# An Open-Label Extension Study of Levoketoconazole (2S,4R-ketoconazole) in the Treatment of Endogenous Cushing*s Syndrome

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The objective of this study is to assess long-term safety and efficacy durability of levoketoconazole as chronic treatment for endogenous Cushing*s Syndrome (CS).

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

## Summary

### ID

NL-OMON49258

**Source**
ToetsingOnline

**Brief title**
OPTICS

### Condition

- Adrenal gland disorders

**Synonym**
Endogenous Cushing□s syndrome

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** Endogenous Cushing Syngdrome, Levoketoconazole, OPTICS

## Outcome measures

**Primary outcome**

When calculating changes from Baseline for efficacy evaluations, Baseline will

be either

or both of:

* Open-label extension (OLE) study Baseline;

* Exploratory efficacy endpoints:

• Proportions of subjects with mean urinary free cortisol (mUFC): 1) Less or

equal to the upper limit of normal (ULN) of the reference range; 2) Above the

ULN to 1.5X the ULN; and 3) Above 1.5X the ULN;

• Changes from Baseline in markers of cortisol including mUFC and late night

salivary cortisol (LNSC);

• Proportion of subjects with LNSC above the ULN of the reference range;

• Changes from Baseline in Clinical Signs and Symptoms of CS, health-related

quality of life (QoL), and symptoms of depression;

• Changes from Baseline in biomarkers of CS comorbidities (fasting blood

glucose [FBG], fasting insulin, homeostatic model assessment-insulin resistance

[HOMA-IR], hemoglobin A1c [HbA1c], blood pressure, total cholesterol,

high-density lipoprotein-cholesterol [HDL-C], low-density

lipoprotein-cholesterol [LDL-C], high-sensitivity C-reactive protein [hsCRP]);

• Frequency of usage and changes from Baseline in frequency of usage of anti-diabetic, anti-cholesterol and anti-hypertensive therapies;

• Compliance (adherence) and persistence with therapy per tablet counts.

Safety endpoints:

Safety will be assessed by incidence and severity of Adverse Events (AEs), Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs) as well as by physical examinations, safety laboratory panels (including adrenocorticotrophic hormone [ACTH], liver function tests [LFTs], blood chemistry, hematology), electrocardiograms (ECGs) (to include assessment of the QTc interval), vital signs and pituitary Magnetic Resonance Imaging (MRI) for subjects with a history of a pituitary tumor.

**Secondary outcome**

na

# Study description

**Background summary**

Levoketoconazole is currently being evaluated in two Phase 3 studies. Study COR-2012- 01 (also known as SONICS) is a single-arm, open-label, dose titration and maintenance study to assess efficacy, safety, tolerability, and pharmacokinetics (PK) of levoketoconazole in subjects with endogenous Cushing*s Syndrome (CS). Following initial Screening and washout periods, as applicable, SONICS comprises three treatment phases: a Dose Titration Phase to achieve an effective and tolerable maximum dose (i.e., the Therapeutic Dose) lasting approximately 2 to 21 weeks; a Maintenance Phase of 6 months treatment at the Therapeutic Dose, and an Extended Evaluation Phase of 6 months of continued treatment. Levoketoconazole is administered as 150 mg immediate release tablets for oral twice daily dosing; total daily dose is titrated in 150 mg increments from a starting dose of 300 mg up to a maximal daily dose of 1200

mg. Ninety-four (94) subjects were enrolled into the Dose Titration Phase of Study COR-2012-01 with a goal of at least 70 subjects completing the 6-month Maintenance Phase.

Study COR-2017-01 (also known as LOGICS) is a double-blind, randomized, placebocontrolled withdrawal following single-arm, open-label levoketoconazole study to assess efficacy, safety, tolerability, and PK of levoketoconazole in subjects with endogenous CS. A blinded-treatment Restoration Phase is included for subjects who do not require early rescue and tolerate the 8-week blinded, randomized-withdrawal through to
completion. Study methodology varies by cohort prior to randomization only. Approximately 35 subjects will be enrolled into the Randomized Withdrawal Phase of the study to provide at least 26 study completers (either completed all visits in the Randomized Withdrawal Phase or required early rescue).

**Study objective**

The objective of this study is to assess long-term safety and efficacy durability of levoketoconazole as chronic treatment for endogenous Cushing*s Syndrome (CS).

