Phase 2 Study of the Safety and Efficacy of CORT125134 in the Treatment of Endogenous Cushing*s Syndrome

Published: 27-07-2016
Last updated: 15-04-2024

The primary objective of the study is to assess the safety of CORT125134 in patients with endogenousCushing*s syndrome. The secondary objective of the study is to assess the evidence of reduction incortisol activity following treatment with...

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

Summary

ID

NL-OMON47012

Source
ToetsingOnline

Brief title
CORT125134-451 in Cushing's Syndrome

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: CORT125134-451, Endogenous Cushing's Syndrome, High blood pressure, Type 2 diabetes

Outcome measures

Primary outcome

Key efficacy assessments

* Oral glucose tolerance test (impaired glucose tolerance/diabetes subgroup

only)

* Ambulatory BP measurement (hypertension subgroup only)

Secondary outcome

Exploratory efficacy assessments

* Physician*s Global Assessment

* HbA1c

* Fructosamine

* Adiponectin

* 24-hour urinary free cortisol (UFC) with creatinine

* Late-night salivary cortisol

* Body weight, waist circumference

* Beck Depression Inventory (BDI-II), Trail Making Test, CushingQoL

* Lipid panel

* Sit-to-stand test

* Sex hormone levels

* Menstrual cycle characterization (premenopausal women not on hormonal birth

control)

* Coagulation tests

* Glucocorticoid receptor (GR) biomarker tests

* Bone markers (serum bone alkaline phosphatase, osteocalcin, urine N telopeptides of type 1 collagen [NTx], calcium from 24-hour UFC)

* Hypothalamic-pituitary-adrenal (HPA) axis markers, including plasma ACTH and serum cortisol concentrations

* ACTH precursors

* High-sensitivity C-reactive protein concentrations

* 24-hour urine calcium and sodium

* Insulin-like growth factor (IGF-1)

* Thyroid function tests

Pharmacokinetics

Blood levels of CORT125134 and metabolites will be measured predose and at 1, 2, 4, 6, and 8 hours postdose at Weeks 2, 6, and 10, and predose only at Weeks 4, 8, and 12/early termination (ET).

Safety

Safety will be assessed by physical examination findings, vital signs, ECG results, pregnancy tests, clinical laboratory test results (hematology and chemistry panels), adverse events (AEs), and concomitant medications.

Study description

Background summary

CORT125134 (relacorilant) is a potent, selective glucocorticoid receptor (GR) antagonist being developed for the
treatment of Cushing*s syndrome. Glucocorticoid receptor antagonism is a proven mechanism of action
for the treatment of the hyperglycemia secondary to hypercortisolism in adult patients with Cushing*s
syndrome. Since its mechanism of action is similar to that of mifepristone, with the exception that it does
not bind the progesterone receptor, CORT125134 may be a treatment of Cushing*s syndrome without the
drawbacks of progesterone receptor antagonism.

Study objective

The primary objective of the study is to assess the safety of CORT125134 in patients with endogenous
Cushing*s syndrome. The secondary objective of the study is to assess the evidence of reduction in
cortisol activity following treatment with CORT125134 in patients with endogenous Cushing*s syndrome
based on improvement in blood glucose control and/or blood pressure (BP).

Study design

This is a Phase 2, open-label study with two dose groups (15 patients/group), each with a two-step dose escalation. Because the study drug formulation has been updated (to enhance stability) for this protocol and has a different exposure/dose relationship than the formulation used in the initial Phase 1 Study CORT125134-120, full steady-state PK profiles will be generated at every dose level 2 weeks following the initial dose and each dose escalation. Dose escalation will be supervised by an independent data review committee (DRC) with the specific aim of keeping patient exposures (AUC0-24h) *40 µg*h/mL (in accordance with the supporting toxicology data).

Intervention

CORT125134, administered to fasting patients orally as capsules containing 50 mg of CORT125134:
Group 1: 100 mg/day for 4 weeks, then 150 mg/day for 4 weeks, then 200 mg/day for 4 weeks

Group 2: 250 mg/day for 4 weeks, then 300 mg/day for 4 weeks, then 350 mg/day for 4 weeks, then 400 mg/day for 4 weeks

Study burden and risks

CORT125134 is a potent and selective GR antagonist being developed for the treatment of
Cushing*s syndrome. Glucocorticoid receptor antagonism was established as a mechanism of
action for the treatment of the hyperglycemia secondary to hypercortisolism in adult patients
with Cushing*s syndrome with the approval of mifepristone. The mechanism of action of
CORT125134 is similar to that of mifepristone, with the exception that CORT125134 does
not bind the progesterone receptor. Thus, an expected benefit of CORT125134 in the
treatment of Cushing*s syndrome is a lack of progesterone receptor antagonism that may
result in untoward endometrial effects*for example, endometrial hypertrophy and the
potential for irregular vaginal bleeding and/or interruption of therapy.
Furthermore, in previous phase I studies CORT125134 was shown safe and generally well tolerated following single doses up to 500 mg or repeated doses up to 250 mg once daily.

