An Open Label Study to Assess the Safety and Efficacy of COR*003 (2S, 4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Published: 11-03-2014
Last updated: 20-04-2024

This study will be a single arm, open-label, dose titration study to assess efficacy, safety, tolerability and PK of COR-003 in subjects with CS with each subject serving as his/her own control.

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

Summary

ID

NL-OMON45174

Source
ToetsingOnline

Brief title
COR-2012-01

Condition

- Adrenal gland disorders

Synonym
Cushing's syndrome or Cushing's desease

Research involving
Human

Sponsors and support

Primary sponsor: Cortendo AB

Source(s) of monetary or material Support: Cortendo AB

Intervention

Keyword: COR-003, Cushing's syndrome, open label, phase 3

Outcome measures

Primary outcome

* To evaluate the clinical responder rate, defined as the proportion of subjects with normal urinary free cortisol (UFC) after 6 months of treatment with COR-003 in the Maintenance Phase without dose increase; and to evaluate the range of effective doses in subjects with various levels of hypercortisolism.

Secondary outcome

* To identify the proportion of subjects with clinical response, defined as reduction in mean 24-hour UFC levels to below or equal to the upper limit of normal (* ULN) after each month of treatment with COR-003 without a dose increase during the Maintenance Phase;

* To identify the proportion of subjects with complete or partial response, defined as *50% reduction of 24 hour UFC levels from Baseline after each of the 6 months of treatment with COR 003 without a dose increase in the Maintenance Phase;

* To characterize changes in 24 hour UFC levels from Baseline during the 6 months of treatment with COR-003 in the Maintenance Phase regardless of dose increases;

* To characterize shifts in normality for 24 hour UFC levels from Baseline during the 6 months of treatment with COR-003 in the Maintenance Phase

regardless of dose increases;

* To characterize changes in serum and late night salivary cortisol

concentrations during the 6 months of treatment with COR-003 in the Maintenance

Phase;

* To assess the effects on Clinical Signs and Symptoms of CS, the quality of

life (QoL) measures obtained from the Cushing QoL questionnaire and the

severity of depression obtained from the Beck*s Depression Inventory II in the

Maintenance Phase;

* To evaluate changes in the biomarkers of CS comorbidities (diabetes,

hypertension, hypercholesterolemia and obesity) in the Maintenance Phase;

* To assess the safety and tolerability of COR-003.

Study description

Background summary

Endogenous Cushing*s syndrome and Cushing's disease (CS) is a rare but serious and potentially lethal endocrine disease caused by inappropriately excessive cortisol exposure to human organs. Treatment options include surgery, radiation therapy and drug treatment. Medical treatment is used to suppress excessive cortisol production or activity and ameliorate its clinical manifestations prior to surgery or in subjects awaiting the effects of radiation therapy as well as in subjects where surgery is contra-indicated or a tumor cannot be found. As such, normalization of 24-hour urinary free cortisol secretion (UFC) or a low-dose overnight dexamethasone suppression test (DST) are considered adequate markers of disease remission.

Racemic ketoconazole (Nizoral®, the mixture of the two enantiomers 2S,4R and 2R,4S) is an approved antifungal agent that, at higher dosages, reduces adrenal steroid production via inhibition of multiple steroidogenic enzymes, e.g. 11*-hydroxylase, 17*-hydroxylase and aldosterone synthase. When subjects are treated with ketoconazole, adrenal insufficiency is avoided by adjusting the dose to allow normal cortisol levels.

Cortendo AB is developing COR-003, the single 2S,4R enantiomer of ketoconazole, as an investigational new drug for the treatment of cortisol hypersecretion in CS. COR-003 is isolated from racemic ketoconazole.

Study objective

This study will be a single arm, open-label, dose titration study to assess efficacy, safety, tolerability and PK of COR-003 in subjects with CS with each subject serving as his/her own control.

