A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BIIB074 in Subjects With Neuropathic Pain From Lumbosacral Radiculopathy

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The primary objective of the study is to evaluate the efficacy of 2 dose regimens of BIIB074 on neuropathic pain in subjects with PLSR.A secondary objective is to evaluate the efficacy of 2 dose regimens of BIIB074 on additional neuropathic pain...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Spinal cord and nerve root disorders
Study type	Interventional

Summary

ID

NL-OMON46236

Source
ToetsingOnline

Brief title
Study to Evaluate the Efficacy and Safety of BIIB074 in Subjects With PLSR

Condition

- Spinal cord and nerve root disorders

Synonym
Hernia, Pain From Lumbosacral Radiculopathy (PLSR)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BIIB074, Leg pain NRS, Lumbosacral radiculopathy, Neuropathic pain, Sodium channel blocker

Outcome measures

Primary outcome

The primary endpoint that relates to this objective is the change from Baseline (Week 2) to Week 14 in the weekly average of the daily neuropathic pain* score on the 11-point PI-NRS. Subjects will be asked every evening to rate their overall neuropathic pain for the last 24-hour period. *Neuropathic pain will be evaluated in the worse affected leg, as identified at Screening.

Secondary outcome

Efficacy endpoints in neuropathic pain:

1. 50% neuropathic daily pain reduction response (yes/no) at Week 14, where a response is defined as a *50% reduction in the weekly average of the daily neuropathic pain score from Baseline (Week 2) to Week 14 *

2. 30% neuropathic daily pain reduction response (yes/no) at Week 14, where a response is defined as a *30% reduction in the weekly average of the daily neuropathic pain score from to Baseline (Week 2) *

3. Changes from Baseline (Week 2) in the weekly average of the daily neuropathic pain score at each visit * Efficacy endpoint in low back pain: *4. Change from Baseline (Week 2) to Week 14 in the weekly average of the daily pain score for low back pain; subjects will be asked every evening to rate

their overall low back pain for the last 24-hour period

Other efficacy endpoints: *

5. Patient Global Impression of Change (PGIC) responder (yes/no) at Week 14, where a responder is defined as either *much improved* or *very much improved* *

6. Change from Baseline (Week 2) to Week 14 on the Oswestry Disability Index *

7. Change from Baseline (Week 2) to Week 14 in the weekly average of the daily sleep score; subjects will be asked every morning to rate on the 11-point Sleep Numerical Rating Scale (S-NRS) how leg pain interfered with their sleep quality

8. Change from Baseline (Week 2) to Week 14 in the Brief Pain Inventory (BPI)-Interference index *

9. Change from Baseline (Week 2) to Week 14 in the BPI-Pain index

10. Change from Baseline (Week 2) to Week 14 on the EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L) health index

11. Change from Baseline (Week 2) to Week 14 in the Short Form 36 Questionnaire (SF-36) *

12. Amount of rescue medication used (dosage/day) Another secondary objective is to investigate the safety and tolerability of 2 dose regimens of BIIB074.

The endpoints that relate to this objective are as follows: AEs and SAEs, Vital signs, ECG parameters, Laboratory safety tests, * Columbia-Suicide Severity Rating Scale (C-SSRS). Another secondary objective is to characterize the PK of BIIB074 in this population.

Study description

Background summary

Pain from lumbosacral radiculopathy (PLSR) is a condition that arises from the compression of the nerve roots due to degenerative changes in the lumbosacral spine. These changes include prolapsed/bulging intervertebral discs, thickening of facet joints, or osteophytes and stenosis of the spinal canal or exit foramina, all of which can impinge on the nerve roots. There can also be associated inflammation around the nerve roots at the sites of compression. The L4, L5, and S1 nerve roots are most commonly affected as a result of spondylotic changes in the lumbar spine at the L3/L4, L4/L5, and L5/S1 levels.

Currently, there are no medications that have been approved for the treatment of PLSR. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of the initial treatment for PLSR. Physical therapy may provide relief, and transforaminal nerve blocks or decompressive surgical interventions are more invasive treatment options. Epidural steroid injections are commonly used, although there are few well-designed efficacy studies and available data on their effectiveness in treating PLSR are inconsistent. Muscle-relaxant drugs are not first-line agents. No studies have documented that these medications change the natural history of the disease. Pharmacotherapy with tricyclic antidepressants, anticonvulsants, or opiates is commonly used, but these are not specifically indicated for this condition. Thus, PLSR represents an area of high unmet medical need with no pharmacological treatments currently indicated for this type of neuropathic pain.

