Clinical trial results:
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

Summary

EudraCT number	2017-000991-27
Trial protocol	GB CZ GR HU ES DK BG NL IT
Global end of trial date	12 April 2021

Results information

Result version number	v1 (current)
This version publication date	25 April 2022
First version publication date	25 April 2022

Trial information

Trial identification

Sponsor protocol code	802NP206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03339336
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, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, 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	12 April 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of BIIB074 in treating pain experienced by subjects with confirmed small fibre neuropathy (SFN) that was idiopathic or associated with diabetes mellitus. The secondary objectives were: (i) 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; (ii) to investigate the safety and tolerability of BIIB074 in subjects with SFN; and (iii) to characterise the pharmacokinetics (PK) of BIIB074 in subjects with SFN.

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorised representative (e.g., legal guardian), as applicable, prior to evaluations performed for eligibility. Subjects or the subject's legally authorised 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	31 May 2018
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	Poland: 46
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Czechia: 29
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Denmark: 3
Worldwide total number of subjects	265
EEA total number of subjects	231

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)	184
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 68 investigative sites in Poland, France, Czech Republic, United Kingdom, Netherlands, Bulgaria, Germany, Hungary, Italy, Spain, Canada, Switzerland, and Denmark from 31 May 2018 to 08 March 2021.

Pre-assignment

Screening details:

The study consisted of screening period of up to 21 days, taper period of up to 14 days, 5-day washout period, and 4-week open-label (OL) run-in period. Number of subjects who completed OL run-in period is number of subjects who completed OL run-in period and were randomised to DB period.

Period 1

Period 1 title	Open-Label (OL) Run-in Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	OL Period: BIIB074 350 milligrams (mg)

Arm description:

Subjects received BIIB074 350 mg, tablets, orally, twice daily (BID), for 4 weeks of the open-label run-in period.

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

Dosage and administration details:

BIIB074 350 mg administered orally, BID for 4 weeks of the open-label run-in period.

Number of subjects in period 1	OL Period: BIIB074 350 milligrams (mg)
Started	265
Completed	123
Not completed	142
Consent withdrawn by subject	7
Adverse event	14
Lost to follow-up	1
Reason not specified	18
Lack of efficacy	11
Failed to meet randomisation criteria	91

Period 2

Period 2 title	Double-Blind (DB) Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	DB Period: Placebo

Arm description:

Subjects received BIIB074-matching placebo, tablets, orally, BID, for 12 weeks of the double-blind period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

BIIB074-matching placebo administered orally, BID, for 12 weeks of the double-blind period.

Arm title	DB Period: BIIB074 200 mg

Arm description:

Subjects received BIIB074, 200 mg, tablets, orally, BID, for 12 weeks of the double-blind period.

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

Dosage and administration details:

BIIB074 200 mg administered orally, BID for 12 weeks of the double-blind period.

Arm title	DB Period: BIIB074 350 mg

Arm description:

Subjects received BIIB074, 350 mg, tablets, orally, BID, for 12 weeks of the double-blind period.

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

Dosage and administration details:

BIIB074 350 mg administered orally, BID for 12 weeks of the double-blind period.

Number of subjects in period 2	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg
Started	41	40	42
Completed	34	35	38
Not completed	7	5	4
Consent withdrawn by subject	-	1	-
Death	1	-	-
Adverse event	2	2	-
Reason not specified	3	2	3
Failed to meet randomisation criteria	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	OL Period: BIIB074 350 milligrams (mg)
Reporting group description:	
Subjects received BIIB074 350 mg, tablets, orally, twice daily (BID), for 4 weeks of the open-label run-in period.	

