# AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE SAFETY OF LONG-TERM USE OF RELACORILANT IN PATIENTS WITH ENDOGENOUS CUSHING SYNDROME

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## Introduction

Endogenous hypercortisolism (Cushing syndrome) is a chronic and debilitating multisystem endocrine disorder associated with high morbidity and mortality[1]

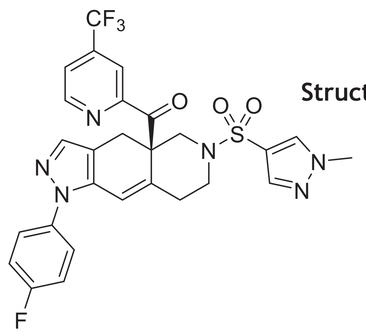
Treatment modalities include surgical resection of the tumor, pharmacologic therapy, pituitary irradiation (in the case of Cushing disease), or bilateral total adrenalectomy[2]

Treatment is focused on reversal of clinical manifestations, avoidance of permanent hormonal deficiency, and management of the comorbidities

Development of novel, safe, and effective medical therapies with a positive benefit-risk ratio would improve the pharmacologic treatment options for participants who have failed surgery or are not candidates for surgery

Relacorilant (CORT125134) is a highly selective GR modulator in clinical development for the treatment of endogenous hypercortisolism

- Relacorilant has similar antagonistic effects at the GR as the FDA-approved GR antagonist mifepristone, but with no activity against the progesterone receptor[3]



Structure of Relacorilant

In a phase 2 study in participants with endogenous hypercortisolism (NCT02804750), relacorilant showed clinically meaningful improvements in hypertension and hyperglycemia without undesirable antiprogesterone effects or drug-induced hypokalemia[4]

Two ongoing global phase 3 studies are evaluating the efficacy and safety of relacorilant in participants with endogenous hypercortisolism and concurrent hypertension and/or hyperglycemia:

- **GRACE (NCT03697109):** Double-blind, placebo-controlled, randomized-withdrawal study evaluating participants with endogenous hypercortisolism of any etiology[5]
- **GRADIENT (NCT04308590):** Double-blind, placebo-controlled, randomized study evaluating relacorilant in participants with endogenous hypercortisolism related to adrenal adenoma(s) or adrenal hyperplasia[6]

**Here, we are presenting the study design of the phase 2/3, open-label extension study evaluating the long-term safety and therapeutic effect of prolonged GR modulation with relacorilant in participants with endogenous hypercortisolism**

