

Glucocorticoid Receptor Antagonism in the Treatment of Cushing Syndrome (GRACE): A Phase 3, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Study of the Efficacy and Safety of Relacorilant

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Primary • To assess the efficacy of relacorilant for the treatment of endogenous Cushing syndrome based on BP control at Week 12 of the Randomized- Withdrawal (RW) phase compared with placebo • To assess the safety of relacorilant for the treatment...

Ethical review	Approved WMO
Status	Completed
Health condition type	Adrenal gland disorders
Study type	Interventional

Summary

ID

NL-OMON54706

Source

ToetsingOnline

Brief title

CORT125134-455 (ICON 0115/0015)

Condition

- Adrenal gland disorders

Synonym

Cushing's syndrome

Research involving

Human

Sponsors and support

Primary sponsor: Corcept Therapeutics Incorporated

Source(s) of monetary or material Support: Corcept Therapeutics

Intervention

Keyword: Cushing's syndrome, Randomized-Withdrawl, Relacorilant

Outcome measures

Primary outcome

The primary efficacy endpoint will be assessed in the RW phase. The study will be considered to have a positive outcome if the primary efficacy endpoint reaches statistical significance:

- In patients with hypertension, the proportion of patients with a loss of response with respect to hypertension from Visit OL22 to RW12 based on 24-hour ABPM as compared between relacorilant and placebo arms, where loss of response is defined as follows:
 - In patients who met only the SBP response criterion, an increase in SBP ≥ 5 mm Hg
 - In patients who met only the DBP response criterion, an increase in DBP by ≥ 5 mm Hg
 - In patients who met both the SBP and DPB response criteria, an increase in either SBP or DBP by ≥ 5 mm Hg
 - Any increase or modification in antihypertensive medication due to worsening

hypertension

- Patients discontinue treatment in RW phase for any reason.
- In all patients, assessment of safety based on treatment-emergent adverse events (TEAEs)

Secondary outcome

Please refer to protocol Am 5 05April 2023, section 3 Study Design: 3.6.2

Secondary Efficacy Endpoints. Other secondary efficacy endpoints are listed by study phase (RW or OL), and by the type of endpoint.

Study description

Background summary

Endogenous Cushing syndrome is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol. In both adults and children, Cushing syndrome is most commonly caused by adrenocorticotrophic hormone (ACTH) secreting pituitary tumor (Cushing disease). Other forms of Cushing syndrome result from autonomous production of cortisol from adrenal cortical tumors or overproduction of ACTH from non-pituitary tumors (ectopic ACTH syndrome). The only curative treatment is resection of the tumor causing the excess cortisol. Depending on the nature of the underlying tumor (ie, benign versus malignant, localized versus metastatic), the selected treatment, radiotherapy, medical therapy, or a combination of these. Pharmacological treatment serves to control the disease after unsuccessful surgery or recurrence (Nieman et al. 2015). It may also be used to lower cortisol activity to improve a patient's condition prior to surgery and is employed as interim therapy under specific circumstances, such as in patients waiting for radiotherapy to be effective (Cuevas-Ramos 2014). Currently, there are four United States (US) Food and Drug Administration (FDA) -approved medical therapies for endogenous Cushing syndrome. The first, mifepristone (Korlym®), was approved for the control of diabetes mellitus / impaired glucose tolerance (DM / IGT) secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have DM / IGT and have failed surgery or are not candidates for surgery. The second, pasireotide (Signifor®), is a somatostatin receptor agonist approved for the treatment of adult patients with Cushing disease for whom pituitary surgery is not an option or has not been curative. The third, osilodrostat (Isturisa®) is a cortisol-synthesis inhibitor approved

for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. Relacorilant (CORT125134) is a potent, selective glucocorticoid receptor (GR) antagonist being developed for the treatment of Cushing syndrome. Relacorilant is a high-affinity antagonist of the GR (inhibition constant $<1\text{nM}$ in a human GR binding assay and $<10\text{nM}$ in a human functional assay). Although the mechanism of action of relacorilant is similar to that of mifepristone, relacorilant does not bind to the progesterone receptor (PR). Given its selective and potent GR antagonism, relacorilant has the potential advantage compared with mifepristone or not having any antiprogestosterone effects, including endometrial hypertrophy and the potential for irregular vaginal bleeding.

Study objective

Primary

- To assess the efficacy of relacorilant for the treatment of endogenous Cushing syndrome based on BP control at Week 12 of the Randomized- Withdrawal (RW) phase compared with placebo
- To assess the safety of relacorilant for the treatment of endogenous Cushing syndrome

Secondary

- To assess changes in cortisol excess-related comorbidities (including DM/IGT and body weight) in patients with endogenous Cushing syndrome treated with relacorilant over the RW phase

Study design

This is a Phase 3, double-blind, placebo-controlled, RW study to assess the efficacy, safety, and PK of relacorilant in patients with endogenous Cushing syndrome and concurrent DM / IGT and / or uncontrolled hypertension.