Reporting group values	OL Period: BIIB074 350 milligrams (mg)	Total	
Number of subjects	265	265	
Age Categorical Units: subjects			
Age Continuous Units: years			
arithmetic mean	57.8		
standard deviation	± 11.33	-	
Gender Categorical Units: subjects			
Female	120	120	
Male	145	145	
Race Units: Subjects			
Asian	2	2	
Black or African American	2	2	
White	244	244	
Not reported due to confidentiality regulations	16	16	
Other	1	1	
Ethnicity Units: Subjects			
Hispanic or Latino	7	7	
Not Hispanic or Latino	242	242	
Not reported due to confidentiality regulations	16	16	

End points

End points reporting groups

Reporting group title	OL Period: BIIB074 350 milligrams (mg)
Reporting group description:	
Subjects received BIIB074 350 mg, tablets, orally, twice daily (BID), for 4 weeks of the open-label run-in period.	
Reporting group title	DB Period: Placebo
Reporting group description:	
Subjects received BIIB074-matching placebo, tablets, orally, BID, for 12 weeks of the double-blind period.	
Reporting group title	DB Period: BIIB074 200 mg
Reporting group description:	
Subjects received BIIB074, 200 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Reporting group title	DB Period: BIIB074 350 mg
Reporting group description:	
Subjects received BIIB074, 350 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Subject analysis set title	DB Period: Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received BIIB074-matching placebo, tablets, orally, BID, for 12 weeks of the double-blind period.	
Subject analysis set title	DB Period: BIIB074 200 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received BIIB074, 200 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Subject analysis set title	DB Period: BIIB074 350 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received BIIB074, 350 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Subject analysis set title	DB Period: Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received BIIB074-matching placebo, tablets, orally, BID, for 12 weeks of the double-blind period.	
Subject analysis set title	DB Period: BIIB074 200 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received BIIB074, 200 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Subject analysis set title	DB Period: BIIB074 350 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received BIIB074, 350 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Subject analysis set title	OL Period: BIIB074 350 mg (PK Analysis)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received BIIB074 350 mg, tablets, orally, BID, for 4 weeks of the open-label run-in period.	

Primary: Change From Baseline to Double-Blind Week 12 in Mean Average Daily Pain (ADP) Score on the 11-point Numerical Rating Scale (NRS)

End point title	Change From Baseline to Double-Blind Week 12 in Mean Average Daily Pain (ADP) Score on the 11-point Numerical Rating Scale (NRS)

End point description:

The ADP score was based on an 11-point NRS, where, 0 = no pain and 10 = worst pain imaginable. Lower scores indicated less pain. Baseline was defined as the 5 days prior to the first dose of study treatment in the open-label run-in period (Day 1). The values reported are mean values. Full analysis set (FAS) included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment. Number of subjects analysed is the number of subjects evaluable in this end point.

End point type	Primary

End point timeframe:

Baseline, DB Week 12

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	38	41	
Units: score on a scale				
least squares mean (standard error)	-3.13 (± 0.311)	-3.99 (± 0.298)	-3.30 (± 0.292)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Analysis was performed using the mixed model for repeated measures (MMRM) model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0501
Method	MMRM
Parameter estimate	Least Squares (LS) mean difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.71
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.43

Statistical analysis title	Placebo vs BIIB074 350 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6951
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.68
Variability estimate	Standard error of the mean
Dispersion value	0.426

Secondary: Change from Randomisation to Double-Blind Week 12 in Mean ADP Score on the 11-point Numerical Rating Scale (NRS)

End point title	Change from Randomisation to Double-Blind Week 12 in Mean ADP Score on the 11-point Numerical Rating Scale (NRS)

End point description:

The ADP score was based on an 11-point NRS, where, 0 = no pain and 10 = worst pain imaginable. Lower scores indicated less pain. Baseline was defined as the 5 days prior to the first dose of study treatment in the open-label run-in period (Day 1). The values reported are mean values. FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment. Number of subjects analysed is the number of subjects evaluable in this end point.

End point type	Secondary

End point timeframe:

Randomisation (Week 5), DB Week 12

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	38	41	
Units: score on a scale				
least squares mean (standard error)	0.92 (± 0.321)	0.07 (± 0.305)	0.60 (± 0.298)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0575
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.74
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.444

Statistical analysis title	Placebo vs BIIB074 350 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4708
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	0.55
Variability estimate	Standard error of the mean
Dispersion value	0.437

Secondary: Change From Baseline to Double-Blind Week 12 in Mean Worst Daily Pain (WDP) Score on the 11-point Numerical Rating Scale (NRS)

End point title	Change From Baseline to Double-Blind Week 12 in Mean Worst Daily Pain (WDP) Score on the 11-point Numerical Rating Scale (NRS)

End point description:

The WDP score is based on an 11-point NRS, where, 0 = no pain and 10 = worst pain imaginable. Lower scores indicated less pain. Baseline was defined as the 5 days prior to the first dose of study treatment

in the open-label run-in period (Day 1). The values reported are mean values. FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment. Number of subjects analysed is the number of subjects evaluable in this end point.