**Study design**

This is a long-term, OLE study of levoketoconazole in subjects with endogenous CS who have completed one or both parent studies or otherwise potentially qualify for this study, as defined in the entry criteria.
Long-term safety, tolerability, and efficacy data will be collected at intervals consistent with recognized standards of care.
Subjects will remain on the previously established Therapeutic Dose of levoketoconazole that they were last receiving prior to entry into this OLE study unless a change in dose is medically indicated. Certain subjects that were enrolled in Study COR-2017-01 when randomization was closed or subjects with a gap in treatment with levoketoconazole may require re-establishment or establishment of a Therapeutic Dose. As a result, dose titration may be required, and the Investigator will consult with the Medical Monitor to determine the starting dose of levoketoconazole. Any planned dose increase of levoketoconazole above the previously established Therapeutic Dose will require the Medical Monitor*s prior approval and will require unplanned visits or additional evaluations to investigate the etiology underlying the need for higher dose levels. If approved, dose increases will generally be made as 150 mg/day and no more frequently than once every 2 weeks, and will be accompanied by clinical examination and laboratory tests to assure and document safe use. Dose decreases may be made as needed for reasons of safety or tolerability and will be documented but do not require prior Medical Monitor approval.
The study comprises Screening and Baseline Visits followed by office visits every 3 months. Dose Adjustment/Safety Monitoring Visits will also be conducted

in the event of a need for a dose increase of levoketoconazole during the study.

### Intervention

Levoketoconazole (2S,4R-ketoconazole); 150-mg immediate release tablets for oral administration. Doses of levoketoconazole can range from a total daily dose of 150 mg up to 1200 mg. Levoketoconazole will be administered daily, approximately every 12 hours, per the individual Therapeutic Dose previously established for each eligible subject during the parent study or as subsequently modified. The minimum daily dose is 150 mg once a day for subjects who cannot tolerate 150 mg twice a day. Dose increases should not be more than 150 mg/day and should occur no more frequently than once every 2 weeks unless first approved by the Medical Monitor or the designee.

There is no predefined completion timeframe for this OLE study, and interim analyses may be performed at the Sponsor*s discretion. Subjects may continue receiving or discontinue levoketoconazole based on the medical judgement of the Investigator while the study remains open. It is anticipated that subjects* participation may continue for at least 3 years.

### Study burden and risks

Individual study subjects benefit directly via their participation. Continued access to an investigational drug that appears to be working well is desirable, particularly when the few commercially available drugs for chronic treatment of CS have been used previously without satisfactory results, the situation of many subjects enrolled in the parent studies (SONICs & LOGICs).

## Contacts

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SE

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

To be eligible for participation in this study, subjects for whom the investigator believes long-term use of levoketoconazole may be beneficial must meet ONE of the following criteria:
1. Completed the Extended Evaluation Phase of Study COR-2012-01 (i.e. M12).
2. Completed the Restoration Phase of Study COR-2017-01 (i.e. RES2).
NOTE: Subjects meeting criteria 1 or 2 above who have had a break in therapy may be eligible
only after discussion with the Medical Monitor. If eligible, such subjects may require re-establishment of the Therapeutic Dose via titration. All subjects who have had a break in therapy should be discussed with the Medical Monitor to determine the starting dose of levoketoconazole.
Prior to resuming treatment with levoketoconazole, other therapies for Cushing*s syndrome
must undergo an appropriate washout period, with minimum washout durations as follows:
* 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;
* Megestrol acetate or medroxyprogesterone acetate (and selected other synthetic progestins): 6 weeks.
3. Currently in a named patient program or other Expanded Access Program receiving
levoketoconazole.
4. Were levoketoconazole-naïve prior to entry and received early rescue therapy with open-label

levoketoconazole in Study COR-2017-01.
5. Achieved a clinically meaningful partial response (with reduction in UFC) in Study COR-2017-01 at dose level 7 or at a maximally tolerated dose of levoketoconazole but did not meet the randomization criteria for Study COR-2017-01 at the end of the Dose Titration and Maintenance Phase when randomization was open.
6. Were levoketoconazole-naïve prior to entry and were enrolled in Study COR-2017-01 in the Dose
Titration and Maintenance Phase when randomization was closed. (NOTE: Such subjects must receive at least 1 dose levoketoconazole before transitioning to this study.), In addition, subjects must meet ALL the following criteria:
1. Willing to participate and 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.
2. A female is eligible to enter and participate in the study if she is:
3. Postmenopausal, defined as age 50 years or older with amenorrhea for more than 1 year or any age with serum follicle stimulating hormone (FSH) at least 23 mIU/mL and estradiol no more
than 40 pg/mL (140 pmol/L) (NOTE: laboratory values obtained during COR-2012-01 or COR-
2017-01 protocol will be utilized).
OR
4. Surgically sterile*documented hysterectomy and/or bilateral oophorectomy or tubal ligation.
OR
5. Of child-bearing potential and agrees to use a highly effective method of birth control while
participating in the study and for 30 days after the last dose of levoketoconazole. Abstinence is
considered acceptable birth control if routinely practiced.
Cortendo AB Protocol COR-2017-OLE
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Fertile men must also agree to use a highly effective method of birth control while participating in
the study and for 90 days after the last dose of levoketoconazole. Abstinence is considered
acceptable birth control if routinely practiced.
6. Able to comprehend and comply with procedures.