Nonclinical and clinical studies show that BIIB074 is broadly efficacious in chronic pain models of inflammatory and neuropathic origin and may have potential utility in treating PLSR with a potentially better tolerability profile than currently available treatments. Based on all available (non)clinical data of BIIB074, the overall safety supports the proposed Phase 2 clinical study.

This study is being conducted to support the continued development of BIIB074 in PLSR.

Study objective

The primary objective of the study is to evaluate the efficacy of 2 dose regimens of BIIB074 on neuropathic pain in subjects with PLSR.

A secondary objective is to evaluate the efficacy of 2 dose regimens of BIIB074 on additional neuropathic pain measures and assessments of low back pain, disability, and quality of life.

Study design

Multicenter, double-blind, randomized, placebo-controlled, parallel-group study.

Approximately 630 subjects will be enrolled to achieve 399 randomized subjects. Following Screening, subjects who meet eligibility criteria will enter a 2-week, single-blind, placebo run-in period. During the first week of the single-blind, placebo run-in period, subjects will be required to undergo a washout of prohibited medications, including all medications used for neuropathic pain. The weekly average of the PI-NRS collected on the 7 days prior to randomization (nominal Days 8 to 14, with randomization on Day 15) will be defined as the baseline. Subjects with at least moderate neuropathic pain intensity (weekly average baseline neuropathic pain score: *4 and *9) will be eligible to continue into the double-blind treatment period. On Day 15, approximately 399 eligible subjects from approximately 65 sites globally will be randomized in a 1:1:1 ratio to receive BIIB074 at 350 mg BID, BIIB074 at 200 mg BID, or matched placebo. An interim analysis may potentially increase sample size to 504 subjects. Double-blind treatment will continue for 12 weeks (Weeks 2 to 14, Days 15 to 99). Subjects will record their daily pain scores (both neuropathic and low back pain components) in the electronic diary using the PI-NRS. Subjects will attend a Follow Up Visit approximately 1 week after the last dose of study treatment.

Intervention

On Day 15, eligible subjects will be randomized in a 1:1:1 ratio to receive BIIB074 at 350 mg BID, BIIB074 at 200 mg BID, or matched placebo. Double-blind treatment will continue for 12 weeks (Weeks 2 to 14, Days 15 to 99).

Eligible subjects will report to the study site to receive study treatment every 2 to 4 weeks for 12 weeks. Study treatment will be administered orally, BID, in the morning and evening (~12 ± 1 hours apart) and may be taken without regard to meals. Subjects will take a tablet from Bottle A and a tablet from Bottle B in the morning and then do the same again in the evening. For clinic visits, subjects should not take their morning dose at home, but instead study staff will administer study treatment at the clinic in the morning from the new kit (except Day 99, on which treatment will be administered from the old kit). Sites will then dispense study treatment to be self-administered at home until the next visit. Study treatment is dispensed to subjects during their clinic visits at Week 0, Day 1; Week 2, Day 15; Week 4, Day 29; Week 6, Day 43; and Week 10, Day 71.

Eligible subjects may continue into the extension study, Study 1014802-204.

Study burden and risks

Possible side effects of the study medicine are listed below:
Very Common (at least 1 in 10 people have had this side effect in clinical studies):
* dizziness
* headache
Common (less than 1 in 10 people have had this side effect in clinical studies):
* somnolence (sleepiness)
* nausea
* abnormal dreams
* blurred vision
It is not known if treatment with BIIB074 may reduce liver function. Abnormal results from liver function tests have been reported in clinical trials of BIIB074. It is not known if BIIB074 affects human fertility or the unborn baby. At present, we do not know if BIIB074 increases the risk of developing cancer in humans. BIIB074 inhibits specific proteins that prevent the buildup of serotonin. Too much serotonin causes symptoms that can range from mild to severe and can be deadly if not treated. Symptoms may include: anxiety, agitation, delirium, sweating, shivering, vomiting, diarrhea, or tremor. The study medicine may interfere with serotonine-enhancing agents and opiates. There are other medicines that may interfere with the study medicine.

