Efficacy, safety and tolerability of multiple doses of oral cebranopadol in subjects with moderate to severe chronic pain due to diabetic peripheral neuropathy

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To assess the analgesic efficacy, safety, and tolerability of once daily orally administered cebranopadol in a total of 3 fixed doses (100 µg, 300 µg, and 600 µg cebranopadol) compared to placebo in subjects with moderate to severe chronic pain due...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peripheral neuropathies
Study type	Interventional

Summary

ID

NL-OMON40164

Source
ToetsingOnline

Brief title
KF6005/08 study

Condition

- Peripheral neuropathies

Synonym
Diabetic peripheral neuropathy (DPN)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: chronic pain, Diabetic peripheral neuropathy (DPN), Neuropathy

Outcome measures

Primary outcome

The primary endpoint will be the change from baseline pain to the average 24 hour pain during Week 6 of the Maintenance Phase. The 24 hour pain will be assessed once daily (evening) using an 11 point numeric rating scale (NRS) and a 24 hour recall period.

Secondary outcome

Not Applicable

Study description

Background summary

Diabetic peripheral neuropathy is a long-term complication of diabetes mellitus causing pain as a result of damage to the peripheral nerves. The most common form of painful DPN causes spontaneous burning or freezing pain, numbness, tingling, aching, cramping, muscle weakness, shooting, electric shock-like pain in the lower extremities.

Despite the relatively high number of patients affected by painful DPN, little consensus exists about the pathophysiology, best diagnostic tools, and primary treatment choices.

Cebranopadol is a new compound developed by Gr*nenthal and 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.

The targeted therapeutic indications are the treatment of severe chronic

nociceptive pain requiring opioid analgesia and chronic peripheral neuropathic pain.

Study objective

To assess the analgesic efficacy, safety, and tolerability of once daily orally administered cebranopadol in a total of 3 fixed doses (100 µg, 300 µg, and 600 µg cebranopadol) compared to placebo in subjects with moderate to severe chronic pain due to DPN.

Study design

This is a Phase II, randomized, multi-site, double-blind, double-dummy, placebo- and active-controlled, parallel-group, dose-ranging trial in approximately 350 allocated subjects with moderate to severe chronic pain due to DPN.

Intervention

Study medication, physical examination including ECG and lab assessments

Study burden and risks

Patients may experience side effects from the use of study medication. The most common and known side effects are described in the patient information documentation.

Blood samples can cause mild pain, redness, bruising and / or irritation at the place where blood has been drawn.

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. Informed consent signed (Visit 1).
2. Male or female subjects aged 18 years to 80 years inclusive at the Enrollment Visit (Visit 1).
3. All subjects must have type 1 or type 2 diabetes mellitus and must have a documented clinical diagnosis of painful DPN with symptoms and signs for at least 3 months and pain present at the Enrollment Visit (Visit 1).
4. The investigator considers the subject*s blood glucose to be controlled by a diet, oral anti-hyperglycemic medication, and/or insulin for at least 3 months prior to Enrollment Visit. This control should be documented. Hemoglobin (HbA1C) should not be greater than 11% at the Enrollment Visit (Visit 1).
5. Subject must require medication (e.g., non-opioids or opioids up to an equivalent dose of 160 mg oral morphine/day) for the treatment of pain due to DPN for at least 1 month prior to Visit 1 and must be dissatisfied with the current treatment (in terms of efficacy and/or tolerability). Medication for the treatment of pain due to DPN should be required on at least 4 of 7 consecutive days.
6. Subjects must be using medically acceptable and highly effective methods of birth control (and willing to use them during the trial):
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 example:
• Hormonal contraceptives for at least 2 months prior to the Enrollment Visit and until at least 4 weeks after Visit 7.
• An intra-uterine device.
Additional barrier contraception must be used by the partner for the duration of the trial. A double-barrier method should be supplemented by the use of spermicidal agents.
Women of non-childbearing potential may be included if surgically sterile (i.e., after hysterectomy) or post-menopausal for at least

2 years.
For men: Men have to use barrier contraception (condom) during sexual intercourse for the duration of the trial. 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.
7. Women of childbearing potential must have a negative urine β-human chorionic gonadotropin (β-hCG) pregnancy test at the Enrollment Visit (Visit 1) and at the Baseline Visit (Visit 3).
8. A baseline pain intensity score >=5 on the 11-point NRS without intake of any analgesic (including rescue medication) at Visit 3. For each of the last 3 days prior to Visit 3, a 24-hour NRS score >=4 is required.
The baseline pain will be calculated as the average over the three 24-hour pain assessments of the last 3 days prior to the Baseline Visit (Visit 3).

