A multicenter, randomized, blinded efficacy and safety study of pasireotide LAR vs octreotide LAR in patients with metastatic carcinoid tumors whose disease-related symptoms are inadequately controlled by somatostatin analogues.

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To compare the long term efficacy of pasireotide LAR vs. octreotide LAR at month 6 in controlling diarrhea and/or flushing in patients with metastatic carcinoid tumors whose disease-related symptoms are inadequately controlled by the maximum...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Neoplastic and ectopic endocrinopathies
Study type	Interventional

Summary

ID

NL-OMON35353

Source
ToetsingOnline

Brief title
Pasireotide LAR vs. Octreotide LAR in Metastatic Carcinoid

Condition

- Neoplastic and ectopic endocrinopathies

Synonym
carcinoid

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Metastatic carcinoid, Pasireotide LAR, SOM230

Outcome measures

Primary outcome

The primary efficacy variable is the proportion of patients who receive clinical benefit in symptom (diarrhea and/or flushing) improvement as defined by the following subgroup specific criteria:

- Patients who over a 14 day period at baseline has diarrhea + flushing with a daily mean number of *4 bowel movements and a total number of 5 or more flushing episodes for which the clinical benefit response criteria in 28 days period at month 6 is < 4 daily mean bowel movements AND * 20% reduction from baseline in the daily mean number of bowel movements AND any reduction in total number of flushing episodes compared to baseline

- Patients who over a 14 day period at baseline has predominantly diarrhea with a daily mean number of *4 bowel movements and a total number of < 5 flushing episodes for which the clinical benefit response criteria in 28 days period at month 6 is < 4 daily mean bowel movements AND * 20% reduction from baseline in the daily mean number of bowel movements

- Patients who over a 14 day period at baseline has predominantly flushing with a total number of *14 flushing episode and a mean daily number of <4 bowel movements for which the clinical benefit response criteria in 28 days period at month 6 is * 30% reduction from baseline in the total number of flushing episodes

Secondary outcome

Secondary efficacy variables include: objective tumor response rate (CR or PR), disease control rate (CR, PR or SD) at month 6 based on RECIST criteria, mean change from baseline in bowel movements alone at month 6, change from baseline in total flushing episodes alone at month 6, proportion of patients who achieved at least a 30% reduction in frequency of bowel movements at month 6, time to symptom response, duration of symptom response, time to symptom progression, and change from baseline in QoL scores at month 6.

Study description

Background summary

Somatostatin analogues are considered standard therapy for the treatment of the disease-related symptoms of carcinoid disease. Octreotide and lanreotide are the only two representatives of this class of compounds approved for clinical use. These agents are known to exert their activity primarily via binding to receptor sst2. These peptides have been shown to be effective in reducing symptoms associated with metastatic carcinoid tumors (known as carcinoid syndrome), specifically diarrhea and flushing.
Somatostatin analogues provide symptomatic improvement in approximately 58% to 76% of carcinoid patients. Although many patients initially respond to treatment with these agents, adequate control cannot be achieved in approximately 50% of patients as early as 12 to 18 months after initiation of therapy.
There is evidence that many tumor cells become resistant to these agents by either down-regulation of sst2 or over

expression of other sst receptors. Pasireotide may have a beneficial effect in patients who have become resistant to these agents via its enhanced binding to other receptor subtypes. Due to the enhanced binding of pasireotide to other receptor subtypes, pasireotide is predicted to have a beneficial effect in patients who have become resistant to these agents. Data from the ongoing Phase II study in patients with metastatic carcinoid tumors further suggests that pasireotide is active in patients refractory/resistant to Sandostatin LAR.
In addition, the requirement for both diarrhea AND flushing does not accurately reflect the known epidemiology of Carcinoid syndrome in that relative few patients actually have both diarrhea and flushing. Patients generally have a predominance of either diarrhea OR flushing but not both. Therefore, the symptom criteria, coupled with the somatostatin analogue dose criteria, actually defined an uncommon patient population that was somewhat counter to the natural presentation of the disease and current treatment practices. Therefore, the inclusion criteria in this study defines 3 subgroups of patients: diarrhea and flushing; predominantly diarrhea and predominantly flushing.
A reduction in the frequency of bowel movements and/or bouts of flushing is deemed clinically meaningful as either symptom alone interferes with daily activities and impacts the quality of life.

The purpose of this randomized, multicenter, Phase III study is to compare the efficacy of pasireotide LAR and octreotide LAR in patients whose disease-related symptoms are inadequately controlled by currently available somatostatin analogues.

Study objective

To compare the long term efficacy of pasireotide LAR vs. octreotide LAR at month 6 in controlling diarrhea and/or flushing in patients with metastatic carcinoid tumors whose disease-related symptoms are inadequately controlled by the maximum approved dose of a somatostatin analogues.

Study design

This is a phase III, multicenter, randomized, blinded, efficacy and safety study of pasireotide
LAR vs. octreotide LAR in patients with metastatic carcinoid tumors whose disease-related symptoms are inadequately controlled on a maximum approved dose of a currently available somatostatin analogue. Patients will be randomized 1:1 and stratified according to disease location (midgut vs. other).
The study will have a screening, blinded treatment phase, follow-up and a treatment extension phase.
The treatment and evaluation period for this study is 6 months, patients will be considered to have completed the study after the 6 month evaluation has been performed. Treatment may be terminated prior to 6 months if symptom control is

not maintained, unacceptable toxicity occurs, or the patient decides to discontinue study participation.
Patients who are receiving clinical benefit from pasireotide LAR and who are not experiencing unacceptable toxicity are permitted to continue treatment after the 6 month treatment period.
Patients who were randomized to octreotide LAR and who are not receiving clinical benefit from this treatment may be offered the option to receive pasireotide LAR treatment.