Study design

The dose-response relationship for COR-003 in this CS population will be established. Following an initial screening and wash-out period, as applicable, this study will be conducted in 3 treatment phases as follows:
* Dose Titration Phase: approximately 2 to 21 weeks to achieve an effective and tolerable maximum dose (the Therapeutic Dose);
* Maintenance Phase: 6 months of treatment at the Therapeutic Dose following the Dose Titration Phase;
* Extended Evaluation Phase: 6 months of continued treatment after the Maintenance Phase; dose adjustments will be allowed as required

After signing the informed consent, subjects will enter the Screening Phase. After the initial assessments, subjects on previous CS medical therapies must enter a washout period before completing all Screening assessments. Baseline measurements will be obtained as part of the Screening assessments.
After confirmation of eligibility at the Baseline Visit, subjects will enter into the Dose titration Phase. Dose titration will occur in increments of 150 mg with a starting dose of 150 mg twice daily (BID) over a period of approximately 2 to 21 weeks to achieve an effective and tolerable maximum dose (the Therapeutic Dose). Decisions for dose increases will be based on each subject*s tolerability, assessment of UFC levels and safety data.
Subjects that reach total daily doses of > 600 mg/day will be monitored more closely and will be asked to return after 4-7 days for additional safety evaluations. Subjects will be advised to contact the Investigator immediately in the event of developing symptom-specific AEs, such as adrenal insufficiency or other AEs at any time.
Once the Therapeutic Dose has been reached and confirmed from the mean of a total of four adequately collected 24 hour urine collections for UFC measurements, subjects will enter into the Maintenance Phase of the study and will be asked to return to the clinic monthly for 6 months for assessment of efficacy and safety. During the Maintenance Phase, doses may not be increased to maintain UFC levels at or below ULN of the assay unless it is confirmed that a dose increase is deemed medically necessary at the discretion of the Investigator. Prior to the End of Maintenance Phase Visit four complete 24-hour urine collections will be obtained and subjects may enter the Extended

Evaluation Phase.

In order to exclude that a treatment effect is due to delayed onset of radiation therapy, previously irradiated subjects must stop treatment with COR-003 for *2 weeks after the end of the 6 month Maintenance Phase (End of Maintenance Phase Visit) and provide four complete 24-hour urine collections for UFC measurements. They may subsequently restart therapy and continue into the 6 month Extended Evaluation phase if UFC is elevated, at the discretion of the Investigator.
In the 6-month Extended Evaluation Phase, subjects will return to the clinical site every three months for safety and efficacy evaluations.
Throughout the study, safety data will be collected at specified times. Adequate medical coverage will be provided at all times during the course of the study to ensure that prompt safety decisions can be made and appropriate medical interventions are provided. The Investigator will provide subjects with instructions on how to access the medical staff regardless of day and time in order to obtain medical care. An independent Data Safety Monitoring Board (DSMB) will review the safety of the drug throughout the study
At the completion of the 6-month Extended Evaluation Phase, subjects will be promptly referred back to their endocrinologist (if not the Investigator) for further management according to the local standard of care, and based on their preceding medical history.

Intervention

After titration to a tolerable effective and/or maximum dose (the therapeutic dose), subjects will enter into the maintenance phase of the study and be treated with COR 003 at the therapeutic dose for 6 months. The maintenance phase will be followed by an extended evaluation phase of 6 months continued treatment. Primary efficacy will be assessed by measuring UFC concentrations. Secondary endpoints being evaluated include (but are not limited to) changes in blood pressure, fasting blood glucose/HgA1C, triglyceride concentrations, and the physical manifestations of CS and CD. A QoL and a BDI-II questionnaire specific to CS will also be evaluated. ECGS and blood samples for the PK determination will be collected throughout the study.

Study burden and risks

Participation in this study can last up to 2 to 21 weeks of screening, plus 12 months of therapy and 1 month after Follow Up. During the trial the patients perform approximately 15 visits to the hospital. During these visits the vital signs will be measured and blood will be collected, no more than approximately 680mL in total. A questionnaire Quality of Life and BDI-II Questionnaire will be completed.
24 hour fine collection and saliva collection the day before the actual visit to the site.

