A multi-center, intra-patient dose escalation phase II study to evaluate the preliminary efficacy, safety and pharmacokinetics of pasireotide (SOM230) subcutaneous (s.c.) followed by pasireotide LAR in patients with dumping syndrome (CSOM230X2203)

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Primary To evaluate the treatment effect of pasireotide s.c. on plasma glucose levels during GTT at the end of s.c. dose escalation phase.Secondary: Pulse rate, hematocrit, insulin, glucagon, GLP-1 and GIP secretion during GTT at the end of s.c....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON36982

Source
ToetsingOnline

Brief title
Pasireotide in patients with dumping syndrome

Condition

- Gastrointestinal conditions NEC

Synonym
dumping syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: dumping syndrome, pasireotide, somatostatin

Outcome measures

Primary outcome

Plasma glucose levels during GTT at the end of s.c. dose escalation phase.

Secondary outcome

Pulse rate, hematocrit, insulin, glucagon, GLP-1 and GIP secretion during GTT

at the end of s.c. dose escalation , LAR and extension phase, glucose levels

during GTT at the end of LAR and extension phase, symptoms, quality of life,

safety, toxicity, PK.

Study description

Background summary

Dumping syndrome is a complication of esophageal and gastric surgeries (such as bariatric and gastric cancer surgeries) estimated to occur in 5-50% of patients. Surgery results in a reduced gastric capacity that causes rapid influx of nutrients to the small intestine This induces a cascade of pathophysiological events immediately after and up to 3 hours after a meal. The arrival of hyperosmolar and undigested contents to the duodenum causes fluid to move from the intravascular compartment to the intestinal lumen, causing a decrease in circulating fluid, tachycardia and, rarely, syncope. The fluid shift into the duodenum can also cause duodenal distention, followed by cramp-like contractions. Gastrointestinal (GI) hormones are inappropriately released as a reaction to the rapid delivery of carbohydrates to the duodenum. This causes changes in gastrointestinal motility and secretion, as well as

hemodynamic effects, such as systemic hemoconcentration and hypotension. A hyperinsulinemic response to a too rapid absorption of glucose may result in hypoglycemia. The diagnosis is confirmed by an adapted 3-hour oral glucose tolerance test (GTT) evaluating the presence of early changes (30 min) in hematocrit and pulse rate and late (120, 180 min) hypoglycemia.
This syndrome can deteriorate patients quality of life, because of the very strict diet they need to follow post-surgery. Currently there are no approved medications to treat dumping syndrome. The addition of food additives is able to slow down GI transit time but studies have shown low compliance due to poor tolerability. Medications that delay carbohydrate absorption have been used in clinical practice. Small studies showed an improvement in glucose tolerance, a decreased release of GI hormones and a reduction in the incidence of hypoglycemia. However, these improve only the late symptoms and have unpleasant side effects.
Somatostatin analogs (SSA) are not approved for use in dumping syndrome. Study results suggest that octreotide may be effective. Octreotide has been shown to delay gastric emptying. In addition, SSA exerts a strong inhibitory effect on the release of insulin and several gut-derived hormones. The suppression of insulin and secretin hormones may be particularly important in the prevention of hypoglycemia.
Pasireotide (SOM230) is a SSA which exhibits a unique binding profile with higher binding affinity to human somatostatin receptors than the current available SSAs. Pasireotide suppresses insulin secretion, with no changes in hepatic or peripheral insulin sensitivity. In addition, pasireotide significantly decreases incretin response right after glucose ingestion during the GTT until 90- 120 minutes. This suppression is expected to be stronger with pasireotide than with octreotide.
The present study was designed to evaluate the efficacy, safety and pharmacokinetics of pasireotide in patients with dumping syndrome. After a dose escalation phase with pasireotide s.c., patients will enter in the LAR phase. LAR is a long acting i.m. formulation of pasireotide.

Study objective

Primary To evaluate the treatment effect of pasireotide s.c. on plasma glucose levels during GTT at the end of s.c. dose escalation phase.
Secondary: Pulse rate, hematocrit, insulin, glucagon, GLP-1 and GIP secretion during GTT at the end of s.c. dose escalation , LAR and extension phase, glucose levels during GTT at the end of LAR and extension phase, symptoms, quality of life, safety, toxicity, PK.