Intervention

Study drug: pasireotide LAR (long-acting release) i.m. 60mg depot injection every 28 days and pasireotide s.c. as rescue medication.
Active control: octreotide LAR i.m., 40mg depot injection every 28 days and octreotide s.c. as rescue medication.

Study burden and risks

Toxicity of pasireotide LAR or octreotide LAR. Site of the injections may cause local pain and some discomfort (swelling, redness)
Radiation exposure of CT-scans.
Obtaining blood samples may cause some discomfort, bruising, bleeding from the site of sampling, formation of a blood clot, and, in rare cases, infection.

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

1. Patients with histopathologically confirmed metastatic carcinoid tumors of the digestive system 2. Patients must have inadequate control of symptoms (i.e. diarrhea and/or flushing) while receiving treatment with the maximum approved dose of a currently available somatostatin analogue for at least a 3 months prior to study entry. Inadequate control is defined by the following groups:
- Diarrhea and Flushing group (D+F): patients with a daily mean of * 4 bowel movements and a total of * 5 flushing episodes over a two-week period (14 days) while receiving treatment with the maximum approved dose of a currently available somatostatin analogue for at least a 3 month period prior to study entry (as specified in Table 4-1 in protocol).
- Predominantly Diarrhea group (D): patients with a daily mean of * 4 bowel movements and a total number of < 5 flushing episodes over a two-week period (14 days) while receiving treatment with the maximum approved dose of a currently available somatostatin analogue for at least a 3 month period prior to study entry (as specified in Table 4-1in protocol).
- Predominantly Flushing group (F): patients with * 14 flushing episodes and a daily mean of < 4 bowel movements over a two-week period (14 days) while receiving treatment with the maximum approved dose of a currently available somatostatin analogue for at least a 3 month period prior to study entry (as specified in Table 4-1 in protocol).
3. Patients must observe the following intervals between the last injection of their previous treatment and the first injection of study drug:
* octreotide LAR <= 28 days
* octreotide s.c <= 8 hours
* lanreotide Autogel <= 28 days
* lanreotide SR <= 14 days
4. Measurable or evaluable disease per RECIST
5. Karnofsky Performance status * 60%
6. Patients with a known history of impaired fasting glucose or diabetes mellitus may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the study.
7. Baseline lab values for adequate organ function:
* Absolute neutrophil count *1.5 × 10^9/L
* Hemoglobin *9 g/dL
* Platelets *100 × 10^9/L

* Hepatic: Serum bilirubin * upper limit of normal (ULN), Aspartate aminotransferase and alanine aminotransferase, *3 × ULN without liver metastases, *5 × ULN if documented liver metastases.
* Renal: Serum creatinine *1.5 mg/dL, calculated creatinine clearance *40 mL/min

Exclusion criteria

1. Patients who have received a somatostatin analogue higher than the maximum approved dose within 3 months of Visit 1. (This exclusion criteria is not applicable to patients who are receiving short acting formulation.)
2. Patients receiving radiolabeled somatostatin analogue therapy within the 3 months or any cytotoxic chemotherapy or interferon therapy within the 4 weeks prior to recording baseline symptoms.
3. Major surgery/surgical therapy for any cause within 1 month or surgical therapy of loco-regional metastases within the last 3 months before recording baseline symptoms
4. Hepatic artery embolization, chemoembolization or radioembolization (yttrium 90 microspheres) within the last 6 months (1 month if there are other sites of measurable disease), or patients who have undergone cryoablation or radiofrequency ablation of hepatic metastasis within the last 2 months before recording baseline symptoms
5. Radiotherapy for any reason within the last 4 weeks (side effects must have been recovered before recording baseline symptoms).
6. Patients who are unwilling to follow dietary restrictions within 3 days of urinary 5-HIAA sample collection or require medications that would interfere with urinary 5-HIAA measurement
7. Patients with known malabsorption syndrome, short bowel or chologenic diarrhea not controlled
8. Patients who are not biochemically euthyroid
9. Diabetic patients on antidiabetic medications with a HbA1C > 8% (fasting)
10. Patients with symptomatic cholelithiasis
11. Any of the following cardiac abnormalities:
* QTcF at screening > 450 msec
* History of syncope or family history of idiopathic sudden death
* Sustained or clinically significant cardiac arrhythmias
* Risk factors for Torsades de Pointes such as hypokalemia, hypomagnesemia, cardiac failure, clinically significant/symptomatic bradycardia, or high-grade AV block
*Concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes, or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure
* Concomitant medication(s) known to increase the QT interval
12. Additional active malignant disease within the last five years (with the exception of basal cell carcinoma or carcinoma in situ of the cervix)
13. The presence of active or suspected acute or chronic uncontrolled infection or with a history of immunocompromise, including a positive HIV test result. A HIV test will not be required.
14. Patients with abnormal coagulation (PT or APTT 30% above normal limits)

15. Female patients who are pregnant or lactating, or are of childbearing potential and not practicing a medically acceptable method of birth control. Male patients who are sexually active are required to use condoms during the study and for three months afterwards. Female partners of these male patients must use a secondary barrier contraception.

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:	Will not start
Start date (anticipated):	30-03-2009
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	pasireotide
Product type:	Medicine
Brand name:	Sandostatin
Generic name:	octreotide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-03-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-08-2009
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-08-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-08-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-02-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-04-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-06-2012

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
EudraCT	EUCTR2007-000739-25-NL
ClinicalTrials.gov	NCT00690430
CCMO	NL26265.042.09