Clinical trial results:
An Uncontrolled, Open-Label Extension Study to Evaluate the Long-Term Safety, Tolerability, and Maintenance of Effect of BIIB074 (Vixotrigine) in Subjects With Neuropathic Pain From Lumbosacral Radiculopathy

Summary

EudraCT number	2015-004796-68
Trial protocol	LV GB SK AT ES CZ BG BE NL IT
Global end of trial date	07 February 2019

Results information

Result version number	v1 (current)
This version publication date	19 February 2020
First version publication date	19 February 2020

Trial information

Trial identification

Sponsor protocol code	1014802-204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02957617
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, +1 866-633-4636, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, +1 866-633-4636, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the long-term safety and tolerability of BIIB074 in subjects with neuropathic Pain From Lumbosacral Radiculopathy (PLSR). A secondary objective is to investigate the maintenance of effect during long-term treatment with BIIB074 in subjects with neuropathic PLSR. For all efficacy assessments, baseline will be prior to randomisation into Study 1014802-203. Another secondary objective is to evaluate the impact of treatment with BIIB074 on quality of life (QoL).

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorized representative were given adequate time to review the information in the informed consent/assent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 82
Country: Number of subjects enrolled	Czech Republic: 63
Country: Number of subjects enrolled	Serbia: 45
Country: Number of subjects enrolled	Georgia: 29
Country: Number of subjects enrolled	Slovakia: 29
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	302
EEA total number of subjects	228

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	256
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 50 investigative sites in 13 countries in Eastern and Western Europe from 10 February 2017 to 07 February 2019.

Pre-assignment

Screening details:

Qualified subjects who participated in study 1014802-203 (203) were enrolled in this open-label extension study 1014802-204 (204). One subject who did not receive Study 203 randomised treatment was dosed in Study 204.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BIIB074 (203:Not Dosed Cohort)

Arm description:

BIIB074 (vixotrigine) 350 mg orally twice daily (BID), which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort includes subjects who were not dosed in Study 203.)

Arm type	Experimental
Investigational medicinal product name	BIIB074
Investigational medicinal product code	
Other name	CNV1014802, GSK1014802, vixotrigine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

BIIB074 tablets, orally, twice daily (BID) for up to 12 months.

Arm title	BIIB074 (203:Placebo Cohort)

Arm description:

BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort includes subjects who received Placebo for up to 12 weeks in Study 203.)

Arm type	Experimental
Investigational medicinal product name	BIIB074
Investigational medicinal product code	
Other name	CNV1014802, GSK1014802, vixotrigine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

BIIB074 tablets, orally, BID for up to 12 months.

Arm title	BIIB074 (203:BIIB074 200 mg Cohort)

Arm description:

BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort includes subjects who received BIIB074 200 mg for up to 12 weeks in Study 203.)

Arm type	Experimental

Investigational medicinal product name	BIIB074
Investigational medicinal product code	
Other name	CNV1014802, GSK1014802, vixotrigine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

BIIB074 tablets, orally ,BID for up to 12 months.

Arm title	BIIB074 (203:BIIB074 350 mg Cohort)

Arm description:

BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort includes subjects who received BIIB074 350 mg for up to 12 weeks in Study 203.)

Arm type	Experimental
Investigational medicinal product name	BIIB074
Investigational medicinal product code	
Other name	CNV1014802, GSK1014802, vixotrigine
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

BIIB074 tablets, orally, BID for up to 12 months.

Number of subjects in period 1	BIIB074 (203:Not Dosed Cohort)	BIIB074 (203:Placebo	BIIB074 (203:BIIB074 200 mg Cohort)
Started	1	104	98
Completed	0	46	43
Not completed	1	58	55
Consent withdrawn by subject	1	7	7
Adverse event	-	5	8
Investigator decision	-	-	1
other	-	38	34
Lost to follow-up	-	-	1
Lack of efficacy	-	8	4

Number of subjects in period 1	BIIB074 (203:BIIB074 350 mg Cohort)
Started	99
Completed	44
Not completed	55
Consent withdrawn by subject	5
Adverse event	2
Investigator decision	-
other	34
Lost to follow-up	-
Lack of efficacy	14

Baseline characteristics

Reporting groups	
Reporting group title	BIIB074 (203:Not Dosed Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally twice daily (BID), which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who were not dosed in Study 203.)	
Reporting group title	BIIB074 (203:Placebo Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who received Placebo for up to 12 weeks in Study 203.)	
Reporting group title	BIIB074 (203:BIIB074 200 mg Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who received BIIB074 200 mg for up to 12 weeks in Study 203.)	
Reporting group title	BIIB074 (203:BIIB074 350 mg Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who received BIIB074 350 mg for up to 12 weeks in Study 203.)	

