A Randomized, Double-Blind, Placebo- and Active-Controlled Study of Carisbamate in the Treatment of Neuropathic Pain in Diabetic Peripheral Neuropathy Followed by a Blinded Extension Phase

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OBJECTIVESPrimary ObjectiveThe primary objective is to evaluate the efficacy, safety, and tolerability of 800 and 1,200 mg/day of carisbamate compared with placebo in reducing the average daily pain in subjects with diabetic peripheral neuropathy (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON33350

Source
ToetsingOnline

Brief title
Persistent Pain in Diabetic Peripheral Neuropathy

Condition

- Diabetic complications
- Peripheral neuropathies

Synonym
nerve pain, neuropatic pain

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen-Cilag B.V.

Intervention

Keyword: Diabetes, Neuropathic Pain, Polyneuropathy

Outcome measures

Primary outcome

EFFICACY EVALUATIONS/CRITERIA

The study will include efficacy evaluations, mostly patient-reported outcome (PRO) measures, at specified time points during the study. Efficacy evaluations include daily pain assessments, Subject Global Impression of Change (SGIC) and Severity (SGIS), Neuropathic Pain Symptom Inventory (NPSI), Short-Form Health Status Survey (SF-36), Brief Pain Inventory (BPI) (Short Form), Medical Resource Utilization (MRU) including work/activity assessment, sleep assessments, and the Medical Outcomes Study (MOS) Sleep scale.

PHARMACOKINETIC EVALUATIONS

Plasma samples will be collected at designated times during the study. Standard population pharmacokinetic parameters in subjects and their inter- and intraindividual variability will be estimated. The effects of covariates such as demographics, concomitant medications, and laboratory values on carisbamate pharmacokinetics will be evaluated.

PHARMACOGENOMIC EVALUATIONS

A pharmacogenomic blood sample (10 mL) will be collected to allow for

pharmacogenomic research, as necessary (where local regulations permit).

SAFETY EVALUATIONS

Safety will be evaluated by the monitoring of frequency and severity of adverse events; clinical laboratory tests (hematology, serum chemistry, urinalysis, pregnancy tests for women of childbearing potential, urine drug screen, blood alcohol test); 12-lead electrocardiograms (ECGs); vital signs measurements; and physical (including body weight and height) and neurologic examinations.

A Data Safety Monitoring Board (DSMB) will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

Secondary outcome

Not applicable

Study description

Background summary

Neuropathic pain is initiated or caused by a primary lesion or intrinsic dysfunction in the nervous system (International Association for the Study of Pain [IASP]) either within the peripheral or central nervous system. Diabetes mellitus is the most common cause of neuropathy in the Western world, with up to 50% of diabetics developing neuropathy as a long-term complication, 10% of whom experience pain (Vinik 1992). Diabetic neuropathy is most commonly distal and symmetrical in distribution with pain due to diabetic neuropathy most often affecting the lower extremities. Pain in response to a normally innocuous stimulus, referred to as allodynia, is an important characteristic in neuropathic pain and one of its diagnostic criteria (Dworkin 2003). Neuropathic pain is often associated with mood changes, fatigue, and sleep disturbance, is worse at night, and may have a profound impact on patients* physical and social functioning and hence well-being (Schmader 2002).

Pain due to diabetic neuropathy can be severe and difficult to treat. Several medications have shown efficacy in treating the pain of DPN, including tricyclic antidepressants, the serotonin noradrenaline reuptake inhibitor

(SNRI) duloxetine (Goldstein 2005; Max 1992; Raskin 2005), anticonvulsants such as pregabalin and gabapentin (Backonja 1998; Jaaskelainen 2005; Lesser 2004), and opioid analgesics such as oxycodone (Backonja 1998; Watson 2003). However, treatment for many patients with painful diabetic neuropathy is limited by modest efficacy and/or by significant side effects associated with these agents. The development of new pharmacotherapeutic agents with greater efficacy and fewer side effects than currently marketed therapies is warranted.
This study is being conducted to support the safety, tolerability, and efficacy of carisbamate in dosages higher than those that have been studied in the previous Phase 2a studies in neuropathic pain states (400 mg/day). Because these previously completed studies suggested a clinically small but consistent benefit of low-dose carisbamate across multiple pain measures, this study will investigate higher dosages in the range of 800 to 1,200 mg/day. The extension phase will enroll eligible subjects who will continue to receive carisbamate or pregabalin in a blinded manner and for which efficacy, safety and tolerability data will be collected.