## Exclusion criteria

Subjects will not be eligible for participation in the study if ANY of the following criteria are met:

1. Discontinued levoketoconazole while participating in Study COR-2012-01 or Study COR-2017-01
or a named patient program or other Expanded Access program, due to safety or tolerability
concerns or lack of efficacy.
2. Pregnant, lactating or intend to conceive while receiving levoketoconazole.
3. Have a medical condition or other circumstances that, in the opinion of the Investigator, might
interfere with the subject*s participation or pose unacceptable risk to the subject.
4. Scheduled for surgical treatment of CS or received surgical treatment of CS within the 6 weeks
prior to Screening.
5. Had non-CS major surgery within the 4 weeks prior to Screening.
6. Treated with mitotane within 6 months prior to enrollment.
7. History of malignancy, including adrenal or pituitary carcinomas (other than low-risk, welldifferentiated
carcinomas of thyroid, breast or prostate that are very unlikely to require further
treatment in the opinion of the treating physician, or squamous cell or basal cell carcinoma of the
skin).
8. QTc interval greater than 470 msec via central-reader interpretation during Screening.
9. Clinically significant abnormality in 12-lead electrocardiogram (ECG) during Screening requiring
medical intervention (may be eligible once stable, to be determined case by case).
10. Clinical or radiological signs of compression of the optic chiasm newly apparent since enrolling in
a parent study.
11. Liver safety tests during the Screening Phase as follows:
* ALT and/or AST above 3X ULN (NOTE: transaminase values up to 5X ULN may be allowed
on an exceptional basis for subjects who have exhibited stable values for at least 3 months)
* AP or TBN above 2X ULN.
o Subjects with isolated indirect TBN up to 3X ULN that are presumed to have Gilbert*s
syndrome may be enrolled if all other liver safety tests are within normal levels.
12. Decreased renal function as defined by eGFR below 40 mL/min/1.73 m2, using MDRD equation
for eGFR.
13. Serum potassium below 3.9 mEq/L (may be supplemented to achieve 3.9 mEq/L or above).
14. Abnormal free thyroxine (FT4), unless subsequently corrected and stable for

at least 4 weeks.
Subjects with thyroid stimulating hormone (TSH) less than the lower limit of normal (LLN) and
normal FT4 are potentially eligible without intervention.
15. Abused alcohol or drugs since enrolling in a parent study (in the Investigator*s opinion).
16. Currently participating in another study or has received any investigational treatment (drug,
biological agent or device) other than levoketoconazole, within prior 30 days of the Screening visit
or five half-lives of treatment, whichever is longer.
17. Current use of any H2-receptor antagonists, proton-pump inhibitors, or sucralfate (all inhibit
absorption of levoketoconazole; subjects may be allowed to enroll after washout). [NOTE: A list
of acceptable oral antacids will be provided; if used, antacids must be ingested at least 2 hours after
dosing of levoketoconazole.]
18. Current use of any prohibited concomitant medication that cannot be discontinued safely and
washed out completely prior to the Baseline Visit, including but not limited to the following (a
more complete list is included in Appendix I of the research protocol):
* Drugs used to treat Cushing*s Syndrome;
* Weight loss medications (prescription or over the counter);
* Acetaminophen (paracetamol) above 2 g total daily dose;
* Strong inducers or inhibitors of CYP3A4 enzyme system that may interfere with the
metabolism of levoketoconazole and cannot be discontinued prior to first dose;
* Herbal preparations: St John*s Wort, echinacea, gingko, goldenseal, yohimbe, red yeast rice,
danshen, Silybum marianum, Asian ginseng, Schissandra sphenanthera, shankhapushpi, and
Asian herb mixture (Xiao chai hu tang and saiboku-to);
* Topical or inhaled corticosteroids (other than low potency products to be discussed with
Medical Monitor first);
* Carbamazepine;
* Drugs that pose unacceptable risk due to overlapping or exaggerated toxicities or
pharmacological action due to presumed pharmacokinetics (PK) or pharmacodynamic (PD)
interactions with levoketoconazole.

# Study design

## Design

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

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Completed |
| Start date (anticipated): | 11-02-2020 |
| Enrollment: | 2 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Levoketoconazole |
| Generic name: | Levoketoconazole |

# Ethics review

Approved WMO

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|---|---|
| Date: | 23-11-2018 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

Approved WMO

| | |
|---|---|
| Date: | 27-02-2019 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

Approved WMO

| | |
|---|---|
| Date: | 29-08-2019 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 05-02-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 06-04-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 02-06-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 10-11-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 17-12-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 09-03-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 16-06-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam |

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|---|---|
| | (Rotterdam) |
| Approved WMO Date: | 14-07-2022 |
| 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 | EUCTR2017-004647-20-NL |
| ClinicalTrials.gov | NCT03621280 |
| CCMO | NL67355.078.18 |