A Phase 2 Placebo-Controlled, Double-Blind, Enriched Enrollment Randomized Withdrawal Study to Evaluate the Efficacy and Safety of BIIB074 (Vixotrigine) in Treating Pain Experienced by Subjects With Confirmed Small Fibre Neuropathy That Is Idiopathic or Associated With Diabetes Mellitus

Published: 21-12-2017
Last updated: 12-04-2024

The primary objective of this study is to evaluate the efficacy of BIIB074 in treating pain experienced by subjects with confirmed SFN that is idiopathic or associated with diabetes mellitus.Sub study objective:Corneal Confocal Microscopy (CCM) as a...

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

Summary

ID

NL-OMON48621

Source
ToetsingOnline

Brief title
Convey

Condition

- Other condition
- Diabetic complications

Synonym
Diabetes, Small Fibre Neuropathy

Health condition

Small Fibre Neurophaty that is Idiopathic or associated with Diabetes Mellitus

Research involving
Human

Sponsors and support

Primary sponsor: Biogen Idec Research Limited
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: BIIB074, diabetes mellitus (DM), small fibre neuropathy (SFN)

Outcome measures

Primary outcome

The primary objective of this study is to evaluate the efficacy of BIIB074 in

treating pain experienced by subjects with confirmed SFN that is idiopathic or

associated with diabetes mellitus.

The primary endpoint that relates to this objective is the change from Baseline

to Week 12 of the double-blind period in the mean average daily pain (ADP)

score on an 11-point Numerical Rating Scale (NRS), where 0 = no pain and 10 =

worst pain imaginable.

A secondary endpoint that relates to the primary objective is the change from

Randomization to Week 12 of the double-blind period in mean ADP score on the

11-point NRS.

Secondary outcome

1. To evaluate the effect on worst pain, neuropathic pain quality, sleep interference due to pain, patient global impression, use of rescue medication, and SFN symptoms
in subjects treated with BIIB074.

The endpoints that relate to this objective are as follows:

• Change from Baseline to Week 12 of the double-blind period in mean worst daily pain (WDP) score on the 11-point NRS.

• Change from Baseline to Week 12 of the double-blind period in mean sleep interference score on the 11-point NRS.

• Change from Baseline to Week 12 of the double-blind period in Neuropathic Pain Symptom Inventory (NPSI) total score and sum score of symptoms of neuropathic pain (burning and pressing).

• Proportion of subjects with at least a 2-point reduction from Baseline to Week 12 of the double-blind period in mean ADP.

• Proportion of subjects with at least a 30% reduction from Baseline to Week 12 of the double-blind period in mean ADP.

• Amount of rescue medication (paracetamol/acetaminophen) used for SFN pain during the double-blind period.

• Patient Global Impression of Change (PGIC) measured at Week 12 of the double-blind period (7-point scale).

• Change from Baseline to Week 12 of the double-blind period in the Brief Pain

Inventory-Short Form (BPI-SF) interference score.

2. To investigate the safety and tolerability of BIIB074 in subjects with SFN.

The endpoint that relates to this objective is the incidence of adverse events

and serious adverse events during the double blind period.

3. To characterize the pharmacokinetics (PK) of BIIB074 insubjects with SFN.

The endpoints that relate to this objective include population-derived PK

parameters and estimates of exposure (maximum observed concentration and area

under the

concentration-time curve) at steady state.

Study description

Background summary

BIIB074 is a state- and use-dependent Nav1.7 channel blocker. Nav1.7 has been validated as a key pain target by human genetic linkage. Sodium channels are important for nerve impulse conduction, including within pain sensitive nociceptive fibres and within the pain pathway in the spinal cord and brain. Based on nonclinical and clinical data, BIIB074 is being tested in a number of neuropathic pain conditions.
Small fibre neuropathy (SFN) is a neuropathic pain condition caused by damage to small unmyelinated (C fibres) and thinly myelinated (A delta) peripheral nerve fibres and is characterized by severe pain that typically begins in the feet or hands [Hovaguimian and Gibbons 2011]. Diabetes and impaired glucose tolerance are the most common causes of SFN, although for a significant portion of patients, SFN is idiopathic as no cause can be identified. With no treatments indicated specifically for this type of neuropathic pain and with other pain medications, including opioids, being used with limited efficacy and poor tolerability, there is a high unmet medical need for new effective

therapies.