Taking into account the proposed approach to introducing CORT125134 to patients with
Cushing*s syndrome to better understand the safety, tolerability, PK, and possible efficacy,
the overall benefit-risk is considered favourable in this patient population.

(see also IMPD section 2.4)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients must meet all of the following inclusion criteria before study entry to be eligible for enrollment into the study:
1. Is a male or female adult, 18*80 years of age
2. Has a diagnosis of endogenous Cushing*s syndrome confirmed by:
At least two of the following test criteria:
* Urinary free cortisol above the upper limit of normal (ULN) (50.0 *g/24 h) in at least 2, and up to 4, complete 24 hour collections within 3 weeks prior to Day 1 (baseline)
* Late-night salivary cortisol above the ULN (at least 2, and up to 4, collections using a salivette) within 3 weeks prior to Day 1 (baseline)
* Lack of cortisol suppression (>1.8 *g/dL serum cortisol) on either 1 mg overnight or 2-mg 48 hour dexamethasone suppression testing during screening or within 12 weeks before the ICF is signed.
And
At least two of the following clinical signs and symptoms of Cushing*s syndrome:
* Facial characteristics of a Cushingoid appearance (moon facies, dorsocervical fat pad, plethora)
* Increased body weight or central obesity
* Proximal muscle weakness
* Low bone mass (dual energy X-ray absorptiometry [DXA] T < *1.0)
* Psychiatric symptoms (including depression or psychosis)
* Hirsutism and/or violaceous striae and/or acne
* Easy bruising;A patient with an adrenal lesion may alternatively qualify if there is autonomous cortisol secretion based on dexamethasone suppression testing and supporting evidence of clinically significant cortisol excess. Such a patient must have:
* Radiologically proven unilateral or bilateral adrenal disease (nodules, hyperplasia)
* Lack of cortisol suppression (>5 µg/dL serum cortisol) on either 1-mg overnight or 2-mg 48

hour dexamethasone suppression testing during screening
* Low or suppressed ACTH (<10 pg/mL) to confirm ACTH-independency
* Presence of at least two comorbidities potentially related to cortisol excess (eg, type 2 diabetes, hypertension, obesity, osteoporosis), of which at least one is inadequately controlled by medical measures
3. Requires medical treatment of hypercortisolemia (ie, those for whom surgery or radiation is contraindicated or has been refused)
Examples include, but are not limited to, patients with Cushing*s disease who are post-surgery and/or post-radiation for whom additional surgery is not recommended; de novo patients with Cushing*s disease who are not eligible for surgery due to comorbidities; and patients with ectopic ACTH-dependent Cushing*s syndrome in which the tumor cannot be localized or completely removed.
4. Meets at least one of the following criteria:
* Has type 2 diabetes mellitus as confirmed at screening visit with a fasting glucose >126 mg/dL and a 2-hour oral glucose tolerance test (oGTT) result for plasma glucose *200 mg/dL at 2 hours
* Has impaired glucose tolerance (2-hour oGTT result for plasma glucose in the range of *140 mg/dL to <200 mg/dL)
* Has hypertension (mean systolic BP of 130*170 mmHg and/or a mean diastolic BP of 85*110 mmHg) based on 24 hour ambulatory BP measurement
5. If taking antidiabetic medication, is on a stable dose (ie, cannot start new medication or change dose within 4 weeks prior to the first dose of study drug)
6. If taking antihypertensive medication, is on a stable dose (ie, cannot start new medication or change dose within 4 weeks prior to the screening ambulatory BP measurement)
7. Has potassium within the normal range (3.5*5.3 mEq/L) at screening or corrected to within the normal range by Day 1
8. Female patients of childbearing potential must be willing to use a highly effective method of contraception from 30 days prior to Day 1 until 30 days after the last dose of study drug. Male patients with a female partner must agree to 2 forms of contraception, one of which must be a double-barrier method, from Day 1 until 30 days after the last dose of study drug. Highly effective methods of contraception include abstinence, oral contraceptives combined with a barrier method, diaphragm with vaginal spermicide, intrauterine device, condom and partner using vaginal spermicide, and surgical sterilization (*6 months post-surgery).
9. (Female patients): Has a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1)
10. Has a life expectancy of at least 6 months
11. Is able to participate in the study for up to 22 weeks in Group 1 and 26 weeks in Group 2, including returning to the investigative site to fulfill the safety and efficacy evaluations outlined in the protocol
12. Is able to read and understand the consent form and communicate with the study staff
13. Provides written consent to participate in the study prior to any study procedures and understands that he/she is free to withdraw from the study at any time