Dietary restrictions are given:
It is not allowed to eat anything with grapefruit or blood oranges throughout the study.
* During at-home urine collections, it is not allowed to do the following:
o Drink more than 4 litres of fluids in each day
o Use of medicines or products with glucocorticoids, such as haemorrhoid or skin creams that contain steroids

* On the days for saliva samples, it is not allowed to do the following:
o Eat genuine liquorice
o Smoke cigarettes
o Chew tobacco

The study medication will cause some side effects.
The more frequently seen side effects so far with COR-003 have been:
* Mild to moderate headache and nausea
* Diarrhea in subjects with type 2 diabetes

The following side effects may occur:
* Moderate changes to the liver. Severe effects on the liver are rare.
* Changes to heart electrical patterns
* Extremely low cortisol levels, also called adrenal insufficiency
* Allergic reactions
* Interactions with other drugs are taking
There may be other side effects that are not yet known.

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

Subjects will be eligible for the study if all of the following criteria are met:
1. Male or female *18 years of age
2. Able to provide written informed consent prior to any study procedures being performed; eligible subjects must be able to understand the informed consent form prior to inclusion into the study.
3. Confirmed diagnosis of newly diagnosed, persistent or recurrent Cushing*s disease (CD) or endogenous CS of other etiology if subjects are not candidates for surgery or radiotherapy within the 18 months after enrollment.
Previous medical records will be collected and used to support the diagnosis of CD or endogenous CS of other etiology, including the following etiologies:
- Ectopic adrenocorticotropic hormone (ACTH) secretion, i.e. ACTH not of pituitary origin
- Ectopic corticotropin-releasing hormone (CRH) secretion
- Adrenal-dependent CS (i.e. adrenal adenoma (NOT carcinoma), adrenal hyperplasia, etc.)
- Etiology unknown.
In the absence of pathological or post-surgical confirmation of the diagnosis of CD (i.e. documented adrenal insufficiency post-adenomectomy or hypophysectomy, which will be considered diagnostic). The following historical evidence will be considered satisfactory to establish the diagnosis of CD:
Plasma corticotropin (ACTH) level >20 pg/mL (4.5 pmol/L) or greater (Note: ACTH *5 pg/mL (1.1 pmol/L) and *20 pg/mL will generally suffice only if accompanied by either a positive CRH stimulation test or Dexamethasone Suppression Test (DST) or combined CRH-DST) PLUS one of the diagnostic strategies described below based on pituitary magnetic resonance imaging (MRI)/computed tomography (CT) findings (Note: pituitary imaging preceding the original diagnosis is a requirement for eligibility):
For tumors *6 mm by imaging:
- Inferior petrosal sinus sampled (IPSS) ACTH central:plasma gradient *2 before CRH or *3 after CRH, OR if IPSS was not done then:
- Positive ACTH and/or cortisol response to CRH/desmopressin or combined CRH-desmopressin stimulation plus high-dose (8 mg) dexamethasone suppression of plasma