Reporting group values	BIIB074 (203:Not Dosed Cohort)	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg Cohort)
Number of subjects	1	104	98
Age Categorical Units: Subjects			
18 to 35 years	0	5	5
36 to 50 years	1	39	28
51 to 70 years	0	54	65
>70 years	0	6	0
Age Continuous			
99999 indicates that standard deviation is not calculated for 1 subject.			
Units: years			
arithmetic mean	36	53.1	53.3
standard deviation	± 99999	± 11.00	± 9.81
Gender Categorical Units: Subjects			
Female	0	66	70
Male	1	38	28

Reporting group values	BIIB074 (203:BIIB074 350 mg Cohort)	Total	
Number of subjects	99	302	
Age Categorical Units: Subjects			
18 to 35 years	3	13	
36 to 50 years	37	105	
51 to 70 years	56	175	

>70 years	3	9	

Age Continuous			
99999 indicates that standard deviation is not calculated for 1 subject.			
Units: years			
arithmetic mean	53.3		
standard deviation	± 9.16	-	
Gender Categorical			
Units: Subjects			
Female	62	198	
Male	37	104	

End points

End points reporting groups

Reporting group title	BIIB074 (203:Not Dosed Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally twice daily (BID), which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who were not dosed in Study 203.)	
Reporting group title	BIIB074 (203:Placebo Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who received Placebo for up to 12 weeks in Study 203.)	
Reporting group title	BIIB074 (203:BIIB074 200 mg Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who received BIIB074 200 mg for up to 12 weeks in Study 203.)	
Reporting group title	BIIB074 (203:BIIB074 350 mg Cohort)
Reporting group description:	
BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204. (Cohort includes subjects who received BIIB074 350 mg for up to 12 weeks in Study 203.)	

Primary: Number of Subjects Experiencing Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects Experiencing Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]
End point description:	
An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product; it does not necessarily have to have a causal relationship with this treatment. An AE could therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. A SAE is any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, is a congenital anomaly / birth defect or is medically important due to other reasons than the above mentioned criteria. Safety Population included all subjects who received at least 1 dose of study treatment in this open-label extension study.	
End point type	Primary
End point timeframe:	
Up to 398 Days in Study 204	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Not Dosed Cohort)	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	104	98	99
Units: subjects				
number (not applicable)				
AEs	0	48	45	41

SAEs	0	4	1	4

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in the Weekly Average of the Daily Neuropathic Pain Score on the Pain Intensity Numerical Rating Scale (PI-NRS)

End point title	Change from Baseline to Week 52 in the Weekly Average of the Daily Neuropathic Pain Score on the Pain Intensity Numerical Rating Scale (PI-NRS)[2]

End point description:

Subjects were asked every evening to rate their overall neuropathic pain in the worse affected leg (identified on Day 1 of Study 203) for the last 24-hour period. PI-NRS is an 11-point pain intensity numerical rating scale (PI-NRS), where 0=no pain and 10=pain as bad as you can imagine. A negative change from Baseline indicates improvement. The efficacy population included all subjects who received at least 1 dose of study treatment in this extension Study 204, and who were randomised and received at least 1 dose of study treatment in the double-blind period in Study 203. Number of subjects analysed is the number of subjects with evaluable data at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline (1-week prior to randomisation in Study 203) to Week 52 in Study 204

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	48	47	
Units: score on a scale				
arithmetic mean (standard deviation)	-3.50 (± 2.644)	-3.31 (± 2.292)	-3.28 (± 2.404)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with 50% Neuropathic Pain Reduction Response

End point title	Number of Subjects with 50% Neuropathic Pain Reduction Response[3]

End point description:

Response is defined as a ≥50% reduction in the weekly average of the daily neuropathic pain score from Baseline to Week 52. The efficacy population included all subjects who received at least 1 dose of study treatment in this extension Study 204, and who were randomised and received at least 1 dose of study treatment in the double-blind period in Study 203. Number of subjects analysed is the number of subjects with evaluable data at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline (1-week prior to randomisation in 203) to Week 52 in Study 204

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	64	65	
Units: subjects				
number (not applicable)	34	28	25	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with 30% Neuropathic Pain Reduction Response

End point title	Number of Subjects with 30% Neuropathic Pain Reduction Response[4]

End point description:

Response is defined as a ≥30% reduction in the weekly average of the daily neuropathic pain score from Baseline to Week 52. The efficacy population included all subjects who received at least 1 dose of study treatment in this extension Study 204, and who were randomised and received at least 1 dose of study treatment in the double-blind period in Study 203. Number of subjects analysed is the number of subjects with evaluable data at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline (1-week prior to randomisation in 203) to Week 52 in Study 204

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	64	65	
Units: subjects				
number (not applicable)	36	34	32	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Each Visit in the Weekly Average of the Daily Neuropathic Pain Score

End point title	Change from Baseline at Each Visit in the Weekly Average of the Daily Neuropathic Pain Score[5]

End point description:

Subjects were asked every evening to rate their overall neuropathic pain for the last 24-hour period using the 11-point PI-NRS, where 0=no pain and 10=pain as bad as you can imagine A negative change from Baseline indicates improvement. The efficacy population included all subjects who received at least 1 dose of study treatment in this extension Study 204, and who were randomised and received at least 1 dose of study treatment in the double-blind period in Study 203. Number of subjects analysed is the number of subjects with evaluable data at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline (1-week period prior to randomisation in 203) through Weeks 2, 4, 13, 26, 39 of Study 204

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	98	99	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 2 (n=99,96,95)	-2.03 (± 2.085)	-1.79 (± 1.841)	-2.07 (± 2.003)	
Week 4 (n=98,94,94)	-2.40 (± 2.077)	-2.06 (± 1.846)	-2.26 (± 1.978)	
Week 13 (n=94,88,84)	-2.80 (± 2.127)	-2.46 (± 1.973)	-2.69 (± 1.881)	
Week 26 (n=89,87,80)	-3.13 (± 2.139)	-2.82 (± 2.113)	-3.09 (± 2.115)	
Week 39 (n=64,58,61)	-3.05 (± 2.437)	-3.21 (± 1.967)	-3.19 (± 2.202)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in the Weekly Average of the Daily Pain Score for Low Back Pain

End point title	Change from Baseline to Week 52 in the Weekly Average of the Daily Pain Score for Low Back Pain[6]

End point description:

Subjects were asked every evening to rate their overall low back pain for the last 24-hour period using the 11-point PI-NRS, where 0=no pain and 10= pain as bad as you can imagine. A negative change from Baseline indicates improvement. The efficacy population included all subjects who received at least 1 dose of study treatment in this extension Study 204, and who were randomised and received at least 1 dose of study treatment in the double-blind period in Study 203. Number of subjects analysed is the number of subjects with evaluable data at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline (1-week prior to randomisation in Study 203) to Week 52 of Study 204

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	48	47	
Units: score on a scale				
arithmetic mean (standard deviation)	-1.93 (± 2.308)	-2.12 (± 2.027)	-1.88 (± 2.350)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patient Global Impression of Change (PGIC) Responders

End point title	Number of Patient Global Impression of Change (PGIC) Responders[7]

End point description:

PGIC is a 7-point self-report scale depicting a subject's rating of overall improvement. Subjects rated their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." A responder is defined as a subject with a response of "very much improved" or "much improved". The efficacy population included all subjects who received at least 1 dose of study treatment in this extension Study 204, and who were randomised and received at least 1 dose of study treatment in the double-blind period in Study 203. Number of subjects analysed is the number of subjects with evaluable data at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline (Day 1 of Study 203) to Week 52 of Study 204

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	64	65	
Units: subjects				
number (not applicable)	34	27	31	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 on the Oswestry Disability Index (ODI)

End point title	Change from Baseline to Week 52 on the Oswestry Disability Index (ODI)[8]

End point description:

The ODI is a 10-item questionnaire that evaluates how back (or leg) pain affects the ability to manage in everyday life: Pain intensity, Personal care, Lifting, Walking, Sitting, Standing, Sleeping, Sex life, Social life and Traveling. Each question is rated on a 6-point scale: 0(best) to 5(worst); with higher scores indicating higher level of pain for a total possible score of 0 to 50.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[9]	0[10]	0[11]	
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[9] - Study was terminated; only Key Secondary endpoints were analysed.

[10] - Study was terminated; only Key Secondary endpoints were analysed.

[11] - Study was terminated; only Key Secondary endpoints were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in the Weekly Average of the Daily Sleep Score as Assessed by the Sleep Numerical Rating Scale (S-NRS)

End point title	Change from Baseline to Week 52 in the Weekly Average of the Daily Sleep Score as Assessed by the Sleep Numerical Rating Scale (S-NRS)[12]

End point description:

Subjects were asked every morning to rate on the 11-point S-NRS how leg pain interfered with their sleep quality where 0=did not interfere with sleep and 10=pain completely interfered with sleep.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[13]	0[14]	0[15]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[13] - Study was terminated; only Key Secondary endpoints were analysed.