End point type	Secondary

End point timeframe:

Baseline, DB Week 12

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	38	41	
Units: score on a scale				
least squares mean (standard error)	-3.02 (± 0.334)	-3.95 (± 0.318)	-3.27 (± 0.311)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0455
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	-0.02
Variability estimate	Standard error of the mean
Dispersion value	0.461

Statistical analysis title	Placebo vs BIIB074 350 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5835
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.455

Secondary: Change From Baseline to Double-Blind Week 12 in Mean Sleep Interference Numerical Rating Scale (S-NRS) Score

End point title	Change From Baseline to Double-Blind Week 12 in Mean Sleep Interference Numerical Rating Scale (S-NRS) Score

End point description:

The sleep interference score (due to SFN pain) is based on an 11-point NRS, where 0 = uninterrupted night's sleep and 10 = worst sleep imaginable. Lower scores indicated less pain. Baseline was defined as the 5 days prior to the first dose of study treatment in the open-label run-in period (Day 1). The values reported are mean values. FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment. Number of subjects analysed is the number of subjects evaluable in this end point.

End point type	Secondary

End point timeframe:

Baseline, DB Week 12

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	37	38	41	
Units: score on a scale				
least squares mean (standard error)	-3.11 (± 0.303)	-3.58 (± 0.289)	-3.18 (± 0.282)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 350 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8545
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.89
upper limit	0.74
Variability estimate	Standard error of the mean
Dispersion value	0.413

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2655
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.36
Variability estimate	Standard error of the mean
Dispersion value	0.42

Secondary: Change from Baseline to Double-Blind Week 12 in Neuropathic Pain Symptom Inventory (NPSI) Total Score

End point title	Change from Baseline to Double-Blind Week 12 in Neuropathic Pain Symptom Inventory (NPSI) Total Score

End point description:

The NPSI is a self-rated questionnaire that includes 10 items corresponding to sensory descriptors (each rated on a numeric scale from 0 [no pain] to 10 [worst pain]) and 2 temporal items assessing pain duration and the number of pain paroxysms. The 10 sensory descriptor items are grouped into 5 dimensions (burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia). The total score for 10 sensory descriptor items ranges from 0 to 100. Baseline was defined as the last value prior to the first dose of study treatment in the open-label run-in period. FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment. Number of subjects analysed is the number of subjects evaluable in this end point.

End point type	Secondary
End point timeframe:	
Baseline, DB Week 12	

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	25	29	
Units: score on a scale				
least squares mean (standard error)	-22.1 (± 3.72)	-24.9 (± 3.61)	-23.4 (± 3.27)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg
Statistical analysis description:	
Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.	
Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.3
upper limit	7.6
Variability estimate	Standard error of the mean
Dispersion value	5.23

Statistical analysis title	Placebo vs BIIB074 350 mg
Statistical analysis description:	
Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.	
Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7906
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	8.5
Variability estimate	Standard error of the mean
Dispersion value	4.94

Secondary: Change from Baseline to Double-Blind Week 12 in Neuropathic Pain Symptom Inventory (NPSI) Sum Score of Symptoms of Neuropathic Pain: Burning and Pressing

End point title	Change from Baseline to Double-Blind Week 12 in Neuropathic Pain Symptom Inventory (NPSI) Sum Score of Symptoms of Neuropathic Pain: Burning and Pressing

End point description:

The NPSI is a self-rated questionnaire that includes 10 items corresponding to sensory descriptors (each rated on a numeric scale from 0 [no pain] to 10 [worst pain]) and 2 temporal items assessing pain duration and the number of pain paroxysms. The 10 sensory descriptor items are grouped into 5 dimensions (burning pain, pressing pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia). The sum score for burning and pressing ranges from 0 to 20. Baseline was defined as the last value prior to the first dose of study treatment in the open-label run-in period. FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment. Number of subjects analysed is the number of subjects evaluable in this end point.