Study design

Multicenter open-label, intra-patient dose-escalation phase II study.
* Screening phase.
* Dose escalation phase (3 months) with pasireotide at a starting dose of 50*g

t.i.d. s.c., increased by 50 *g t.i.d. s.c. up to 200 *g t.i.d. based on GTT results.
* LAR phase (3 months) with pasireotide LAR 10 or 20 mg once every 4 weeks, depending on the final dose in the s.c. dose escalation phase.
* LAR extension phase (6 months), all patients experiencing benefit with pasireotide LAR treatment. Dose can be up-titrated up to maximum 60 mg, based on efficacy.
In all study phases the dose can be down titrated due to safety concerns.
Approx. 43 patients.

Intervention

Treatment with pasireotide s.c. and LAR.

Study burden and risks

Risk: Adverse events of study medication.
Burden: Study duration approx. 1 year. 19 visits.
3 months t.i.d. 1 s.c. injection (1 mL), thereafter q4w i.m. injection (2 mL ???).
Every visit: physical examination, blood tests (250 mL in total).
GTT 16 times. Duration approx. 3 h, 7 blood samples.
PK blood samples (2,5 mL): 3 days with extended sampling (parallel to GTT) 7 samples in approx. 3 h (and after any dose increase during escalation phase).
During 13 visits 1 sample.
Urine testing 15 times.
ECG 14 times.
CT/MRI (in case malignancy is involved) at screening
Questionnaires quality of life (2) and dumping symptoms (1) 18 times.
Completion takes approx. 15 min per occasion.

Contacts

Public
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

1. Males or females * 18 years of age.
2. Post-gastric or esophageal bypass surgery, matching one of the criteria below:
* Bariatric surgery: > 6 months before
* Esophageal cancer surgery: disease free at study entry
* Gastric cancer surgery: stage 0 or I and must be disease free at study entry.
3. Documented diagnosis of Dumping Syndrome defined as having:
*History of/or active symptoms associated with dumping syndrome
and
* Documented history of hypoglycemia based on either: plasma glucose < 2.8 mmol/L or a plasma glucose value < 3.3 mmol/L at 120, 150 or 180 min during an GTT.
4. * 1 glucose level < 3.3 mmol/L at 120, 150 or 180 min during the GTT at screening.
5. Patients with esophageal cancer must have a negative CT or MRI scan (neck, thoracic, and upper abdominal) and albumin * 3.5g/dL at baseline.
6. Patients with gastric cancer must have a negative CT or MRI scan (total abdomen).
7. Karnofsky Performance Status * 60.
8. Patients on other therapies for dumping syndrome must have stopped all treatments and allow a wash out period (see protocol page 31, section 5.2 for details).

Exclusion criteria

1. Bariatric patients who have lap band.
2. Diabetes Mellitus.
3. Prior failure on treatment with somatostatin analogues for dumping syndrome
4. Prior treatment with somatostatin analogues (appropriate wash-out period required see protocol for details

5. Hypersensitivity to somatostatin analogues.
6. Patients receiving anti-cancer therapy (chemotherapy and/or radiotherapy)
7. Patients who have any severe and/or uncontrolled medical conditions or other conditions (e.g. acute or chronic infection, history of immunodeficiency, including a positive HIV test result, life-threatening autoimmune and ischemic disorders)
8. Inadequate end organ function and
9. Inadequate bone marrow function:
10. History of liver disease, such as cirrhosis or chronic active hepatitis B and C, presence of HbsAg and/ or presence of anti-HCV
11. History of, or current alcohol and/or drug misuse/abuse within the past 12 months
12. Patients with symptomatic cholelithiasis
13. Patients with abnormal coagulation and/or patients on continuous anticoagulation therapy.
14. Patients who are hypothyroid and not on adequate replacement therapy
15. Major surgery within 1 month.
16. History of a primary malignancy (or *another* primary malignancy for patients with gastric or esophageal cancer) within the last 1 year. For exceptions see protocol page 32.
17. QTcF at screening > 470 msec, history of syncope or family history of idiopathic sudden death, clinically significant cardiac arrhythmias, risk factors for Torsades de Pointes such as hypokalemia, hypomagnesemia, cardiac failure, clinically significant/symptomatic bradycardia, high-grade AV block, concomitant disease(s) that could prolong QT, family history of long QT syndrome and concomitant medications known to prolong the QT interval,
18. Significant acute illness within the two weeks prior to dosing.

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):	15-01-2013
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Signifor
Generic name:	pasireotide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-07-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-11-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-04-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2013
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-11-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
Other	clinicaltrials.gov; registratienummer n.n.b.
EudraCT	EUCTR2012-001534-34-NL
CCMO	NL41005.042.12