Blood will be drawn during the study. Possible side effects of having blood drawn are tenderness, pain, bruising, bleeding and/or infection where the needle goes into the skin and blood vein. Having blood drawn may also cause nausea and/or lightheadedness.

ECG: Occasionally there may be some minor skin irritation from the electrodes.

A subject should not expect any direct benefit from taking part in this study, and leg and back pain may stay the same, improve, or worsen, however the information obtained from this study may help treat future patients with leg and lower back pain and will provide important information about how well people respond to BIIB074.

Contacts

Public
Biogen Idec Research Limited

Innovation House, 70 Norden Road N/A
Maidenhead SL6 4AY
GB
Scientific
Biogen Idec Research Limited

Innovation House, 70 Norden Road N/A
Maidenhead SL6 4AY
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening or at the timepoint specified in the individual eligibility criterion listed:;1. Is able to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.;2. Is aged 18 to 75 years, inclusive, at the time of informed consent.;3. All women of childbearing potential and all men must practice effective contraception during the study and for 5 weeks for women and 14 weeks for men, after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.;4. Has body weight *50 kg for men and *45 kg for women.;5. Must have diagnosis of neuropathic PLSR with ALL of the following characteristics:;a. Pain perceived in 1 or both legs at areas consistent with the area innervated by the L4, L5, or S1 nerve roots.;b. Evidence of asymmetrical sensory symptoms (hypoesthesia, hyperesthesia, or;allodynia) in the affected areas (typically, the pain may be perceived in the buttock, thigh, calf, foot, or toes).;c. History of pain suggestive that the cause of PLSR is due to injury of the lumbosacral nerve root(s) by degenerative disease of the vertebrae in the lumbosacral spine or associated soft tissues including the intervertebral discs, or secondary to spinal injury and not due to infection/abscess, hematoma, or malignancy.;d. Pain in the legs must be more severe than pain in the back and must be asymmetrical.;6. Has computed tomography (CT) or magnetic resonance imaging (MRI) available that does not show evidence of exclusionary pathology (see exclusion criteria); if not available or has not been conducted within 12 months prior to Screening, MRI must be conducted at Screening. CT is acceptable for subjects with contra-indications for MRI (e.g. metallic implants).;7. Has duration of neuropathic (leg) pain of at least 6 months before Screening.;8. Has stable intensity of neuropathic (leg) pain, with fairly continual pain (but

may be worse during rest or at night) for the 4 weeks prior to Screening, based on clinical history.;9. Has an intensity of *4 and *9 on the Numerical Rating Scale based on a paper-based question at Screening and on Day 1 that asks for the average pain intensity of neuropathic (leg) pain due to PLSR over the last week;10. If taking approved concomitant pain medications (i.e., NSAIDs), must be on a stable regimen for at least 4 weeks before Day 1.;Inclusion Criteria: Randomization;To be eligible to be randomized in this study, candidates must meet the following eligibility criteria at the Randomization Visit (Day 15, Week 2):;1. Continues to meet inclusion criteria (above).;2. Has a baseline weekly average daily pain score for neuropathic pain (leg pain) due to PLSR *4 and *9 on the electronic diary PI-NRS; baseline is defined as the 7 days prior to randomization (nominal Days 8 to 14, with randomization on Day 15).;3. Completed washout of concomitant pain medications except NSAIDs (see Section 7).

Exclusion criteria

Diagnosis
1. Is unable to reliably delineate or assess his or her neuropathic pain by anatomical location/distribution.
2. Has pain of a different type in the legs (e.g. due to arthritis) that may interfere with the assessment of neuropathic pain in the legs.
3. Has lumbar canal stenosis in which the pain occurs solely on walking and not at rest.
4. Has a lumbar CT scan or MRI demonstrating Grade 2 or higher spondylolisthesis, unstable structural lesion of the spine, or moderate or severe lumbar stenosis, or any other structural lesion not consistent with a diagnosis of PLSR (for example, tumor, abscess, syringomyelia)
5. Has planned surgical intervention for PLSR within the duration of the study. (Subjects with persistent radicular pain after prior surgery are eligible.);Medical History
1. Is pregnant or lactating (female subjects only).
2. Male subject whose partner is pregnant.
3. Has a history of suicide attempt within 6 months before Screening.
4. Has a history of any liver disease within the last 6 months, with the exception of known Gilbert*s disease.
5. Received nerve blocks and/or steroid injections for neuropathic pain within 3 months before Day 1.
6. Has a history of peripheral neuropathy (e.g., due to diabetes, alcohol consumption, other causes, or idiopathic) or evidence of peripheral neuropathy upon neurological examination.
7. Has a history of alcohol or substance abuse (as determined by the Investigator) or a positive drug/alcohol test at Screening or Day 1.
8. Has a history or risk of seizures or a history of epilepsy, clinically significant head injury, or related neurological disorders.
9. Currently has a history of uncontrolled or poorly controlled hypertension.
10. Has a history or presence of significant cardiovascular, gastrointestinal, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs.

