A Phase III, multi-center, double-blind, randomized withdrawal study of LCI699 following a 24 week, single-arm, open-label dose titration and treatment period to evaluate the safety and efficacy of LCI699 for the treatment of patients with Cushing*s disease

Published: 21-08-2014
Last updated: 21-04-2024

To assess the efficacy and safety of LCI699 in CD patients

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON47814

Source
ToetsingOnline

Brief title
CLCI699C2301: A fase III study with LCI699 for patients with Cushing D.

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Cushing's Disease

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis

Intervention

Keyword: Cushing's Disease, LCI699

Outcome measures

Primary outcome

Proportion of patients with mUFC <= 1 ULN at week 24, and the dose of LCI699 is

not increased above the level establised at the end of period 1

Secondary outcome

Proportion of patients with mUFC <= 1 ULN at week 24, and the dose of LCI699 is

increased above the level establised at the end of period 1

Study description

Background summary

For patients with Cushing*s disease (CD), surgical removal of the pituitary adenoma is the first line therapy. Pituitary irradiation is another treatment option, for patients who are not surgical candidates or have persistent or recurrent hypercortisolism following primary pituitary surgery. However, the response to pituitary irradiation is slow and can cause long-term complication (hypopituitarism, secondary malignant tumors and possible increased risk of death from cerebrovascular disease post-radiation).

Medical therapy is an attractive option for patients with CD who have persistent of recurrent hypercortisolism after prior surgery, and for patients with de novo CD who are not candidates for pituitary surgery or refuse to undergo surgery. Pasireotide (Signifor), a second generation somatostatin analoque, is the only drug currently approved in EU for the treatment of CD. Several other drugs, like ketoconazole and metyrapone have been used off-label for the treatment of CD. The off-label use is based on limited data and not

prospectively studied in randomized multi-center trials. Bilaterale adrenalectomy is deferred until all other options have been exhausted. A consequence of bilateral adrenalectomy is immediate and permanent primary adrenal insufficiency, which requires life-long glucocorticoid and mineralocorticoid replacement therapy and monitoring.
Therefore, a safe and effective targeted medical therapy is highly desirable in this patient population. There is an unmet medical need for the treatment of CD as medical treatment options are limited. Recent trials have showed that LCI699 shows promising results in fulfilling this unmet medical need.

Study objective

To assess the efficacy and safety of LCI699 in CD patients

Study design

This is a global, multicenter, randomized , dubbel-blind fase III study.
After a screenings period of 35 days, patients who meet all eligible criteria will start with period 1 (week 1-12) this is the individual dose titration period. In period 2 (week 13-24) the efficacy and safety of LCI699 at the therapeutic dose determined in period 1 will be assessed. The patients who are considered complete responders at week 24 will be eligible for randomization. The other patients will be followed for long-term safety. In period 3 (26-34) the complete responders will enter the 8 week double-blind, placebo-controlled randomized withdrawal period. In period 4 (week 35-48) all patients will receive open-label LCI699 treatment, the dose may remain unchanged, increased, decreased or withheld, depending on the mUFC level.
At the end of the 48 week treatment periode, the patients have the choice to discontinue LCI699 or to enter the extension period. The extension period will last one year.

Intervention

Treatment with LCI699

Study burden and risks

Toxicity of LCI699
Radiation exposure, DXA scan
Frequent visits and blood sampling

An overiew of all procedures during the visits are given in appendix C of the patient information
The side effects can be found in appendix D of the patient information

it is not certain that participation in the study benefits directly, the data

can be useful for future patients.
The burden on the patients is as expected for a phase III trial

Contacts

Public
Novartis

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Scientific
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Adult patients with confirmed persistent of recurrent Cushings disease
2. Patients with history of pituary surgery must be at least 30 days post-surgery
3. Patients that received glucocorticoid replacement therapy post-operatively must have discontinued such therapy for at least one week prior screening
4. Patients with de de novo Cushing's disease can be included only if they are not considered candidates for surgery (e.g. poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical

treatment, or surgical treatment is not available)
5. Patients with a history of pituitary irradiation can be included, provided that at least 3 years have elapsed from the tie of radiation to the time of enrollementinto this study.
6. Patients are permitted to washout current drug therapy to meet these entry criteria if they have a known diagnosis of Cushing's disease.

Exclusion criteria

1. Use of other investigational drugs at time of enrollment, or within 30 days of time of enrollment
2. History hypertensitivity to LCI699 or other drugs of similar chemical classes
3. History of malignancy of any organ systems, treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
4. Patients with risk factors for QTc prolongation or Torsade de pointes, including: patients with baseline QTcF > 470 ms, personal of familiy history of long QT syndrome, or concomitant medications known to prolong the QT interval, hypokalemia, hypocalcaemia or hypomagnesemia
5. Pregnant or nursing women
6. Women with child-bearing potential, unless tehy use higly effective contraception
7. Fertile males, unless they use a condom during intercource.
8. Patients with the compression of the optic chiasm, in order to exclude patients with a tumor caushing chiasmal compression requiring surgery
9. Patients who have a known inherited syndrome as the cuase for hormone over secretion
10. Patients with Cushing's syndrome due to ectopec ATCH secretion or ATCH-independent Cushing's syndrome.
11. Patients who have undergone major surgery within 1 month prior to screening
12. Hypertensive patients with uncontrolled blood pressure defined as SBP > 180and / or DBP > 100
13. Diabetic patients with a poorly controlled diabetes as evidenced by HbA1c > 9%
14. Patients who are not biochemically euthyroid
15. Patients who have a history of: congestive heart failure (NYHA Class III or IV) unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, acute MI less than one year prior to study entry, or clinically significant impairment in cardiovascular function.
16.Patients with moderate to severe renal impairment (estimated GFR < 60 mL/min by the MDRD formula, or serum creatinine > 2.0 x ULN
17. Patients with liver disease such as cirrhosis, chronic active hepatitis, or chronic persistenthepatitis, or patients with serum ALT/ASR > 3x ULN, or serum bilirubin > 1.5 ULN.
18. Patients who have any current or prior medical condition that can interfere

with the conduct of the study or the evaluation of its results in the opinion of the investigator or the sponsor's medical monitor
19. Patients who have a history of alcohol or drug abuse in the 6 month period prior to the study treatment

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-08-2015
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NVT
Generic name:	osilodrostat

Ethics review

Approved WMO

Date:	21-08-2014
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	25-05-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2020
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	EUCTR2013-004766-34-NL
ClinicalTrials.gov	NCT02180217
CCMO	NL49292.078.14