Efficacy, safety, and tolerability of oral cebranopadol versus morphine sulfate PR in subjects with chronic moderate to severe pain related to cancer.

Published: 04-07-2013
Last updated: 24-04-2024

The primary objective is to evaluate the efficacy of orally administered cebranopadol in comparison with morphine sulfate PR in subjects suffering from chronic moderate to severe pain related to cancer.The secondary objective is to compare the...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON41472

Source
ToetsingOnline

Brief title
CORAL study

Condition

- Other condition

Synonym
pain related to cancer

Health condition

Pijn bij kanker

Research involving

Human

Sponsors and support

Primary sponsor: Grunenthal
Source(s) of monetary or material Support: Gruenenthal GmbH

Intervention

Keyword: cancer, pain

Outcome measures

Primary outcome

The primary endpoint is the average amount of daily rescue medication intake

over the last 2 weeks of the Maintenance Phase.

Secondary outcome

The secondary efficacy endpoint is the proportion of subjects with clinically

relevant pain reduction over the last 2 weeks of the Maintenance Phase.

Definition of clinically relevant pain reduction:

* Average pain intensity of <4 points on the 11-point NRS

Or

* Reduction in average pain intensity by *30% (compared to the baseline

assessment)

Or

* Reduction in average pain intensity by *2 points (compared to the baseline

assessment)

(The average pain intensity is the average of the 24-hour pain intensities over

the last 2 weeks of the Maintenance Phase)

The secondary safety endpoint is the frequency of treatment emergent adverse

events (TEAEs).

Study description

Background summary

The most widely accepted algorithm for the treatment of chronic malignant tumor-related pain was developed by the World Health Organization.
Step III of the WHO ladder is treatment with a *strong opioid* such as morphine.
Morphine has been widely accepted as gold standard in the analgesic management of severe pain and cancer pain

Despite the high analgesic efficacy, treatment with strong opioids in pain is influenced by their side effect profile such as nausea, vomiting, sedation, constipation, addiction, development of tolerance, and respiratory depression.

Cebranopadol is a highly potent mixed nociceptin/orphanin FQ peptide (NOP)/opioid receptor agonist with central antinociceptive activity found to be highly effective in animal models of acute pain, visceral and inflammatory pain as well as chronic mono- and poly-neuropathic and bone cancer pain. In acute pain, cebranopadol is approximately equi-potent to the strong opioid fentanyl. In neuropathic pain, cebranopadol is about 10 times to 100 times more potent than in acute pain whereas classical opioids generally have the same potency in both pain conditions.

Cebranopadol is currently in pghase 2/ 3 clinical development for the treatment of chronic pain indications in EU and US.
The proposed trial is part of a comprehensive clinical development plan designed to meet the requirements of the Note for Guidance for Nociceptive Pain (CPMP/EWP/612/00). This guideline requests that several pain models are investigated including cancer pain as a model for severe chronic pain to achieve the targeted indication.

The main goal of this trial is to explore the efficacy and safety of treatment with cebranopadol compared to a standard treatment with morphine sulfate PR in patients suffering from moderate to severe chronic cancer pain.
The trial is designed as a non-inferiority trial for efficacy. The trial does not include a placebo arm for ethical and feasibility reasons.
Morphine sulfate PR (twice daily formulation) was chosen as active comparator, as this medication shares the μ-agonistic mechanism of action with cebranopadol, and is one of the most commonly used opioid analgesics in this

patient population.

Study objective

The primary objective is to evaluate the efficacy of orally administered cebranopadol in comparison with morphine sulfate PR in subjects suffering from chronic moderate to severe pain related to cancer.

The secondary objective is to compare the safety and tolerability of cebranopadol and morphine sulfate PR.

Study design

This is a randomized, multi-site, double-blind, double-dummy, active control, parallel group, multiple dose, oral administration, Phase III trial, in approximately 524 subjects. Scheduled during the Treatment Period are a 16-day Titration Phase and a 28-day Maintenance Phase.

The maximum duration of the trial, including the Enrollment Period, Treatment Period, and the Follow-up Period, for an individual subject will be approximately 10 weeks. The sponsor may decide to offer an extension trial to subjects who complete this trial. If this trial will be offered, it will be a separate trial protocol and the option to take part will also depend on approvals by local authorities and IECs, however, these may not be the only reasons.

Intervention

Subjects who comply with all inclusion criteria and do not meet any of the exclusion criteria will be randomly assigned to one of the 2 treatment arms (Cebranopadol versus Morphine sulfate PR) in the ratio 1:1

The IMP will be taken orally twice daily from the next day of Visit 2 throughout the Titration Phase and the Maintenance Phase, and on the day of Visit 11 (including the evening dose). The IMP intake must be documented in the e-diary during the treatment period on a daily basis.

The different daily doses during the Titration Phase and the Maintenance Phase will be administered using the available dose strengths of cebranopadol (200 µg, 400 µg, 600 µg) and morphine (15 mg, 30 mg, and 45 mg) and the matching placebo tablets or capsules.

Cebranopadol
The starting dose of cebranopadol will be 200 µg per day.
The maximum daily dose of cebranopadol is 1000 µg.
The minimum daily dose of cebranopadol is 200 µg.

The incremental/decremental dose of cebranopadol is 200 µg per day.

Morphine sulfate PR
The starting dose of morphine sulfate PR will be 30 mg per day (divided into 2 intakes).
The maximum daily dose of morphine sulfate PR is 150 mg (divided into 2 intakes).
The minimum daily dose of morphine sulfate PR is 30 mg (divided into 2 intakes).
The incremental/decremental dose of morphine sulfate PR is 30 mg per day (divided into 2 intakes).