Study objective

OBJECTIVES
Primary Objective
The primary objective is to evaluate the efficacy, safety, and tolerability of 800 and 1,200 mg/day of carisbamate compared with placebo in reducing the average daily pain in subjects with diabetic peripheral neuropathy (DPN).
Secondary Objectives
The secondary objectives of this study are:
· To evaluate the impact of 800 and 1,200 mg/day of carisbamate on:
- Pain symptoms
- Functional health status (including physical and social functioning) and well-being
- Rescue medication use
- Sleep interference
· To evaluate global assessments of improvement and severity from subject perspective
· To characterize the population pharmacokinetics of carisbamate in subjects with DPN
· To evaluate long-term safety of carisbamate in subjects with DPN
Exploratory Objectives
· To explore effects of 800 and 1,200 mg/day of carisbamate on:
- The impact of pain severity and interference with activities of daily living
- Changes in sleep dimensions and daytime somnolence
- Medical resource utilization (MRU) including work activity assessment
· To compare descriptively the safety and efficacy of 800 and 1,200 mg/day of carisbamate with pregabalin 300 mg/day

Study design

This is a randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study with an (optional) blinded extension phase with comparator in subjects with DPN. Up to 440 subjects who have chronic neuropathic pain associated with DPN will participate in this study. The study will consist of a pretreatment phase including a screening, washout and baseline period, a double-blind treatment phase with a titration and a fixed dose period, an optional blinded extension phase, and a posttreatment phase (including a follow-up visit and telephone contact). The duration of the study (excluding the pretreatment phase) is approximately 58 weeks for subjects who will decide to enter the blinded extension phase and approximately 19 weeks for the other subjects.
Subjects who meet the entry criteria will be identified at Visit 1 (Days -14 to -8), and will discontinue all prohibited medications. Beginning at Visit 2 (Days -7 to -1), subjects will document the use of rescue medication (acetaminophen up to 1,000 mg/day) taken each day via the Interactive Voice Response System (IVRS). Rescue medication will be allowed throughout the study.
At Visit 3 (Day 1), subjects will be randomly assigned in a 1:1:1:1 ratio to carisbamate 800 or 1,200 mg/day or pregabalin 300 mg/day or placebo. Subjects will be titrated to the assigned treatment over a period of 3 weeks per dosing schedule.
Subjects will be provided with instructions to call the IVRS once each evening to report daily pain and sleep interference assessments, indicating the degree to which their DPN pain interfered with sleep the previous night, and rescue medication usage throughout the double-blind treatment phase. During the 7 days prior to baseline and the last 7 days of the double-blind treatment phase, subjects will be asked to report responses to 5 additional sleep questions via IVRS.
All subjects who complete the double-blind treatment phase will be offered the option to enter the 9-month blinded extension phase of the study. Subjects previously treated with carisbamate or with placebo will receive carisbamate that will be titrated to their individually best dose up to 1,200 mg/day; subjects previously treated with pregabalin will receive pregabalin that will be titrated to their individually best tolerated dose up to 300 mg/day.
Subjects will continue to record pain scores, use of rescue medication, and sleep interference assessments in 7-day blocks preceding study visits throughout the extension phase up to Visit 13 via IVRS.
The posttreatment visit will be scheduled within 7 to 14 days after the last dose of study drug of the double-blind treatment or blinded extension phase, depending on participation in the optional blinded extension part of the study for safety and efficacy evaluations. During the posttreatment phase, subjects will be allowed to take pain medications as clinically indicated while study treatment is down titrated. Between 30 and 33 days after the subject*s last dose of study drug, the study site will call subjects to inquire about adverse events occurring in the interval since their last visit.

A Data Safety Monitoring Board (DSMB) has been commissioned for this study.