cortisol, ideally on more than one occasion, performed and interpreted according to internationally recognized standards of diagnosis
- In the absence of IPSS and the combination of tests described, an individual might be eligible if CD was otherwise confirmed via adequate testing. Such cases must be discussed with and explicitly approved by the Medical Monitor, and the specific diagnostic criteria used to establish the diagnosis of CD must be documented.
For tumors <6 mm or not visible by MRI:
- IPSS with ACTH central:plasma gradient *2 before CRH or *3 after CRH
- In the absence of IPSS, an individual might be eligible if CD was otherwise confirmed via adequate testing. Such cases must be discussed with and explicitly approved by the Medical Monitor, and the specific diagnostic criteria used to establish the diagnosis of CD must be documented.
4. Regardless of the etiology of endogenous CS, subjects MUST have elevated mean 24 hour UFC levels *1.5X ULN based on the normative range of the central lab assay and on a minimum of four measurements from adequately collected urine. Urine will ideally be collected on sequential days.
5. In addition to elevated mean UFC, presence of abnormal values from one of the following tests:
* Abnormal DST: Elevated 8 AM serum cortisol *1.8 *g/dL (50 nmol/L) after 1 mg dexamethasone orally at 11 PM the evening prior (if not conducted already in the diagnostic workup of the subject within the previous 2 months before start of Screening Phase; in that case previous test results and details of conduct will need to be available by the Baseline Visit)
* Elevated late night salivary cortisol concentrations (at least two measurements) >ULN
NOTE: For subjects with estimated glomerular filtration rate (eGFR as determined by Modified Diet in Renal Disease MDRD equation) >40 and <60 mL/min/1.73 m2 in addition to meeting the UFC criteria, late night salivary cortisol test results (*2 measurements) MUST also demonstrate evidence of CS.
6. Previously irradiated subjects with CD or endogenous CS of other etiology will be allowed as long as the radiation treatment occurred > 4 years ago and subjects have not exhibited evidence for improvement in their underlying CD for 6 months prior to the Screening visit. The total number of previously irradiated subjects enrolled in this study will not exceed 10.
7. Subjects with CD or CS of other etiology who are not candidates for surgery, refuse surgery, or in whom surgery will be delayed for at least 18 months following enrollment. Subjects may be allowed to participate in the trial while awaiting surgery, but must agree to complete this study prior to surgery. For subjects who have already undergone surgery, a minimum of 6 weeks should have elapsed before the subject can be deemed a surgical failure. Subjects who have undergone surgery should be stable post-surgery (i.e., no significant post operative sequelae remain and the risk of such sequelae is considered negligible).
8. Subjects on treatment for CD or endogenous CS of other etiology for whom treatment has been inadequate or not well tolerated must agree to the following minimum washout periods prior to the Baseline Visit:
* Ketoconazole or metyrapone: 2 weeks
* Dopamine agonists: bromocriptine (2 weeks), cabergoline (8 weeks)
* Octreotide acetate LAR, lanreotide Autogel®, pasireotide LAR: 12 weeks
* Lanreotide SR: 8 weeks

* Octreotide acetate (immediate release) or short-acting pasireotide: 1 week
* Mifepristone (RU 486, KORLYM®): 4 weeks
9. Subjects on megestrol acetate or medroxyprogesterone acetate (and selected other synthetic progestins) must agree to a washout period of at least 6 weeks prior to the Baseline Visit
10. A female is eligible to enter and participate in the study if she is of:
Non-child bearing potential (i.e. physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy and/or bilateral oophorectomy or tubal ligation.
Post-menopausal females are defined as being amenorrheic for greater than 1 year with an appropriate clinical profile, e.g. age > 45 years, in the absence of hormone replacement therapy. However, in questionable cases, a blood sample with follicle stimulating hormone (FSH) > 40MIU/ml and estradiol < 40pg/ml (<140 pmol/L) is confirmatory.
OR
Child-bearing potential and agrees to use highly effective methods of birth control while participating in the study and for 2 weeks after the study is completed.
11. Fertile men must also agree to use a medically acceptable form of birth control while on study drug and up to 2 weeks after the study is completed.
12. Able to comprehend and comply with procedures.

Exclusion criteria

Subjects will be excluded from the study if any of the following criteria are met:
1. Subjects with Pseudo-Cushing*s syndrome based on assessment of the Investigator.
2. Subjects with cyclic CS based on assessment of the Investigator
3. Subjects with a non-endogenous source of hypercortisolism such as exogenous source of glucocorticoids or therapeutic use of ACTH.
4. Known inherited syndrome as the cause of hypercortisolism, including but not limited to multiple endocrine neoplasia Type 1, McCune Albright Syndrome and Carney Complex
5. Subjects with adrenal carcinoma
6. History of malignancy, other than thyroid, early stage prostate, squamous cell and basal cell carcinoma, within 3 years prior to the Screening Phase. Subjects with history of such allowed carcinoma must have a life expectancy of >18 months and must be considered medically stable. Subjects with early stage prostate cancer undergoing no treatment due to low grade potential may be enrolled.
7. Clinical or radiological signs of compression of the optic chiasm.
8. Major surgery within 1 month prior to enrollment (informed consent form signing)
9. Subjects with clinically significant abnormality in 12-lead ECGs during the Screening Phase needing medical intervention.
10. Subjects with QTc interval of >470 msec during the Screening Phase.
11. Subjects with a history of Torsades des Pointes, or ventricular tachycardia, or ventricular fibrillation, or history of prolonged QT syndrome (including family history), or use of medications resulting in QT/QTc prolongation, or hypokalemia <3.0 meq/L.
12. Pre-existing hepatic disease; subjects with mild to moderate hepatic steatosis consistent