Study objective

The primary objective of this study is to evaluate the efficacy of BIIB074 in treating pain experienced by subjects with confirmed SFN that is idiopathic or associated with diabetes mellitus.

Sub study objective:
Corneal Confocal Microscopy (CCM) as a Screening, Predictive, and Surrogate Endpoint Biomarker for study 802NP206: A Phase 2 Placebo-Controlled, Double-Blind, Enriched Enrollment Randomized Withdrawal Study to Evaluate the Efficacy and Safety of BIIB074 in Treating Pain Experienced by Subjects With Confirmed Small Fibre Neuropathy That is Idiopathic or Associated With Diabetes Mellitus.

Exploratory Objectives:
To evaluate the relationship of quantitative corneal nerve morphology via CCM with SFN diagnosis.
To evaluate the relationship of quantitative corneal nerve morphology via CCM with initial response to BIIB074.
To evaluate the relationship of quantitative corneal nerve morphology via CCM with response to continued BIIB074 treatment or placebo for 12 weeks.

Study design

This is a multicenter, double-blind, enriched enrollment randomized withdrawal study designed to evaluate the efficacy and safety of 200 mg and 350 mg twice daily (BID) of BIIB074 compared with placebo in treating pain experienced by subjects with confirmed SFN that is idiopathic or associated with diabetes mellitus (glycosylated hemoglobin A1c [HbA1c] <=11%).
The duration of study participation will be approximately 26 weeks, including a screening assessment period of up to 21 days, a taper period (if applicable) of up to 14 days, a 5-day washout period, a 4-week open-label run-in period, a 12-week double-blind period, and a 4-week follow-up period.
Subjects who meet all eligibility criteria including a confirmed abnormality in a single skin biopsy during the screening assessment period, will enter the taper period (if applicable). During the taper period, subjects will be required to titrate down, if needed. Subjects can enter the washout period as soon as they discontinue the medications used for pain.
Subjects who meet all screening assessments and are not taking any medications used for pain can enter the 5-day washout period directly from the screening assessment period. No medications used for pain will be allowed during the washout period (see Section 7).

During the open-label run-in period all subjects will receive BIIB074 at 350 mg BID. Subjects who respond to BIIB074 (350 mg BID) in the open-label run-in period and meet all other randomization criteria (see Section 8.6) will be randomly assigned to receive either BIIB074 at 200 mg or 350 mg BID or placebo BID during the 12-week
double-blind period.
Rescue medication (paracetamol/acetaminophen) may be used within dosing limitations, if needed, to treat SFN pain during the open-label run-in and double-blind periods of the study.

Intervention

The duration of study participation will be approximately 26 weeks, including a screening assessment period of up to 21 days, a taper period (if applicable) of up to 14 days, a 5-day washout period, a 4-week open-label run-in period, a 12-week double-blind period, and a 4-week follow-up period.
Subjects who meet all eligibility criteria including a confirmed abnormality in a single skin biopsy during the screening assessment period, will enter the taper period (if applicable).
During the taper period, subjects will be required to titrate down, if needed. Subjects can enter the washout period as soon as they discontinue the medications used for pain.
Subjects who meet all screening assessments and are not taking any medications used for pain can enter the 5-day washout period directly from the screening assessment period. No medications used for pain will be allowed during the washout period.
During the open-label run-in period all subjects will receive BIIB074 in 2 tablets at total concentration of 350 mg BID for 2 times a day. Subjects who respond to BIIB074 (350 mg BID) in the open-label run-in period and meet all other randomization criteria (will be randomly assigned to receive either BIIB074 at 200 mg or 350 mg BID or placebo BID 2 times a day during the 12-week double-blind period.
Rescue medication (paracetamol/acetaminophen) may be used within dosing limitations, if needed, to treat SFN pain during the open-label run-in and double-blind periods of the study

Study burden and risks

There are no therapies specifically indicated for the treatment of pain associated with SFN. Management of SFN is focused on addressing the underlying disease and/or pain management. Pain medications, including opioids, have been used with limited efficacy and poor tolerability.

