 1:1 to double-blinded treatment with relacorilant or placebo (**Figure 3**)

STUDY OBJECTIVES

- Primary
  - Assess the efficacy of relacorilant for the treatment of endogenous CS based on glycemic control and blood pressure (BP) control during the randomized-withdrawal phase
  - Evaluate the safety of relacorilant
- Secondary
  - Assess changes in cortisol excess–related comorbidities, including:
    - Cushing Quality of life (QoL)
    - Global Clinical Response[4]
    - Weight
    - Beck Depression Inventory® II

STUDY PARTICIPANTS

Table 2. Key Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• 18-80 years old	• Severe, uncontrolled DM or HTN
• Confirmed biochemical diagnosis of endogenous CS per Endocrine Society guidelines[5]	• Uncontrolled, clinically significant hypo- or hyperthyroidism
• ≥2 clinical signs/symptoms of CS	• Severe renal insufficiency
• IGT/DM and/or uncontrolled HTN at baseline	• LFTs >3x upper normal range

CS, Cushing syndrome; DM, diabetes mellitus; HTN, hypertension; IGT, impaired glucose tolerance; LFTs, liver function tests.

STUDY ENDPOINTS

- Safety assessed through evaluations of treatment emergent AEs
- Comparisons of biochemical and clinical assessments will be analyzed at the following time points:
  - End of open-label vs end of randomized-withdrawal phase
  - Baseline vs randomization
  - Baseline vs end of randomized-withdrawal phase
    - Rate and degree of relapse of symptoms

SUMMARY

- The phase 3 GRACE study (currently enrolling) is a randomized-withdrawal trial to evaluate relacorilant in the treatment of CS
- The study's use of two robust and validated endpoints, blood glucose control and BP control, will help inform the potential of relacorilant to treat patients with endogenous CS

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DISCLOSURES

RJA, JWF: Consultant, Corcept Therapeutics.

AGM: Employee, Corcept Therapeutics.

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