The aim of the titration is to reach the subject*s individual optimal dose defined as a balance between self-reported analgesia and side effects. The investigator will have access to each subject*s recordings of daily pain ratings and usage of rescue medication, and should take these into account in titration decisions.
If the tolerability is considered acceptable by both the subject and the investigator, and there appears to be sub-optimal efficacy, i.e., high pain intensity and/or the need to use rescue medication, the investigator should titrate the subject to a higher dose. If the tolerability is considered unacceptable by the subject or the investigator, the investigator should down-titrate the dose.

The selected dose at the end of the Titration phase will be used by the subjects during the Maintenance Phase. To ensure adequate efficacy assessments, changes in dose during the Maintenance Phase will be prohibited.

Subjects will receive morphine sulfate IR (10 mg) as rescue medication in addition to the IMP. Subjects will be instructed on the maximum allowable dosage of rescue medication during the various stages of the trial, to be used e.g. in case of breakthrough pain. The daily use of rescue medication will be recorded in the electronic diary and will be discussed with the investigator.

Study burden and risks

Burden for the subject
Within the 10 weeks of study participation, the subject will visit the hospital 7 times and have 6 telephone appointments with the study doctor.

The duration of the hospital visits will approximately be 1.5 hours. During these visits the following actions occur: physical examination, collection of demographic data, discussion of medical history, checking eligibility criteria, making 12-lead ECG, blood collection, urinalysis, urine drug test, pregnancy test (if applicable), discussing adverse events, discussing concomitant medication and explaning the use of the electronic diary. During three of those visits the subject will complete various questionnaires.

The telephone appointments will take about 15 minutes during which side effects, pain experience, use of rescue medication, use of concomitant medication, usage of the electronic diary and dose titration will be discussed.

During the entire period subjects take their study medication twice daily. These intakes will be recorded in an electronic diary together with the pain scores as well as any rescue medication they have taken.

All female subjects of childbearing potential must use adequately acceptable methods of birth control to prevent pregnancy. Male subjects have adequate contraception use in research to prevent pregnancy of their partners

Medication-related risks
Known side effects of Cebranopadol are dizziness, drowsiness, headache, nausea and constipation.
Most Common side effects of Moriphine Sulphate are drowsiness, nausea, vomiting and constipation.

Blood sampling related risks
During six hospital visits blood samples will be taken. The insertion of the needle can be painful or there may be blue spots developing at the injection site. In addition, the subject may suffer from dizziness, light headedness or fainting.

Contacts

Public
Grunenthal

Zieglerstrasse 6
Aachen 52099
DE
Scientific
Grunenthal

Zieglerstrasse 6
Aachen 52099
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects must have signed an informed consent form (ICF) indicating that they understand the purpose of and procedures required for the trial and are willing to participate in the trial.
2. Subjects must be at least 18 years of age at the Enrollment Visit (Visit 1).
3. Women of childbearing potential must have a negative pregnancy test at Visit 1 and Visit 2 and must not be lactating at Visit 1. Subjects must be willing to use medically acceptable and highly
effective methods of birth control. For women of childbearing potential a medically acceptable and highly effective method of birth control is defined as any form of contraception with a low failure rate defined as <1% per year. For men: Men have to use barrier contraception (condom) during sexual intercourse from the first administration of IMP until 4 weeks after the End of Treatment Visit. The male subject has to take care that the female sexual partner uses at least 1 additional method of contraception with a low failure rate defined as <1% per year (e.g., oral
contraceptives) during this time frame. A double-barrier method should be supplemented by the use of spermicidal agents.
4. Subjects fulfilling the following 4 criteria:
* Requiring daily basic pain analgesia diagnosed with active cancer including hematological malignant diseases.
* Receiving daily opioid treatment at doses not higher than 90 mg oral morphine or its equivalent (including World Health Organization [WHO] Step II and Step III analgesics) for an appropriate length of time.
* Dissatisfied (due to lack of efficacy or poor tolerability) with their current pain treatment.
* Suffering from cancer-related but not cancer therapy-related chronic pain for a period of *4 weeks prior to Visit 1.
5. Performance Status: Eastern Cooperation Oncology Group (ECOG) *2.;Additional inclusion criteria at Visit 2
6. Subjects with a mean score of *5 points (11-point NRS) for the *average pain intensity over the last 24 hours* calculated from the pain assessments recorded during the last 3 days prior to Visit 2
7. Compliance with the use of the e-diary defined as at least 3 out of 4 of the 24 hour NRS entries available during the last 4 days prior to and including the day of Visit 2.

Exclusion criteria

1. Evidence of ongoing alcohol/drug abuse or history of alcohol/drug abuse within the last 2 years in the investigator*s judgment, based on patient history and physical examination.
2. The subject has a clinically significant disease other than cancer which in the investigator's opinion may affect efficacy or safety assessments e.g., significant unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, infectious disease, psychiatric (resulting in
disorientation, memory impairment or inability to report accurately) or metabolic disorders.
3. Subjects with any gastrointestinal disorder that could, in the investigator*s opinion, affect the absorption and/or elimination of IMP.
4. Any pre-scheduled major surgery during the trial.
5. Known to or suspected of not being able to comply with the trial protocol and the use of IMP.
6. History of seizure disorder and/or epilepsy or any condition associated with a significant risk of seizure or epilepsy.
7. Known history and/or presence of cerebral tumor or cerebral metastases.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	cebranopadol
Product type:	Medicine
Brand name:	Morphine sulphate PR
Generic name:	MST Continus

Ethics review

Approved WMO Date:	04-07-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-12-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	14-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	26-06-2014

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	08-01-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	01-04-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

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	EUCTR2012-001316035-GB
EudraCT	EUCTR2012□001316□35-NL
CCMO	NL44650.098.13