11. Has a history or presence of any clinically significant abnormality in vital signs, ECG, or laboratory tests or has any medical or psychiatric condition that, in the opinion of the Investigator, may interfere with the study procedures or compromise subject safety.
12. Has had an episode of major depression within 6 months before Screening.;Screening Vitals and Laboratory Procedures
13. Has BP *160 mmHg systolic and/or *100 mmHg diastolic at Screening after repeated measurements.
14. Has a QT interval corrected using Fridericia*s formula (QTcF) *450 msec (males) or *470 msec (females) [average of 3 measurements at least 5 minutes apart and done within 15 minutes] at Screening.
15. Has a positive pregnancy test at Screening (women of childbearing potential only).
16. Has AST or ALT *2 × the upper limit of normal (ULN) or has alkaline phosphatase or bilirubin *1.5 × ULN at Screening.
17. Has a history or a positive test result at Screening for human immunodeficiency virus.
18. Has a history or a positive test result at Screening for hepatitis C virus antibody or hepatitis B virus [defined as positive for hepatitis B surface antigen or hepatitis B core antibody].
19. Has a positive drug screen for drugs of abuse at Screening (amphetamine, barbiturates, benzodiazepines, cocaine, opiates, tetrahydrocannabinol) except if explained by use of allowed prescription medicines).;Other Screening Assessments
20. Has a positive response on Item 4 or 5 on the C-SSRS at Screening.;Concomitant Medications
21. Unable to discontinue prior to Day 1 any prohibited concomitant monoamine oxidase inhibitors (MAOIs), potent CYP3A4 inducers or inhibitors, potent UGT inducers or inhibitors, including over the counter preparations, herbal remedies, vitamin, mineral supplements, food or drinks as detailed in 11.5.1.2.;General
22. Is mentally or legally incapacitated.
23. Is receiving or seeking full-time long-term disability insurance payments or government benefits related to his or her PLSR, or is in litigation about insurance issues related to his or her PLSR
24. Is unable to comply with the restrictions related to prohibited concomitant therapy restrictions (see Section 11.5).
25. Has previously participated in a clinical study with BIIB074.
26. Previous registration in this study.
27. Has participated in an interventional study and received study treatment within 3 months before Screening.
28. Is currently enrolled or plans to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 5 half-lives plus 30 days for women or 5 half-lives plus 90 days for men prior to Day 1.
29. Has been exposed to more than 4 new chemical entities within 12 months before the first dosing day of the single-blind, placebo run-in period.
30. Has donated blood or blood products within a 30-day period prior to Screening.
31. Is unable to comply with study requirements.
32. Other unspecified reasons that, in the opinion of the Investigator or spnsor, make the subject unsuitable for enrollment.;Exclusion Criteria: Randomization
Candidates will be excluded from randomization in this study if any of the following exclusion

criterion exist at the Randomization Visit (Day 15, Week 2):
1. Has missed more than 2 of 7 daily neuropathic pain score entries during the last 7 days of treatment prior to randomization.
2. Has a daily neuropathic pain score of *2 on 1 or more days during the last 7 days of treatment prior to randomization.
3. Has a difference between the lowest and highest daily neuropathic pain score of *4 during the last 7 days of treatment prior to randomization.
4. Has less than 80% or more than 120% study treatment compliance during the singleblind, placebo run-in period of the study, as assessed by tablet count.
5. Has used paracetamol/acetaminophen at a daily dose of equal to or more than 2.5g/day on 5 or more days during 7 consecutive days in the run in phase.
6. Has met any of the exclusion criteria during the period between Screening and Randomization.

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):	24-08-2017
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not yet determined
Generic name:	Raxatrigine (proposed)

Ethics review

Approved WMO Date:	01-06-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2015-004775-78-NL
CCMO	NL56026.091.16