A Phase 3, Randomized, Placebo-controlled, Parallel-group, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Not Adequately Controlled by Somatostatin Analog (SSA) Therapy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON41315

Source
ToetsingOnline

Brief title
LX1606.1-301-CS TELESTAR

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Carcinoid tumor; Carcinoid Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Lexicon Pharmaceuticals Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: LX1606.301, Phase 3, TELESTAR, Telotristat etiprate

Outcome measures

Primary outcome

The primary objective of the study is to confirm that at least 1 or more doses of telotristat etiprate compared to placebo is effective in reducing the change from baseline in the number of daily BMs averaged over the 12-week double-blind portion of the trial (Treatment Period) in patients with carcinoid syndrome not adequately controlled to current SSA therapy.

Secondary outcome

The secondary objectives of this study are:

To assess the effects of telotristat etiprate versus placebo over the 12-week double-blind portion of the study in patients who are not adequately controlled to current SSA therapy as determined by:

* Change from baseline in stool consistency averaged across all time points

* Change from baseline in the number of cutaneous flushing episodes

* Change from baseline in abdominal pain averaged across all time points

* Durability, defined as the proportion of responders with >=30% reduction in daily number of BMs for >=50% of time over the double-blind portion of the study

* Change in the frequency of rescue short-acting SSA used to treat

bowel-related CS symptoms

Study description

Background summary

Currently, no approved therapy exists for the treatment of symptoms driven by underlying serotonin pathophysiology of CS in patients whose disease is not adequately controlled to SSA therapy. In the placebo-controlled study, the 250 and 500 mg tid dose levels showed clinical improvement in BM frequency over the 4 weeks. Clinical improvement in BM frequency was sustained to at least 12 weeks in the open-label LX1606.203 study. In utilizing a placebo group receiving standard of care as a concurrent comparator arm, evaluation of telotristat etiprate, as an add-on therapy to SSAs for up to 12 weeks, may be performed without placing the patient at undue risk. (See Protocol LX1606.301 section 3.4 Rationale for Study Design and Control Groups)

Study objective

The primary objective of the study is to confirm that at least 1 or more doses of telotristat etiprate compared to placebo is effective in reducing the change from baseline in the number of daily bowel movements (BMs) averaged over the 12-week double-blind portion (Treatment Period) of the trial in patients with carcinoid syndrome not adequately controlled to current SSA therapy

Study design

The study will be conducted as a Phase 3, randomized, placebo controlled, parallel-group, multicenter, double-blind study in patients with CS not adequately controlled to SSA therapy to evaluate 2 oral dose levels of telotristat etiprate, 250 and 500 mg 3 times daily (tid), versus placebo. Patients will enter into a Screening/Run-in Period of at least 3 weeks to establish baseline symptoms. During the Run-in Period, patients will continue to receive stable-dose SSA therapy in order to establish baseline characteristics and symptomatology. For the purposes of this study, stable-dose SSA therapy is defined as long acting release (LAR) or Depot SSA therapy or a continuous subcutaneous infusion via a pump at the same dose level and frequency for at least 3 months prior to the Run-in Period. In addition, therapy with rescue, short-acting SSA will be permitted. Only those who complete the Screening/Run-in Period and are 75% compliant with diary entries will be considered eligible for the Treatment Period of the study.

Following the Screening/Run-in Period, patients will be randomly assigned (1:1:1) on Day 1 to receive 1 of 2 dose levels of telotristat etiprate (250 or

500 mg) or placebo given 3 times daily (tid). A blinded titration period will occur during the first 7 days. During the titration period, all patients will be administered 2 tablets tid; given as 1 x 250 mg tablet plus 1 placebo tablet or 2 placebo tablets. After 7 days, patients will receive their assigned dose levels for 11 weeks. All patients must remain on their baseline dose of SSA therapy during the Treatment Period.

Added comments based on METc MMC questions (20FEB2013)
• ABR question K2 English summary Study design Placebo: There will be 2 different doses of the study drug -250 mg and 500 mg. Each of these will be administered 3 times a day. In order to keep the blinding the placebo will also be administered 3 times a day. In this way all subjects will actually take 2 tablets 3 times a day.

• ABR question K2 English summary Study design Dosage: The dose groups in the previous phase 2 studies were 150, 250, 350, and 500 mg given three times daily. Lexicon has chosen 2 of these dose groups to further evaluate.

Added comments based on METc MMC questions (08MAY2013)
Overall, while the Sponsor believes that the 500 mg TID dose will prove to have superior efficacy, the Sponsor wishes to emerge from this Phase 3 study with confidence that dose response has been explored, and that a potentially useful dose (250 mg TID) has been fully assessed.

Based on the Sponsor's assessment of the evidence thus on dose response, the 500 mg TID dose is most likely to be optimal. The best evidence for the optimal dose is found in the LX1606.203 study. The progression of most patients to the top dose of TE (500 mg TID) in this study suggests that this dose is the most effective of any of the tested doses in reducing symptoms, and also that the TE was well tolerated throughout. Starting from smaller doses, patients progressed, per the study design, successively to the next dose, if they had not yet achieved clinically relevant improvement in symptoms at that dose, and if they had not experienced a dose-limiting toxicity. Of the 14 patients who completed the 12-week treatment period. 12 (86%) progressed to the 500 mg TID dose. With increasing doses during the 8 weeks of the dose-escalation period, the mean number of BMs per day improved successively, and improvements were then maintained for the remaining four weeks of the treatment period, during which doses remained stable. No dose-limited toxicity was reported, and no patient was discontinued due to an adverse event. Most patients continued on to the extension phase, which is still ongoing.