Based on limitations associated with currently available treatment, including limited efficacy, and/or serious side effects, there is a need for the development of alternative treatments for neuropathic pain associated with SFN

that are both effective and generally well tolerated.
A recent study in patients with idiopathic SFN showed that a portion of patients had a mutation in the SCN9A or SCN10A gene encoding the sodium channel Nav1.7 or Nav1.8, respectively, and a mutation in Nav1.7 has also been found in patients with inherited pain-disorders such as inherited EM or paroxysmal extreme pain disorder [Waxman 2013].

BIIB074 is a state- and use-dependent Nav1.7 channel blocker. Based on its mechanism of action, nonclinical safety profile, and experience in clinical studies to date, BIIB074 may provide an effective treatment for pain associated with SFN.

Contacts

Public
Biogen Idec Research Limited

Biogen Iden Research Limited Innovation House, 70Norden Road
Maidenhead, Berkshire SL6 4AY
GB
Scientific
Biogen Idec Research Limited

Biogen Iden Research Limited Innovation House, 70Norden Road
Maidenhead, Berkshire SL6 4AY
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Key Inclusion Criteria:
1. This study will be conducted in subjects who have had a diagnosis of at least probable SFN length-dependent distribution for >=6 months and <=10 years , based on clinical diagnosis and confirmed by intraepidermal nerve fibre density (IENFD) values, and
weekly mean average daily pain (ADP) score of >=5 and <=9 on an 11-point Pain Intensity Numeric Rating Scale (PI-NRS) over the last 7 days of Screening.
2. In addition to these criteria, subjects with diabetes will be required to have HbA1c <=11%, treated with oral hypoglycemics and/or subcutaneous insulin or diet, no evidence of ulcers, advanced retinopathy (defined as greater than State 3 [moderate non-proliferative diabetic retinopathy]) (DCCT/EDIC Research Group 2017), severe nephropathy, or clinically significant obstructive atherosclerotic disease (e.g. current unstable angina or myocardial infacrtion within 6 months of Screening), or current class IV heart failure to be eligible for the study.
NOTE: Other protocol defined Inclusion criteria may apply

Exclusion criteria

Key Exclusion Criteria:
1. Previous exposure to BIIB074 (formerly known as CNV1014802 or GSK1014802).
2. Use of capsaicin patch within 3 months prior to Screening.
3. Unable or unwilling to discontinue concomitant medications for neuropathic pain during the 2 week
taper period, which overlaps the first week of the openlabel run-in period.
4. Unable or unwilling to comply with the prohibited concomitant medication restrictions, including but not limited to UDPglucuronosyltransferase
(UGT) inducers and inhibitors, monoamine
oxidase inhibitors (MAOIs), and Nav blockers.
5. Use of over-the-counter medications, vitamin and mineral supplements, herbal remedies (including St. John's wort), dietary supplements, or foods (including
grapefruit juice) that affect UGTs.
6. Unable or unwilling to discontinue medications that are P-glycoprotein substrates with a narrow therapeutic
index, including but not limited to digoxin.
7. History of hemophilia or Von Willebrand's disease, or use of anticoagulants that may result in bleeding risk during the skin biopsy.

8. Any contraindication, as determined by the Investigator, to performing a skin biopsy for intraepidermal nerve fibre analysis.
9. Current hepatitis C infection (defined as positive hepatitis C virus [HCV] antibody and detectable HCV ribonucleic acid [RNA}. Participants with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study (United States Centers for Disease Control and Prevention).

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):	14-06-2018
Enrollment:	46
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BIIB074
Generic name:	Vixotrigine

Ethics review

Approved WMO

Date:	21-12-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	04-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2017-000991-27-NL
CCMO	NL62483.018.17