A randomized, double-blind, multicenter, phase III study to evaluate the efficacy and safety of pasireotide LAR in patients with Cushing*s disease

Published: 09-08-2011
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To assess the efficacy and safety of two Pasireotide LAR regimens in CD patients.

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

Summary

ID

NL-OMON39251

Source
ToetsingOnline

Brief title
CSOM230G2304

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, pasireotide LAR, SOM230, somatostatin analogue

Outcome measures

Primary outcome

proportion of patients with mUFC * 1 x ULN at month 7 regardless of up

titration at Month 4

Secondary outcome

proportion of patients with mUFC * 1 x ULN at month 7 for patients who did not

up titrate dose at Month 4

Study description

Background summary

For patients with Cushing's disease (CD), surgical removal of the pituitary adenoma is the first line therapy. Irradiation of the pituitary is another treatment option but it may take many years to be effective and it is curative in only 15 to 45% of the cases.
When surgery and/or irradiation fail, or for those patients for whom such therapies are not an option, the remaining alternatives are pharmacological treatment or bilateral adrenalectomy. No drugs are currently approved for the treatment of Cushing*s disease and the ones which physicians have available for use are fraught with suboptimal results and significant side effects (and the majority are limited to inhibit steroidogenesis at the adrenals, not targeting the pituitary adenoma. Bilateral adrenalectomy is a definite cure of Cushing*s disease but results in irreversible primary adrenal insufficiency and patients need lifelong replacement therapy with glucocorticoids and mineralocotricoids and have a higher likelihood to develop Nelson*s syndrome.
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 the subcutaneously administered form of pasireotide is efficacious in CD patients. This study aims to find out if and which dose of the Long Acting Release form is efficacious in CD.

Study objective

To assess the efficacy and safety of two Pasireotide LAR regimens in CD patients.

Study design

This is a global, multi-center, randomized, double-blind, phase III study.
After a screening period, patients who meet all eligibility criteria will be randomized in a 1:1 ratio to receive one of two pasireotide LAR regimens (starting dose of either 10 mg or 30 mg i.m. administered once every 28 days for 4 months, followed by dose up-titration or continuation of the starting dose). Randomization will be stratified based on baseline mean Urinary Free Cortisol (mUFC) values to ensure a balanced distribution of baseline mUFC in the 2 treatment arms. Patients will be evaluated monthly for 12 months where mUFC will be determined over 14 days. The primary efficacy variable will be assessed at Month 7.
After Month 7, all patients will be assessed for mUFC response by the investigator and may be allowed to continue in the study up to Month 12. Investigators and pertinent study staff only will be unblinded after the patient has completed the Month 7 visit. At the end of the 12 month treatment period, patients will be evaluated for mUFC response and will either discontinue or continue on to the extension study.
Total duration of the core study will be 14 months including 1 month of screening, 12 months of treatment, and a follow-up visit. The extension study will be 12 months of treatment.

Intervention

Treatment with pasireotide LAR.

Study burden and risks

Toxicity of pasireotide LAR therapy.
Radiation exposure, DXA scan;
Frequent visits and blood sampling

An overview 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 research directly benefit, the data can be useful for future patients.
The burden on the patients is as expected for a phase III trial.

Contacts

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Novartis

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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

2. Adult patients with confirmed diagnosis of ACTH-dependant Cushing*s disease
3. Patients with de novo Cushing*s disease can be included only if they are not considered candidates for pituitary surgery (e.g. poor surgical candidates, surgically unapproachable tumors, patients who refuse to have surgical treatment)
4. Confirmation that pseudo-Cushing*s is excluded for patients with mUFC * 3 x ULN
6. Karnofsky performance status * 60 (i.e. requires occasional assistance, but is able to care for most of their personal needs)
7. For patients on medical treatment for Cushing*s disease the washout periods must be completed before screening assessments are performed
8. Patients with a known history of impaired fasting glucose or DM may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the study and adjusted as necessary.

Exclusion criteria

1. Patients who are considered candidates for surgical treatment at the time of study entry
2. Patients who have received pituitary irradiation within the last ten years prior to visit 1
3. Patients who have had any previous pasireotide treatment
4. Patients who have been treated with mitotane during the last 6 months prior to Visit 1
5. Patients with compression of the optic chiasm causing any visual field defect that requires surgical intervention
6. Diabetic patients with poor glycemic control as evidenced by HbA1c >8%
7. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTcF > 470 ms, hypokalemia, hypomagnesemia, uncontrolled hypothyroidism, family history of long QT syndrome, or concomitant medications known to prolong QT interval
8. History of HIV infection, including a positive HIV test result (Elisa and Western blot). An HIV test will not be required, however, previous medical history will be reviewed
9. Patients with Cushing*s syndrome due to ectopic ACTH secretion
10. Patients with hypercortisolism secondary to adrenal tumors or nodular (primary) bilateral adrenal hyperplasia
11. Patients who have a known inherited syndrome as the cause for hormone over secretion (i.e. Carney Complex, McCune-Albright syndrome, MEN-1)
12. Patients with a diagnosis of glucocorticoid-remedial aldosteronism (GRA)
13. Patients who are hypothyroid and have clinical symptoms of hypothyroidism despite adequate replacement therapy
14. Patients who have undergone major surgery within 1 month prior to starting the study
15. Patients with symptomatic cholelithiasis
16. Patients with abnormal coagulation (PT or PTT elevated by 30% above normal limits)
17. Patients receiving anticoagulants that affect PT or PTT
18. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, advanced heart block, history of acute MI less than one year prior to study entry or clinically significant impairment in cardiovascular function
19. Patients with history of liver disease such as cirrhosis, chronic active hepatitis B and C, or patients with ALT/AST more than 2 X ULN, serum bilirubin >1.5 X ULN
20. Patients with serum creatinine >2.0 X ULN,
21. Patients with WBC >3 X 109/L; Hgb 90% > LLN; PLT >100 X 109/L
31. Presence of Hepatitis B surface antigen (HbsAg)
32. Presence of Hepatitis C antibody (anti-HCV)
33. Known gallbladder or bile duct disease, acute or chronic pancreatitis

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-04-2012
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	pasireotide LAR

Ethics review

Approved WMO Date:	09-08-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-11-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-03-2012
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-05-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	20-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2015
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	EUCTR2009-011128-70-NL
ClinicalTrials.gov	NCT01374906
CCMO	NL37725.078.11