Intervention

Please refer to the protocol section 5 Study Treatments and Management

Study burden and risks

Glucocorticoid receptor antagonism is a proven mechanism of action for the treatment of DM / IGT secondary to hypercortisolism in adult patients with Cushing syndrome (Fleseriu et al.2012). Because the mechanism of action of relacorilant is similar to that of mifepristone, with the exception that it does not bind the PR, relacorilant is expected to effectively treat Cushing syndrome, but without the drawbacks or progesterone receptor antagonism that may result in untoward reproductive effects and / or interruption of therapy.

In the Phase 2 study (Study CORT125134-451) in patients with endogenous Cushing syndrome, relacorilant showed evidence of clinical benefit based on improvement of cortisol-excess-related comorbidities. The drug was generally well-tolerated, with the upper bound on dosing being typically musculoskeletal complaints, a tolerability issue that patients can report.

Compared with the predecessor drug mifepristone, relacorilant offers two key safety advantages: lack of affinity for the PR, and lack of significant cortisol rise (a driver of hypokalemia in the marketed GR antagonist mifepristone).

Based on the mechanism of action of relacorilant, there is a theoretical risk of excessive GR antagonism, which could manifest by weakness, tiredness, dizziness, hypoglycemia, dehydration, weight loss, nausea, vomiting, diarrhea, and muscle aches. Since relacorilant does not affect the mineralocorticoid receptor, it is unlikely that hypotension would occur in the absence of antihypertensive medication. Because plasma glucocorticoid levels are not decreased with relacorilant administration, a biochemical diagnosis or excessive GR antagonism is not possible; diagnosis must rely on clinical assessment. In cases of suspected excess GR antagonism, study drug will be interrupted for 3 days and supplemental glucocorticoid will be given in high doses to overcome the GR antagonism.

The safety profile of relacorilant in study patients will be monitored by AEs, physical examinations, measurement of vital signs, 12-lead electrocardiograms (ECGs), and blood tests for clinical chemistry and hematology parameters.

Patients meeting response criteria will be randomized 1: 1 to continue relacorilant or receive a placebo equivalent (ie, have relacorilant withdrawn). Patients proceeding into the RW phase will be at risk for relapse of symptoms of Cushing syndrome, including worsening of diabetes, hypertension, and weight gain.

In vitro data indicate that relacorilant is metabolized by multiple CYP enzymes (CYP3A4, CYP2C8, and CYP3A5) and by carbonyl reductases. Data also indicate the potential for relacorilant to perpetuate drug-drug interactions via inhibition of CYP3A and transporter pathways. Patients taking any prohibited medication are excluded from this study (refer to section 5.4 of protocol). If a concomitant medication is required to treat an AE, in selecting the appropriate concomitant medication, the Investigator must consider the risk of drug-drug interaction. The Medical Monitor must approve all concomitant medications required to treat an AE if there is a potential for drug-drug interaction. If necessary, the patient will be withdrawn from the study.

Study procedures include venous blood sampling and noninvasive procedures, including ECG recording, imaging, and vital-sign measurement. During cannulation, more than 1 attempt may be needed to insert the cannula in a vein

or a patient and it is possible that bruising and / or inflammation may be experienced at the site of cannulation. The total volume of blood collected will not exceed 850 ml, unless the Investigator or designee considers additional unplanned collection (s) are required for safety laboratory tests.

More information on the risks and benefits of relacorilant is provided in the Investigator's Brochure.

Contacts

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

To enroll in the study, each patient must meet the following key inclusion criteria: 1. Male or female, 18 to 80 years of age, inclusive 2. Has a confirmed biochemical diagnosis of endogenous Cushing syndrome based on the

presence of at least 2 of the following: • UFC $\geq$ upper limit of normal (ULN) in at least 2 complete 24-hour tests within the screening window • Late-night salivary cortisol $\geq$ ULN in at least 2 tests (using a salivette) within the screening window (Note: Test is not appropriate for night shift workers and cannot be used to evaluate eligibility) • Lack of cortisol suppression ($\geq 1.8 \mu\text{g/dL}$ serum cortisol) on either 1-mg overnight or 2-mg 48-hour dexamethasone suppression testing during Screening, or within 12 weeks before signing the informed consent

3. Has at least 2 of the following clinical signs and symptoms of Cushing syndrome: • Bodily characteristics of a Cushingoid appearance (e.g., facial rubor, moon facies, dorsocervical fat pad, 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

4. Has at least 1 of the following at Baseline: • DM (fasting plasma glucose $\geq 126 \text{ mg/dL}$ and/or 2-hour oGTT plasma glucose $\geq 200 \text{ mg/dL}$ at 2 hours or HbA1c $\geq 6.5\%$) or IGT (plasma glucose $\geq 140 \text{ mg/dL}$ and $\leq 200 \text{ mg/dL}$ on a 2-hour oGTT glucose) (American Diabetes Association 2020) • Uncontrolled hypertension (mean SBP ≥ 135 to $\leq 170 \text{ mm Hg}$ and/or mean DBP ≥ 85 to $\leq 110 \text{ mm Hg}$) based on 24-hour ABPM

5. If receiving medical treatment for DM/IGT or hypertension, there has been no increase in medication dosage for at least 4 weeks prior to Baseline assessment.