Exclusion criteria

Patients who meet any of the following exclusion criteria will not be eligible to participate in the study:
1. Has a non-endogenous source of hypercortisolemia
2. Has pseudo-Cushing*s syndrome. Patients with known or suspected pseudo-Cushing*s 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 to rule-in or rule-out this possibility.
3. Has uncontrolled, clinically significant hypothyroidism or hyperthyroidism
4. Has poorly controlled hypertension, defined as systolic BP >170 mmHg or diastolic BP >110 mmHg at screening
5. Has Stage *4 renal failure (ie, glomerular filtration rate *29 mL/min)
6. Has elevated total bilirubin >1.5×ULN or elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3×ULN
7. For patients with diabetes or abnormal oGTT at screening: has glycated hemoglobin (HbA1c) of >12% within 3 months of first dose of study drug
8. Has a screening hemoglobin level of <9 g/dL
9. Has a clinically significant electrocardiogram (ECG) abnormality at screening, which, in the opinion of the Investigator, will make the patient an unsuitable candidate for the study
10. Has a confirmed screening QTcF interval >450 ms for males and >470 ms for females (using Fridericia*s correction) in the presence of a normal QRS interval (QRS <120 ms) or a history of additional risk factors for torsades de pointes
11. Is currently receiving chemotherapy for a tumor related to Cushing*s syndrome
12. Had radiation therapy for Cushing*s syndrome-related tumor within 1 year of screening period
13. Is planning surgery or radiation therapy for Cushing*s syndrome-related tumor during the study
14. Has used or plans to use any of the following treatments for Cushing*s syndrome, as specified:
* Adrenostatic medications: metyrapone, ketoconazole, fluconazole, aminoglutethimide, or etomidate from 4 weeks prior to baseline (Day 1) through the follow-up visit
* Adrenolytic medications:
o In Group 1, any patients taking mitotane
o In Group 2 only, patients with adrenocortical carcinomas taking mitotane whose dose has not been stable for at least 2 months prior to baseline (Day 1) or in whom increases in the mitotane dosage are expected through the end of dosing
* Neuromodulator drugs that act at the hypothalamic-pituitary level: serotonin antagonists (cyproheptadine, ketanserin, retanserin), dopamine agonists (bromocriptine, cabergoline), gamma-aminobutyric acid agonists (sodium valproate), and somatostatin receptor ligands (octreotide long-acting release [LAR], pasireotide LAR, lanreotide) from 8 weeks before baseline (Day 1) through the follow-up visit. Use of short-acting somatostatin analogs (octreotide, pasireotide) from 4 weeks prior to baseline (Day 1) through the follow-up visit.
* Mifepristone, from 6 weeks before baseline (Day 1) through the follow-up visit
15. Has started or increased (or plans to start or increase) the dose of an antidepressant medication (eg, selective serotonin reuptake inhibitors or tricyclic compound) from 6 weeks before baseline (Day 1) through the end of the study dosing period
16. Has started or increased (or plans to start or increase) the dose of a lipid-lowering drug from 4 weeks before baseline (Day 1) through the follow-up visit

17. Is lactating
18. Has an acute or unstable medical problem that could be aggravated by treatment with the investigational study drug
19. Has a history of hypersensitivity or severe reaction to the study drug, to a similar class of drug, or to the study drug*s excipients
20. Has taken any investigational drug within 30 days before baseline (Day 1), or within a period of less than five times the drug*s half life, whichever is longer
21. In the Investigator*s opinion, should not participate in the study or may not be capable of following the study schedule
22. Has known HIV or hepatitis B or C infection
23. Is a family member of one of the Sponsor*s employees, the Investigator, or the site staff directly working on the study

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-10-2017
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	CORT125134

Ethics review

Approved WMO Date:	27-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	06-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-06-2018
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	ID
EudraCT	EUCTR2016-000899-23-NL
ClinicalTrials.gov	NCT02804750
CCMO	NL58452.078.16