End point type	Secondary

End point timeframe:

Baseline, DB Week 12

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	27	25	29	
Units: score on a scale				
least squares mean (standard error)	-5.08 (± 0.829)	-5.56 (± 0.802)	-5.01 (± 0.723)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6852
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	1.84
Variability estimate	Standard error of the mean
Dispersion value	1.162

Statistical analysis title	Placebo vs BIIB074 350 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9472
Method	MMRM
Parameter estimate	LS mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	2.26
Variability estimate	Standard error of the mean
Dispersion value	1.095

Secondary: Percentage of Subjects with at least a 2-Point Reduction from Baseline to Double-Blind Week 12 in Mean Average Daily Pain (ADP)

End point title	Percentage of Subjects with at least a 2-Point Reduction from Baseline to Double-Blind Week 12 in Mean Average Daily Pain (ADP)

End point description:

Baseline was defined as the 5 days prior to the first dose of study treatment in the open-label run-in period (Day 1). FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment.

End point type	Secondary
End point timeframe:	
Baseline, DB Week 12	

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	41	
Units: percentage of subjects				
number (not applicable)	55.0	75.0	70.7	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg
Statistical analysis description:	
Logistic regression was adjusted for treatment, baseline ADP score and SFN etiology.	
Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	5.97

Statistical analysis title	Placebo vs BIIB074 350 mg
Statistical analysis description:	
Logistic regression was adjusted for treatment, baseline ADP score and SFN etiology.	
Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1019
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	6.43

Secondary: Percentage of Subjects with at least a 30% Reduction from Baseline to Double-Blind Week 12 in Mean Average Daily Pain (ADP)

End point title	Percentage of Subjects with at least a 30% Reduction from Baseline to Double-Blind Week 12 in Mean Average Daily Pain (ADP)

End point description:

Baseline was defined as the 5 days prior to the first dose of study treatment in the open-label run-in period (Day 1). FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment.

End point type	Secondary

End point timeframe:

Baseline, DB Week 12

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	41	
Units: percentage of subjects				
number (not applicable)	52.5	72.5	68.3	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Logistic regression was adjusted for treatment, baseline ADP score and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1305
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	5.96

Statistical analysis title	Placebo vs BIIB074 350 mg
Statistical analysis description:	
Logistic regression was adjusted for treatment, baseline ADP score and SFN etiology.	
Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1212
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	5.99

Secondary: Mean Daily Amount of Rescue Medication Used for SFN Pain During Double-Blind Period

End point title	Mean Daily Amount of Rescue Medication Used for SFN Pain During Double-Blind Period
End point description:	
Use of rescue medication (paracetamol/acetaminophen) was monitored and dosage was recorded on a daily basis by the subject using an electronic Diary (eDiary). Baseline was defined as the 5 days prior to the first dose of study treatment in the open-label run-in period (Day 1). The values reported are mean values. FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment.	
End point type	Secondary
End point timeframe:	
Baseline, DB Week 12	

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	41	
Units: milligrams per day				
arithmetic mean (standard deviation)	83.08 (± 307.919)	99.10 (± 314.715)	24.87 (± 73.841)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patient Global Impression of Change (PGIC) Responders at Double-Blind Week 12

End point title	Percentage of Patient Global Impression of Change (PGIC) Responders at Double-Blind Week 12

End point description:

A PGIC responder is defined as someone who has answered 'very much improved' or 'much improved' on the PGIC questionnaire. PGIC is a 7-point scale that assesses a subject's perceived change in overall status. Subjects rated their change as 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, or 7=very much worse relative to the start of the study (since taking study drug). FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment.

End point type	Secondary

End point timeframe:

Week 12 of the DB Period

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	40	40	41	
Units: percentage of responders				
number (not applicable)	30.0	37.5	48.8	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Based on logistic regression adjusted for treatment and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7376
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	3.14

Statistical analysis title	Placebo vs BIIB074 350 mg

Statistical analysis description:	
Based on logistic regression adjusted for treatment and SFN etiology.	
Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.058
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	6.99

Secondary: Change from Baseline to Double-Blind Week 12 in Brief Pain Inventory-Short Form (BPI-SF) Interference Score