Exclusion criteria

Presence of other pain that could confound the assessment of, or contribute to, painful DPN. Such pain could include, but is not limited to, pain due to nerve entrapment (e.g., tarsal tunnel syndrome, osteoarthritis of the knee), peripheral vascular disease, radiculopathy, plantar fasciitis, tendonitis, mononeuritis multiplex, postherpetic neuralgia, complex regional pain syndrome, or fibromyalgia.
2. Neuropathy due to etiologies other than diabetes. These neuropathies include, but are not limited to, those associated with autoimmune disorders, inflammatory neuropathies (e.g., chronic inflammatory demyelinating polyneuropathy), thyroid disease or endocrine disorders (other than diabetes), heavy metal or toxic neuropathy, nutritional deficiency, metabolic disorders, vasculitis, infections, injury, or paraneoplastic syndromes.
3. Severe or extensive diabetic ulcers or amputations of the limbs (i.e., more than 2 toes) or Charcot*s joints due to diabetes. Subjects who have had an amputation for a reason other than diabetes (e.g., injury) may be eligible for this trial.
4. Any clinically significant disease or laboratory findings that in the investigator*s opinion may affect efficacy or safety assessments or may compromise the subject*s safety during trial participation, e.g., significant unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, metabolic, neurological, or psychiatric disorders.
5. Any medical or other reason (e.g., known or suspected inability of the subject to comply with the protocol and with the use of the IMP) that, in the investigator*s opinion, might indicate that the subject is unsuitable for the trial.
6. Conditions that require treatment with forbidden medication (see Section 10.6.2).
7. Use of forbidden concomitant medication as specified in Section 10.6.2.

8. Previous or current alcohol or drug abuse or opioid dependency, according to the investigator*s judgment, based on the subject*s history, examination, and the result of the drugs of abuse test. Subjects with positive urine drug test explained by a medically indicated treatment are allowed to participate in the trial as long as not specified otherwise in Section 10.6.2.
9. Subjects with severe functional hepatic impairment corresponding to Child-Pugh classification C. Subjects with impaired hepatic cellular integrity indicated by AST or ALT greater than 3 x ULN.
10. History of acute hepatitis within 3 months of Visit 1 or chronic hepatitis or a positive result on anti-hepatitis A IgM antibody within the past 6 months, hepatitis B surface antigen, or anti-hepatitis C antibody.
11. Subjects with impaired renal function with a creatinine clearance less than 60 mL/min at the Enrollment Visit (Visit 1) (calculated from the Cockcroft-Gault [1976] formula).
12. History of any major gastrointestinal prior procedures (e.g., gastric bypass) or gastrointestinal conditions (e.g., acute diarrhea, blind loop syndrome, gastric dumping syndrome, Whipple*s disease) that might affect the absorption or metabolism of cebranopadol.
13. Presence of risk factors for (e.g., heart failure, hypokalemia, or bradycardia), or history of, torsade de pointes and/or marked prolongation of the corrected QT (Fridericia) (QTcF >450 ms).
14. History of seizure disorder and/or epilepsy or any condition associated with a significant risk for seizure disorder or epilepsy at the discretion of the investigator.
15. History or presence of malignancy with the exception of curative treated subjects or subjects being in remission of cancer for at least 2 years and not requiring treatment.
16. Any scheduled surgery or painful procedure during the course of the trial.
17. Clinically relevant history of hypersensitivity, allergy, or contraindications to any of the IMP*s excipients as well as to opioids, pregabalin or paracetamol.
18. Significant vascular disease (e.g., peripheral occlusive arterial disease, Fontaine Class III-IV; post-thrombotic syndrome, venous insufficiency Stage III/IV).
19. Subjects whose BMI is lower than 18 kg/m2 or greater than 40 kg/m2.
20. History of human immunodeficiency virus (HIV) infection.
21. Severe signs of suicidal behavior and/or suicidal ideation within the past 3 months based on the results of the C-SSRS (suicidal ideation rating of 4 or 5 or any suicidal behavior) a.
22. Female subjects who are pregnant or breastfeeding.
23. Concurrent participation in another trial, or within 30 days before the Enrollment Visit of this trial.
24. Previous participation in this trial (unless enrollment failure due to technical reason or in- and exclusion criteria that were changed in Amendment 03) or participation in another trial with cebranopadol (unless enrollment failures, i.e., not allocated to IMP).
25. Employees of the investigator, trial site, or sponsor with direct involvement in the

proposed trial or other trials under the direction
of that investigator, trial site, or sponsor, as well as family members of employees or the investigator.
26. Failure to complete the required medication washout by Baseline
Visit (Visit 3) or use of forbidden concomitant medications as specified in Section 10.6.2.
27. Previous or current alcohol or drug abuse or opioid dependency,
according to the investigator*s judgment, based on the subject*s history, examination, or the result of the drugs of abuse test. Subjects with positive urine drug test explained by a medically indicated treatment are allowed to participate in the trial as long as not specified otherwise in Section 10.6.2.

Study design

Design

Study phase:	2
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):	01-09-2013
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cebranopadol film coated tablets
Generic name:	cebranopadol
Product type:	Medicine
Brand name:	Lyrica

Generic name:	Pregabalin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-06-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2014

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2013-000473-68-NL
ClinicalTrials.gov	NCT01939366
CCMO	NL44667.056.13