6. If receiving medical treatment for depression, there has been no increase in medication dosage for at least 6 weeks prior to Baseline

7. For women of childbearing potential, has a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline

Exclusion criteria

Patients who meet any of the following criteria will not be permitted entry to the study:

1. Has severe, uncontrolled hypertension (mean SBP $\geq 170 \text{ mm Hg}$ or mean DBP $\geq 110 \text{ mm Hg}$ at Screening), based on 24-hour ABPM
2. Has poorly controlled DM (HbA1c $\geq 12\%$ at Screening)
3. Has a known *long term* history of both hypertension and diabetes (defined as both hypertension and diabetes diagnosed ≥ 10 years prior to the initial diagnosis of endogenous CS)
4. Has a history of cyclic Cushing's syndrome with fluctuating clinical manifestations.
5. Has DM Type 1.
6. Has abnormal liver test results (total bilirubin $\geq 1.5 \times \text{ULN}$ or elevated alanine aminotransferase or aspartate aminotransferase $\geq 3 \times \text{ULN}$ at Baseline)
7. Has severe renal insufficiency (glomerular filtration rate $\leq 29 \text{ mL/min}$ at Baseline)
8. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism
9. Has prolonged QT interval corrected for heart rate using Fridericia's equation (QTcF) ($\geq 450 \text{ ms}$ for men and $\geq 470 \text{ ms}$ for women) with normal QRS interval ($\leq 120 \text{ ms}$) or QTcF interval $\geq 500 \text{ ms}$ with wide QRS interval ($\geq 120 \text{ ms}$)
10. Has received stereotactic radiation therapy for a Cushing syndrome-related tumor within 24 months of Baseline or conventional pituitary radiation therapy within 36 months of Baseline.
11. Has undergone pituitary

surgery ≤ 3 months prior to Screening 12. Has used or plans to use any of the following treatments for Cushing syndrome within 4 weeks prior to Baseline: - Mifepristone - Adrenostatic medications: metyrapone, osilodrostat, ketoconazole, fluconazole, aminoglutethimide, or etomidate - Serotonin antagonists: cyproheptadine, ketanserin, or ritanserin - Dopamine agonists: bromocriptine or cabergoline - Gamma-aminobutyric acid agonists: sodium valproate - Short-acting somatostatin analogs: octreotide, lanreotide, or pasireotide 13. Has used or plans to use somatostatin receptor ligands: long-acting octreotide or pasireotide within 8 weeks prior to Baseline 14. Patients who require inhaled glucocorticoid use and have no alternative option if their condition deteriorates during the study. 15. Has adrenocortical carcinoma 16. Has used mitotane prior to Baseline. 17. Has ectopic Cushing syndrome and a life expectancy of ≤ 3 years or receiving chemotherapy. 18. Has pseudo-Cushing syndrome. Patients with known or suspected pseudo-Cushing syndrome based on medical history (such as patients with severe obesity, major depression, or a history of alcoholism) should undergo a dexamethasone-CRH DDAVP stimulation test (Yanovski et al. 1993, Giraldi et al. 2007, Yanovski et al. 1998) to rule-in or rule-out this possibility 19. Has taken any investigational drug within 4 weeks prior to Baseline, or within less than 5 times the drug's half-life, whichever is longer 20. Ongoing use of antidiabetic, antihypertensive, antidepressant or lipid-lowering medications that are highly dependent on CYP3A for clearance and that cannot undergo dose modification upon coadministration with strong CYP3A inhibitors 21. Ongoing use of any strong CYP3A4 inducer or any other prohibited medications (Section 5.4.4) 22. Is pregnant or lactating 23. Is a female patient of childbearing potential (including all women ≤ 50 years old, women whose surgical sterilization was performed ≤ 6 months ago, and women who have had a menstrual period in the last 2 years) who cannot use a highly effective method of contraception (Section 4.6.2) 24. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug 25. Has a history of hypersensitivity or severe reaction to the study drug, to a similar class of drug, or to the study drug's excipient 26. In the Investigator's opinion, should not participate in the study or may not be capable of following the study schedule 27. Has known HIV or hepatitis B or C infection 28. Is a family member of one of the Sponsor's employees, the Investigator, or the site staff directly working on the study 29. Has a history of unexplained vaginal bleeding or unexplained endometrial abnormalities.

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Completed
Start date (anticipated):	29-06-2020
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not yet known
Generic name:	Relacorilant

Ethics review

Approved WMO	
Date:	11-12-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	19-06-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	29-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	25-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	01-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	31-05-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	31-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	15-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	23-05-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	28-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO	
Date:	01-02-2023
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	11-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	10-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	22-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	08-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	
Date:	22-07-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register

EudraCT
ClinicalTrials.gov
CCMO

ID

EUCTR2018-003096-35-NL
NCT03697109
NL68116.078.18

Study results

Date completed: 15-04-2024

Results posted: 14-01-2025

First publication

13-12-2024