End point title	Change from Baseline to Double-Blind Week 12 in Brief Pain Inventory-Short Form (BPI-SF) Interference Score
End point description:	
The BPI-SF is a self-administered questionnaire for subjects to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Item 9 of the BPI-SF measures how much pain has interfered with 7 daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. Each activity is rated on a scale of 0 (does not interfere) to 10 (completely interferes). The BPI-SF interference score is calculated as the mean of the 7 interference item scores. Baseline was defined as the last value prior to the first dose of study treatment in the open-label run-in period. FAS included all randomised subjects who received at least one dose of double-blind study treatment and have at least 1 post-randomisation efficacy assessment. Number of subjects analysed is the number of subjects evaluable in this end point.	
End point type	Secondary
End point timeframe:	
Baseline, DB Week 12	

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	16	7	16	
Units: score on a scale				
least squares mean (standard error)	-2.60 (± 0.668)	-2.01 (± 0.835)	-3.25 (± 0.606)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB074 200 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 200 mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5863
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	2.84
Variability estimate	Standard error of the mean
Dispersion value	1.081

Statistical analysis title	Placebo vs BIIB074 350 mg

Statistical analysis description:

Analysis was performed using the MMRM model, fitting treatment timepoint, treatment*timepoint interaction, baseline score, baseline score*timepoint interaction and SFN etiology.

Comparison groups	DB Period: Placebo v DB Period: BIIB074 350 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4791
Method	MMRM
Parameter estimate	LS Mean difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	1.22
Variability estimate	Standard error of the mean
Dispersion value	0.903

Secondary: Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) During Double-Blind Period

End point title	Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) During Double-Blind Period

End point description:

An AE was any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An SAE was any untoward medical occurrence that at any dose resulted in

death; in the view of the investigator, placed the subject at immediate risk of death (a life-threatening event); required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity; resulted in a congenital anomaly/birth defect. Double-blind (DB) safety population included all randomised subjects who received at least 1 dose of DB treatment.

End point type	Secondary

End point timeframe:

From randomisation of subjects who received at least 1 dose of double-blind treatment to end of study (up to approximately 140 weeks)

End point values	DB Period: Placebo	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	41	40	41	
Units: percentage of subjects				
number (not applicable)				
AEs	61.0	47.5	43.9	
SAEs	9.8	2.5	2.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Plasma Concentration During Open-Label Period

End point title	Mean Plasma Concentration During Open-Label Period

End point description:

OL pharmacokinetic (PK) population included OL safety subjects who have at least one post-baseline PK concentration measurement. Here, ”n” signifies number of subjects evaluated at specific timepoint in this end point.

End point type	Secondary

End point timeframe:

Pre-dose and 2 hours post-dose on open-label (OL) Day 1, OL Week 2; pre-dose on OL Week 4 and OL follow-up visit

End point values	OL Period: BIIB074 350 mg (PK Analysis)			
Subject group type	Subject analysis set			
Number of subjects analysed	264			
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
OL Day 1: Predose (n=258)	36.39 (± 419.388)			
OL Day 1: 2 Hours Post-dose (n=255)	2974.93 (± 1194.403)			
OL Week 2: Predose (n=234)	2337.68 (± 1299.573)			

OL Week 2: 2 Hours Post-dose (n=234)	5286.11 (± 1869.361)			
OL Week 4: Predose (n=207)	2159.29 (± 1043.990)			
OL Follow-up visit: Predose (n=2)	2165.75 (± 3046.570)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Plasma Concentration During Double-Blind Period

End point title	Mean Plasma Concentration During Double-Blind Period

End point description:

DB PK population included DB safety subjects who have at least one post-randomisation PK concentration measurement. Here, ”n” signifies number of subjects evaluated at specific timepoint in this end point.