with fatty infiltration (non-alcoholic fatty liver disease [NAFLD] are allowed).
13. Positive for hepatitis B surface antigen (HbsAg) or positive hepatitis C test.
14. History or symptoms of recurrent symptomatic cholelithiasis or pancreatitis.
15. Liver function tests (LFT) must not be above the following cut-offs during the Screening Phase:
* Alanine transaminase (ALT) and/or aspartate transaminase (AST) >3 X ULN
* Total bilirubin (TBN) >2 X ULN
If all LFTs are within normal limits (WNL) and TBN is elevated, examination of direct and indirect bilirubin may be conducted. Subjects with isolated indirect TBN up to 3X ULN are presumed to have Gilbert*s syndrome and may be enrolled if all other LFTs are within normal levels.
16. History of documented or suspected drug-induced liver injury requiring drug discontinuation of ketoconazole or any azole antifungals.
17. Pregnant or lactating women
18. Human immunodeficiency virus (HIV)-positive.
19. History of persistent uncontrolled hypertension (>180/120 mmHg) despite medical intervention.
20. Subjects with hypercholesterolemia who are currently treated with atorvastatin, lovastatin or simvastatin and not willing or unable to change to alternative therapies, i.e. pravastatin, fluvastatin, or rosuvastatin within 2 weeks of start of the Screening Phase.
21. Body habitus preventing repeated venipuncture as required by protocol.
22. Subject is currently in another study or has received any investigational treatment (drug, biological agent or device) within 30 days or five half-lives of treatment, whichever is longer.
23. Repeated hospitalization for hyperglycemia or for any complication of hyperglycemia and diabetes during the last 12 months
24. Subjects with decreased renal function as defined by eGFR <40 mL/min/1.73 m2, using MDRD equation.
25. Any other clinically significant medical condition, as determined by the Investigator that precludes enrollment and participation in the study through completion, including conditions that would preclude the subject from being able to follow instructions or to perform the necessary procedures (for example, psychiatric instability or severe disability).
26. Abnormal free thyroxine (T4). Subjects with thyroid stimulating hormone (TSH) < lower limit of normal (LLN) and normal free T4 are permitted to participate in the study.
27. Subjects who have a history of alcohol or drug abuse in the 6-month period prior to enrollment.
28. Subjects who have been treated with mitotane within 6 months of the Screening Phase.
29. Subjects who are currently taking any H2 receptor antagonists, proton-pump inhibitors, or sucralfate (all of which inhibit absorption of COR-003). A list of orally acceptable antacids (for example, Mylanta and Maalox) will be provided, and can only be taken a minimum of 2 hours after dosing of COR-003.
30. Subjects who receive any prohibited concomitant medication and cannot discontinue it safely prior to the Baseline Visit, including but not limited to the following:
* Weight loss medications (prescription or over the counter);
* Acetaminophen (paracetamol) >3 g total daily dose;
* Strong inducers or inhibitors of CYP3A4 enzyme system that may interfere with the metabolism of COR-003 and cannot be discontinued prior to first dose;
* Herbal preparations: St John*s Wort, echinacea, gingko, goldenseal, yohimbe, red rice

yeast, danshen, silybum marianum, Asian ginseng, schissandra sphenanther, shankhapushi, and Asian herb mixture (Xiao chai hu tang and Salboku-to);
* Topical or inhaled corticosteroids;
* Carbamazepine, fenofibrate, carbenoxolone;
* Drugs that might pose unacceptable risks due to overlapping toxicities (e.g. QT prolongation, liver toxicity);
* Genuine licorice.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-12-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	2S, 4R(-)-Ketoconazole, levoketoconazole

Ethics review

Approved WMO

Date:	11-03-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	10-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-10-2015
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-10-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2018
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	EUCTR2013-002133-37-NL
ClinicalTrials.gov	NCT01838551
CCMO	NL47787.078.14