[14] - Study was terminated; only Key Secondary endpoints were analysed.

[15] - Study was terminated; only Key Secondary endpoints were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in the Brief Pain Inventory (BPI)-Interference Index

End point title	Change from Baseline to Week 52 in the Brief Pain Inventory (BPI)-Interference Index[16]

End point description:

BPI Interference Index is an 11-point numeric rating scale (0 - no interference to 10 - interferes completely) to assess pain-related interference in 7 areas: general activity, mood, walking ability, normal work, including outside the home and housework, relations with other people, enjoyment of life and sleep.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[17] - Study was terminated; only Key Secondary endpoints were analysed.

[18] - Study was terminated; only Key Secondary endpoints were analysed.

[19] - Study was terminated; only Key Secondary endpoints were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in the BPI - Pain Index

End point title	Change from Baseline to Week 52 in the BPI - Pain Index[20]

End point description:

BPI- Pain Index for pain intensity, is used to assess potential pain quality descriptors that may describe subjects' pain on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[21]	0[22]	0[23]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[21] - Study was terminated; only Key Secondary endpoints were analysed.

[22] - Study was terminated; only Key Secondary endpoints were analysed.

[23] - Study was terminated; only Key Secondary endpoints were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 on the EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L) Health Index

End point title	Change from Baseline to Week 52 on the EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L) Health Index[24]

End point description:

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. It is a health questionnaire that consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels (possible responses): no problems, slight problems, moderate problems, severe problems and extreme problems.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[25]	0[26]	0[27]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[25] - Study was terminated; only Key Secondary endpoints were analysed.

[26] - Study was terminated; only Key Secondary endpoints were analysed.

[27] - Study was terminated; only Key Secondary endpoints were analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Short Form 36 Questionnaire (SF-36)

End point title	Change from Baseline to Week 52 in Short Form 36 Questionnaire (SF-36)[28]

End point description:

SF-36 is a self-administered, generic health status questionnaire consisting of 36 questions that measure 8 health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health. Each of the 8 health concepts has a total possible score of 0-100.

End point type	Secondary

End point timeframe:

Baseline to Week 52

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not all arms in the Baseline Period are applicable for this endpoint.

End point values	BIIB074 (203:Placebo Cohort)	BIIB074 (203:BIIB074 200 mg	BIIB074 (203:BIIB074 350 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[29]	0[30]	0[31]	
Units: units on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[29] - Study was terminated; only Key Secondary endpoints were analysed

[30] - Study was terminated; only Key Secondary endpoints were analysed

[31] - Study was terminated; only Key Secondary endpoints were analysed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 398 Days in Study 204

Adverse event reporting additional description:

Safety Population included all subjects who received at least 1 dose of study treatment in this open-label extension study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	BIIB074 (203:Not Dosed Cohort)

Reporting group description:

BIIB074 (vixotrigine) 350 mg orally twice daily (BID), which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort includes subjects who were not dosed in Study 203.)

Reporting group title	BIIB074 (203:Placebo Cohort)

Reporting group description:

BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort includes subjects who received Placebo for up to 12 weeks in Study 203.)

Reporting group title	BIIB074 (203:BIIB074 200 mg Cohort)

Reporting group description:

BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort includes subjects who received BIIB074 200 mg for up to 12 weeks in Study 203.)

Reporting group title	BIIB074 (203:BIIB074 350 mg Cohort)

Reporting group description:

BIIB074 (vixotrigine) 350 mg orally BID, which could be reduced to 200 mg based on tolerability for up to 12 months in Study 204.
(Cohort incudes subjects who received BIIB074 350 mg for up to 12 weeks in Study 203.)