Intervention

DOSAGE AND ADMINISTRATION
Subjects will be randomly assigned in a 1:1:1:1 ratio to 4 treatment groups. The double-blind phase treatment of this study will employ a fixed dosing regimen after titration to the assigned treatment over a period of 3 weeks. Treatment will consist of either 800 or 1,200 mg/day of carisbamate or matching placebo or matching pregabalin 300 mg/day, administered in equally divided doses twice daily, with or without food. In the second and third weeks of the titration period, the dose can be decreased to the previous dose level in subjects with tolerability issues. As of Day 22, subjects should remain on the dose achieved on Day 21. No further dose adjustment will be allowed.
Subjects who elect not to continue in the blinded extension phase will be tapered over a period of 1 week in a blinded way. At the end of double-blind treatment phase, subjects treated with pregabalin will receive 75 mg twice daily for an additional 6 days, subjects on placebo will continue to receive placebo for 6 days, those treated with carisbamate 400 mg twice daily will receive 200 mg twice daily for 6 days prior to discontinuation, and those on carisbamate 600 mg twice daily will receive 400 mg twice daily for 3 days and 200 mg twice daily for 3 days.
All subjects entering the blinded extension phase will be blindly transitioned to extension treatment. Subjects previously on placebo will start to receive carisbamate on Day 107 starting with 200 mg twice daily. The dose can be increased as of Day 114 to 400 mg twice daily and on Day 121 to 600 mg twice daily. The dose can be adjusted by the investigator per clinical response and tolerability within the total daily dose range of 400 to 1,200 mg/day. Subjects previously on pregabalin will continue to receive pregabalin on Day 107 starting with 75 mg twice daily. The dose can be increased as of Day 114 to 150 mg twice daily. The dose can be adjusted by the investigator per clinical response and tolerability within the total daily dose range of 150 to 300 mg/day. Subjects previously on 800 or 1,200 mg/day carisbamate will continue on prior dose levels while subjects previously on 400 mg/day carisbamate will receive 800 mg/day starting on Day 107. All dose levels may be adjusted by the investigator per clinical response and tolerability within the total daily dose range of 400 to 1,200 mg/day carisbamate.

Study burden and risks

See dutch version

Contacts

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Nederland
Scientific
Janssen-Cilag

Postbus 90240
5000 LT Tilburg
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Potential subjects must satisfy all of the following criteria to be enrolled in the study:
· Men or women between 18 and 75 years of age, inclusive
· Have diabetes mellitus (Type 1 or Type 2)
· Subjects must meet the following criteria at the end of the baseline period to be randomly assigned into the double-blind treatment phase of the study:
- Documented daily average DPN pain assessments (ie, evening ratings for pain over the past 24 hours) for at least 5 days in the baseline period
- Mean Daily Average DPN Pain score of at least 4 on an 11-point scale during the baseline period
· Have symptoms of diabetes-related painful peripheral neuropathy in the distal extremities for at least 6 months prior to study entry. The pain symptoms must be attributable to DPN confirmed by history and findings on neurologic examination.
· Experienced lower extremity pain due to diabetic neuropathy on a nearly daily basis for the previous 3 months
· Have hemoglobin A1c (HbA1c) levels £11%

· Have a stable diabetic treatment regimen, including oral hypoglycemics, insulin, or diet for 3 months before screening
· Willing to discontinue treatment for chronic pain with AEDs (including gabapentin or pregabalin), opioids or opioid-containing analgesics, or SNRIs or tricyclic antidepressants for any indication. Willing to discontinue other prohibited medications (see Attachment 1).
· Women must be:
- postmenopausal (for at least 2 years)
- surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy)
- abstinent (at the discretion of the investigator/per local regulations)
- if sexually active, be practicing a highly effective method of birth control (eg, prescription oral contraceptives provided the subject is receiving a dosage that has been adjusted for concomitant use of any drug known to significantly affect the metabolism of hormonal contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel], male partner sterilization) as local regulations permit
before entry, and must agree to continue to use the same method of contraception throughout the study.
· Women of childbearing potential must have a negative urine pregnancy test at screening; and at the time of random assignment to treatment on Day 1.
· Negative urine drug screen and blood alcohol test at screening
· Negative for hepatitis B infection, according to the interpretation of hepatitis B serology test results
· Negative for anti-hepatitis C virus antibody (anti-HCV)
· Able and willing to read and comprehend written instructions, to complete study questionnaires, and to make daily phone calls to the IVRS to report daily DPN pain and sleep assessments
· Willing/able to adhere to the prohibitions and restrictions specified in this protocol
· Subjects must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.
· To participate in the optional pharmacogenomic component of this study, subjects must have signed the informed consent form for pharmacogenomic research indicating willingness to participate in the pharmacogenomic component of the study (where local regulations permit). Refusal to give consent for this component does not exclude a subject from participation in the clinical study.