**FDA,** US Food and Drug Administration; **GR,** glucocorticoid receptor.

## Study Design (NCT03604198; EudraCT 2018-001616-30)[7]

Endogenous Hypercortisolism

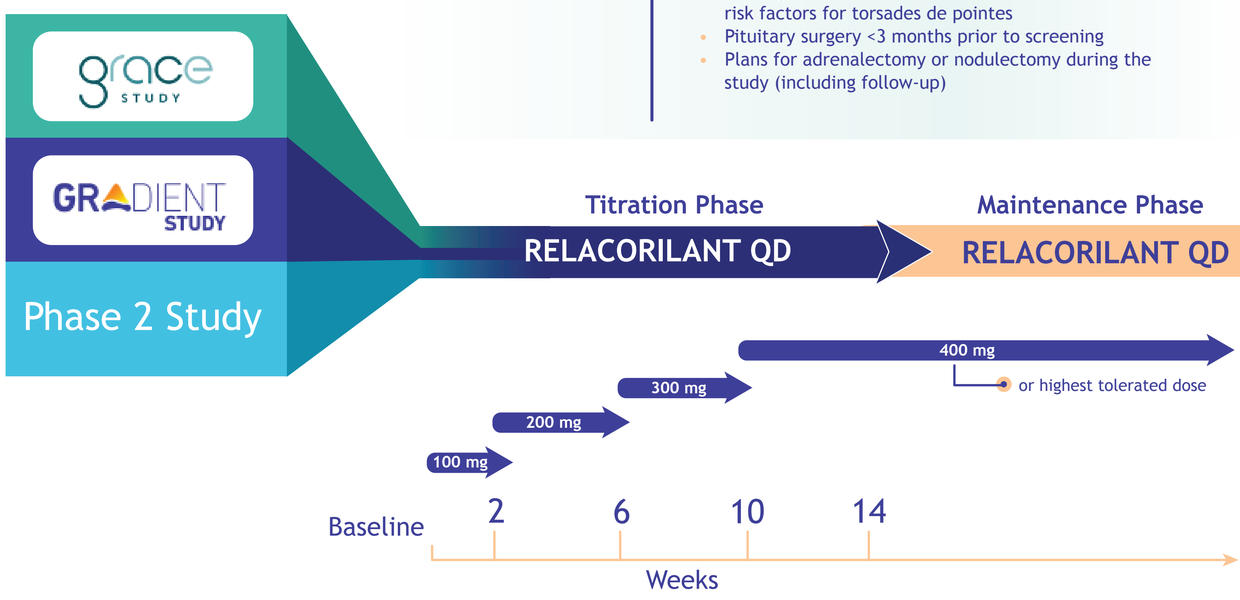
### Long-term Extension Study

**Key inclusion criteria:**

- Must have successfully completed a phase 2 or 3 study of relacorilant in endogenous hypercortisolism (phase 2 study, GRACE, GRADIENT)[4-6] and, in the investigator's opinion, may benefit from further treatment with relacorilant
- For participants entering the study >12 weeks after last dose of parent study, confirmation of hypercortisolism consistent with the parent study is required

**Key exclusion criteria:**

- Uncontrolled, clinically significant hypothyroidism or hyperthyroidism
- Uncorrected, clinically significant hypokalemia (serum potassium <3 mEq/L) ≤2 weeks prior to enrollment
- Renal failure (serum creatinine ≥2.2 mg/dL)
- Total bilirubin >1.5 x the ULN or elevated ALT or AST ≥3 x ULN
- Prolonged QT interval and/or history of additional risk factors for torsades de pointes
- Pituitary surgery <3 months prior to screening
- Plans for adrenalectomy or nodulectomy during the study (including follow-up)




**Dosing**

- Relacorilant oral capsules at the last dose received in the parent study unless dose modification is indicated by the investigator's clinical judgment
- Dose titration required for participants entering from a blinded placebo-controlled study or if the last relacorilant dose was >4 weeks before enrollment

**Treatment with relacorilant may continue for participants who receive a clinical benefit, in the investigator's opinion, until relacorilant is commercially or otherwise available or until the study is stopped by the sponsor***

Clinic visits occur at 3-month intervals for assessment of safety, tolerability, and treatment effect

- Monthly contact between visits to capture adherence, adverse events, and medication changes; additional visits will accompany dose titrations

Currently ongoing at centers in Europe, Israel, and North America

*Germany: up to 2 years of dosing

**ALT,** alanine aminotransferase; **AST,** aspartate aminotransferase; **QD**, once daily; **ULN,** upper limit of normal.

## Objectives and Endpoints

**Primary Objective**

- To assess the long-term safety of relacorilant in the treatment of signs and symptoms of endogenous hypercortisolism

**Exploratory Objectives**

- To assess the long-term benefit of relacorilant in the treatment of signs and symptoms of endogenous hypercortisolism
- To assess GR activity biomarkers

**Primary Endpoints**

- Incidence of treatment-emergent adverse events
- Changes from baseline in:
  - Clinical laboratory tests (hematology and chemistry panels)
  - Physical examination and vital sign measurements
  - 12-lead ECGs
  - Pituitary tumor size based on MRI in participants with Cushing disease

**Key Exploratory Endpoints**

- Changes from baseline in:
  - HbA1c and insulin resistance indices in participants with diabetes mellitus or glucose intolerance at baseline in the parent study
  - BP by ABPM in participants with uncontrolled HTN at baseline in the parent study and in participants with controlled HTN taking at least one anti-HTN medication
  - Body weight and waist circumference
  - CushingQoL questionnaire
  - Serum osteocalcin, plasma ACTH, serum cortisol, lipid metabolism, sex steroid hormones, bone mineral density measured by DXA scans, coagulation panels, clinical appearance (based on photography) for GRACE participants only
- Measurement of mRNA expression of GR-activity biomarkers (eg, glucocorticoid-induced gene panel)

**ABPM,** ambulatory blood pressure measurement; **ACTH,** adrenocorticotropic hormone; **BP,** blood pressure; **DXA,** dual-energy x-ray absorptiometry; **ECG,** electrocardiogram; **GR,** glucocorticoid receptor; **HbA1c,** glycated hemoglobin; **HTN,** hypertension; **MRI,** magnetic resonance imaging; **mRNA,** messenger RNA; **QOL,** quality of life.

## Summary

Relacorilant is a selective GR modulator in development for the treatment of endogenous hypercortisolism of all etiologies

In a phase 2 study, relacorilant showed clinically meaningful improvements in cortisol-related comorbidities

These findings are being further evaluated in 2 ongoing phase 3 studies

The presented ongoing, open-label phase 2/3 extension study investigates the long term safety and efficacy of relacorilant treatment in endogenous hypercortisolism

Enrollment is ongoing

**GR,** glucocorticoid receptor.

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