Serious adverse events	BIIB074 (203:Not Dosed Cohort)	BIIB074 (203:Placebo	BIIB074 (203:BIIB074 200 mg Cohort)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	4 / 104 (3.85%)	1 / 98 (1.02%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 1 (0.00%)	1 / 104 (0.96%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer recurrent			

subjects affected / exposed	0 / 1 (0.00%)	0 / 104 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 1 (0.00%)	0 / 104 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 104 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 1 (0.00%)	1 / 104 (0.96%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 104 (0.96%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1 (0.00%)	1 / 104 (0.96%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 104 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			

subjects affected / exposed	0 / 1 (0.00%)	0 / 104 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BIIB074 (203:BIIB074 350 mg Cohort)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 99 (4.04%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer recurrent			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbosacral radiculopathy			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			

subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal osteoarthritis			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BIIB074 (203:Not Dosed Cohort)	BIIB074 (203:Placebo	BIIB074 (203:BIIB074 200 mg Cohort)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	17 / 104 (16.35%)	18 / 98 (18.37%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	7 / 104 (6.73%)	5 / 98 (5.10%)
occurrences (all)	0	8	5
Headache			
subjects affected / exposed	0 / 1 (0.00%)	8 / 104 (7.69%)	5 / 98 (5.10%)
occurrences (all)	0	11	6
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	2 / 104 (1.92%)	5 / 98 (5.10%)
occurrences (all)	0	2	6
Nausea			

subjects affected / exposed	0 / 1 (0.00%)	6 / 104 (5.77%)	4 / 98 (4.08%)
occurrences (all)	0	7	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)	3 / 104 (2.88%)	1 / 98 (1.02%)
occurrences (all)	0	6	1

Non-serious adverse events	BIIB074 (203:BIIB074 350 mg Cohort)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 99 (14.14%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 99 (4.04%)		
occurrences (all)	8		
Headache			
subjects affected / exposed	4 / 99 (4.04%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 99 (2.02%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	7 / 99 (7.07%)		
occurrences (all)	11		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 99 (5.05%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2016	Amendment 1 Version 2: • Clarification was added to clinic procedures and laboratory tests for safety assessments, eligibility criteria, prohibited medications, adverse event reporting, and treatment compliance, and to the timing of interim sample size re-estimation. • Information on serotonin syndrome was added, as requested by the FDA.
14 July 2016	Amendment 2 Version 3: •The maximum dose of paracetamol/acetaminophen in prolonged therapy was reduced to 2.5 g/day, and a restriction to the duration of prolonged therapy was added along with a related discontinuation criterion. •The number of contraceptives to be used for highly effective contraception was reduced from 2 to 1 (thereafter stated as "effective contraception"). •Additional follow-up phone call was added to assess safety (SAEs) and C-SSRS. •Updates to liver chemistry stopping criteria were made. •Information on the symptoms of serotenergic syndrome was included. •Guidance text related to inclusion criteria associated with QTc and C-SSRS was added. •Ethinyl estradiol as a prohibited medication was added. •Clarification around eligibility of male subjects whose partners are pregnant and the need for males to withdraw if their partner becomes pregnant during the study was added. •Changes to the withdrawal criteria and inclusion and exclusion criteria were made to consolidate the protocol across different countries.
05 May 2017	Amendment 3 Version 4: This amendment superseded Version 3 and was implemented to update the nonclinical experience. Specifically, further detail around metabolites and the in vivo safety pharmacology study findings were added to reflect updated data from toxicology studies as well as updated exposure and exposure margin calculations, which are based on current industry-accepted practices. Other major changes involved: •Adding assessments for unscheduled visits. •Updated text related to the dose regimen rationale to describe the probability of human exposure exceeding the exposure at which seizure was observed in 1 dog following administration of a 35 mg/kg BID dose. •Clarified text related disallowed concomitant therapy.
24 May 2017	Amendment 4 Version 5: This amendment superseded Version 4 and was implemented primarily to clarify that pregnancy of a female partner should not impact the study status of a male subject during his participation in the study.
17 October 2017	Amendment 5 Version 6: This amendment was not implemented. The primary reason for the amendment was to extend the duration of the study to 24 months from 12 months in order to collect more longitudinal data.

07 June 2018	Amendment 6 Version 7: This amendment superseded Version 5 and was implemented primarily to permit the concomitant use of inhibitors or inducers of cytochrome 3A4 (CYP3A4). Other major changes involved: •Adjustments to the order of safety assessments. •Updates to the nonclinical information related to toxicology. •Updates to the clinical information related to exposure, PK and safety data, including new SAEs. •Addition of a benefit/risk statement. •Removal of vital signs, ECG parameters, laboratory safety tests, and C-SSRS from the primary endpoint. •Changes to procedure or follow-up when a subject discontinues study treatment due to a rash. •Addition of text to describe how abuse potential will be assessed during the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 January 2019	The study was terminated. The parent study did not meet its primary or secondary efficacy endpoints; therefore, Sponsor decision to discontinue development in this indication. 09 January 2019 was selected as the last possible dosing date.	-

Notes:

Limitations and caveats

None reported