Exclusion criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:
· History of poor response to 3 or more classes of medications for DPN.
Note: Poor response is defined as treatment with medications in the following classes of therapy for greater than 1 month at clinically accepted therapeutic dosages without at least moderate improvement in the judgment of the investigator:

- AEDs
- tricyclic antidepressants
- SNRIs
- opioid analgesics
- lidocaine patch

· Known allergies, hypersensitivity, or intolerance to carisbamate or its excipients (refer to Section 14.1, Physical Description of Study Drug(s)

· History of allergic reaction or other clinically significant or treatment-limiting side effect due to pregabalin

•A history (at any time in life) of Stevens Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, a drug-related exfoliative rash, any drug-related rash requiring hospitalization, or rash associated with an AED that involved conjunctiva or mucosae, or a maculopapular rash
that required discontinuation of an AED

· Currently taking Coumadin® (warfarin)

· Use of disallowed therapies: see Attachment 1

· Prior neurolytic treatment (destruction of nerves by the application of chemicals, heat, or cold), neurosurgery, intrathecal pumps, or spinal cord stimulators for their DPN pain

· Use of herbal topical creams or ointments for pain relief within 48 hours, capsaicin within 6 months, or systemic corticosteroids within 3 months before the baseline period

· Dermatologic or vascular disease in the limbs affected by the neuralgia that may interfere with assessment, including a diabetic ulcer or any toe or limb amputation

· History of a chronic pain condition (eg, joint osteoarthritis or low back pain) that is more severe than their DPN or that requires daily analgesic treatment

· Hospitalized within the past 1 month for episodes of hypoglycemia/hyperglycemia

· Clinical diagnosis of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) or any immune deficiency

· History of progressive or neurologic disorders (eg, multiple sclerosis, amyotrophic lateral sclerosis) that may interfere with completion of the study or interpretation of study results

· Medically unstable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel [including liver enzymes, other specific tests], hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the subject's source documents and initialed by the investigator. The values must be contained within 1.5 times the ULN for ALT and AST, and must be below the ULN for total bilirubin.

· History of liver impairment or renal insufficiency; significant or unstable cardiac, vascular, pulmonary, endocrine, rheumatologic or gastrointestinal conditions including moderate to severe gastroparesis, or an anticipated need for surgery

· Glomerular filtration rate (GFR) less than 50 mL/min as estimated by the Modification of Diet in Renal Disease Study Equation:
GFR = 175 x (standardized serum creatinine)-1.154 x (age)-0.203 x 0.742 (if subject is female) or x 1.212 (if subject is black)

· Known malignancy or history of malignancy within the past 5 years with the exception of basal cell carcinoma that has been treated and is no longer present

· History of or suggested clinical diagnosis of schizophrenia, bipolar disorder, dementia due to

any cause, or any other psychotic illness
· History of suicide attempts or suicidal ideation in the past year
· Active, major depression or generalized anxiety disorder, recent episode of either disorder within the past 3 months
· History of alcohol or drug abuse within the past 2 years; the subject*s neuropathy should not be attributable to present or past alcohol use, based on the judgment of the investigator
· Have taken medications known to cause neuropathies in the last year
· Received an investigational drug or used an investigational medical device within 30 days before the planned start of treatment
· Prior exposure to carisbamate
· Women who are not using an effective method of birth control, who are pregnant, or who are breast-feeding
· Unable to take their medication (for example, unable to swallow solid oral dosage forms whole with the aid of water, or having swallowing difficulties) or to perform study procedures
· Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements
· Employees of the investigator or study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center, as well as family members of the employees or the investigator
4.4. Prohibitions and Restrictions
Potential subjects must be willing/able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:
· Discontinue all prohibited medications including those used to treat pain (Refer to Attachment 1)
· Must not take any of the prohibited medications and treatments listed in Attachment 1
· Must not take rescue medication for at least 3 hours before reporting daily DPN pain and sleep assessments to the IVRS
· Women must remain on a highly effective method of birth control (see Section 4.2, Inclusion Criteria).

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):	15-06-2009
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Comfyde
Generic name:	carisbamate
Product type:	Medicine
Brand name:	Lyrica
Generic name:	pregabalin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-04-2009
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-04-2009
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-10-2009
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-10-2009
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-11-2009
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-12-2009
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-01-2010
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2008-008753-33-NL
CCMO	NL27623.028.09