An additional arm was added to the LX1606.301 trial in order to gain additional information on dose response in a larger trial. The specific 250 mg TID dose was chosen for several reasons. First, in both Phase 2 studies, this dose showed a clear clinical response in reducing stool frequency and in reducing urinary 5-HIAA levels. Second, since 250 mg is half the 500 mg dose, there is natural convenience in titration between the two doses. Further, the

availability of the 250 mg dosage form will make it possible to titrate to the 500 mg TID gradually, as is recommended to reduce nausea.

Intervention

Three arms are used and there will be 2 different doses of Telotristat etiprate and an placebo
- arm 1: 2 tablets with 250 mg Telotristat etiprate will be administered 3 times a day
- arm 2: 2 tablets with 500 mg Telotristat etiprate will be administered 3 times a day
- arm 3: 2 tablets of Placebo will be administered 3 times a day

In this way all patients will actually take 2 tablets 3 times a day.

Study burden and risks

Taking part in this study may or may not make your health better. Study doctors hope LX1606 will be helpful in treating carcinoid syndrome compared to the standard treatment; there is no proof of this yet. We do know that the information from this study will help study doctors learn more about LX1606 as a treatment for carcinoid syndrome. This information could help future carcinoid syndrome patients.

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 >=18 years of age at the time of the Screening visit;2.Histopathologically-confirmed, well-differentiated metastatic NET with extent documented by computed tomography (CT), magnetic resonance imaging (MRI), or radionuclide imaging;3.A documented history of CS, and currently experiencing an average of >=4 bowel movements per day during the Run-in Period. Confirmation of eligibility will be determined by measuring the mean number of bowel movements;4.Currently receiving a stable-dose SSA therapy. For the purposes of this study, stable-dose SSA therapy is defined as long acting release (LAR) or Depot SSA therapy or a continuous subcutaneous infusion via a pump. Patients must have been receiving the same dose level and frequency for at least 3 months prior to entering the Run-in Period.;5.Minimum dose of LAR or Depot SSA therapy (higher dose or more frequent intervals will fulfill the minimum dose requirement). SSA therapy must be approved for use in CS in the patient*s country of residence or prescribers* country of practice.
a.Octreotide LAR at 30 mg every 4 weeks
b.Lanreotide Depot at 120 mg every 4 weeks
c.Patients who cannot tolerate SSA therapy at a level indicated above will be allowed to enter at their highest tolerated dose;6.Patients of childbearing potential must agree to use an adequate method of contraception (defined as having a failure rate of < 1% per year) during the study and for 12 weeks after the Follow-up visit. Adequate methods of contraception for patients or partner include condoms with spermicide gel, diaphragm with spermicide gel, coil (intrauterine device), surgical sterilization, vasectomy, oral contraceptive pill, depot progesterone injections, progesterone implant, and abstinence during the study and for 12 weeks after the Follow-up Visit.;a. Childbearing potential is defined as those who have not undergone surgical sterilization, or those who are not considered postmenopausal. Postmenopause is defined as absence of menstruation for at least 2 years. If necessary, follicle-stimulating hormone (FSH) results >50 IU/L
at Screening are confirmatory in the absence of a clear postmenopausal history.;7.Ability and willingness to provide written informed consent prior to participation in any study-related procedure

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participating in the study: ;1.Presence of diarrhea attributed to any condition(s) other than CS(including, but not limited to fat malabsorption or bile acid malabsorption) ;2.Presence of more than 12 watery bowel movements per day associated with volume contraction, dehydration, or hypotension compatible with a *pancreatic cholera*-type clinical syndrome, as judged by the Investigator;3.Positive stool examination for enteric pathogens, pathogenic ova or parasites, or Clostridium difficile at Screening;4.Karnofsky Performance Status <=60% ;5.Clinical laboratory values for hematology (at Screening):;a.Absolute neutrophil count (ANC) <=1500 cells/mm3; or
b.Platelets <=750,000 cells/mm3; or
c.Hemoglobin (Hgb) <=9 g/dL for males and <=8 g/dL for females;6.Hepatic laboratory values (at Screening) such that:;a.Aspartate transaminase (AST), or alanine aminotransferase (ALT):
•>=5.5 x upper limit of normal (ULN) if patient has documented history of hepatic metastases; or
•>=2.5 x ULN if patient does not have documented history of hepatic metastases
b.Total bilirubin >1.5 x ULN (unless patient has a documented history of Gilbert*s Syndrome); or
c.Alkaline phosphatase (ALP) >=5 x ULN, if total bilirubin is >ULN
•No upper limit on the ALP value if the total bilirubin is <=ULN;7.Serum creatinine >=1.5 x ULN;8.Treatment with any tumor directed therapy including, but not limited to: interferon, chemotherapy, mTOR inhibitors <=4 weeks prior to Screening; or hepatic embolization, radiotherapy, radiolabelled SSA, and/or tumor debulking <=12 weeks prior to Screening;9.Major surgery defined as procedures requiring general anesthesia or major regional anesthesia within 8 weeks prior to Screening;10.A history of short bowel syndrome (SBS);(See Protocol LX1606.301 section Exclusion Criteria)
Clinically significant cardiac arrhytmia, bradycardia or tachycardia that would compromise patient safety or the outcome of the study.

Study design

Design

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

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-02-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Telotristat etiprate
Generic name:	Telotristat etiprate

Ethics review

Approved WMO Date:	07-01-2013
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	04-09-2013
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	20-11-2013
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	18-03-2014
Application type:	Amendment

Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	21-10-2014
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	29-01-2015
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	21-04-2015
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

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	EUCTR2012-003460-47-NL
ClinicalTrials.gov	NCT01677910
CCMO	NL43019.015.12