End point type	Secondary

End point timeframe:

Pre-dose and 2 hours post-dose on double-blind (DB) Day 1, DB Week 4, DB Week 8, DB Week 12; pre-dose on DB follow-up visit

End point values	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	41		
Units: ng/mL				
arithmetic mean (standard deviation)				
DB Day 1: Predose (n=37,41)	2332.38 (± 1058.584)	2105.78 (± 938.915)		
DB Day 1: 2 Hours Post-dose (n=39,40)	4031.64 (± 1728.923)	4817.95 (± 1951.975)		
DB Week 4: Predose (n=37,38)	1476.57 (± 811.089)	2007.55 (± 1076.381)		
DB Week 4: 2 Hours Post-dose (n=39,38)	3057.69 (± 872.572)	4771.23 (± 1800.318)		
DB Week 8: Predose (n=35,37)	1272.58 (± 608.584)	2158.51 (± 831.852)		
DB Week 8: 2 Hours Post-dose (n=34,38)	2976.65 (± 1022.002)	4992.63 (± 1750.338)		
DB Week 12: Predose (n=32,31)	1342.66 (± 634.202)	2250.81 (± 1027.830)		
DB Week 12: 2 Hours Post-dose (n=31,37)	3076.13 (± 893.203)	4789.19 (± 1637.541)		
DB Follow-up visit: Predose (n=7,9)	300.81 (± 673.591)	108.87 (± 221.032)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening to the end of study (up to approximately 159 weeks)	
Adverse event reporting additional description:	
OL safety population included all enrolled subjects who received at least 1 dose of treatment with BIIB074 during the OL run-in period. DB safety population included all randomised subjects who received at least 1 dose of DB treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	DB Period: BIIB074 200 mg
Reporting group description:	
Subjects received BIIB074, 200 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Reporting group title	DB Period: BIIB074 350 mg
Reporting group description:	
Subjects received BIIB074, 350 mg, tablets, orally, BID, for 12 weeks of the double-blind period.	
Reporting group title	DB Period: Placebo
Reporting group description:	
Subjects received BIIB074-matching placebo, tablets, orally, BID, for 12 weeks of the double-blind period.	
Reporting group title	OL Period: BIIB074 350 mg
Reporting group description:	
Subjects received BIIB074 350 mg, tablets, orally, BID, for 4 weeks of the open-label run-in period.	

Serious adverse events	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	DB Period: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)	1 / 41 (2.44%)	4 / 41 (9.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac arrest			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	0 / 41 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	0 / 41 (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
Pulmonary embolism			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	0 / 41 (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			
Appendicitis			

subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal peritonitis			
subjects affected / exposed	1 / 40 (2.50%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 pneumonia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	0 / 41 (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
Herpes zoster			
subjects affected / exposed	0 / 40 (0.00%)	1 / 41 (2.44%)	0 / 41 (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
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	OL Period: BIIB074 350 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 265 (1.89%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac arrest			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 265 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 265 (0.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Focal peritonitis				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Covid-19 pneumonia				
subjects affected / exposed	2 / 265 (0.75%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Electrolyte imbalance				
subjects affected / exposed	0 / 265 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	DB Period: BIIB074 200 mg	DB Period: BIIB074 350 mg	DB Period: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 40 (15.00%)	7 / 41 (17.07%)	12 / 41 (29.27%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 40 (0.00%)	3 / 41 (7.32%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	0 / 41 (0.00%)
occurrences (all)	0	0	0

Headache			
subjects affected / exposed	1 / 40 (2.50%)	1 / 41 (2.44%)	5 / 41 (12.20%)
occurrences (all)	1	1	11
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 40 (2.50%)	2 / 41 (4.88%)	4 / 41 (9.76%)
occurrences (all)	1	2	5
Nausea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	4
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	2 / 40 (5.00%)	1 / 41 (2.44%)	1 / 41 (2.44%)
occurrences (all)	2	1	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 40 (5.00%)	2 / 41 (4.88%)	3 / 41 (7.32%)
occurrences (all)	2	2	5
Urinary tract infection			
subjects affected / exposed	2 / 40 (5.00%)	0 / 41 (0.00%)	3 / 41 (7.32%)
occurrences (all)	2	0	3

Non-serious adverse events	OL Period: BIIB074 350 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 265 (21.51%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 265 (1.51%)		
occurrences (all)	4		
Nervous system disorders			
Dizziness			
subjects affected / exposed	25 / 265 (9.43%)		
occurrences (all)	28		
Headache			
subjects affected / exposed	25 / 265 (9.43%)		
occurrences (all)	32		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	6 / 265 (2.26%) 8 11 / 265 (4.15%) 12		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	1 / 265 (0.38%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	6 / 265 (2.26%) 6 3 / 265 (1.13%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2017	To clarify that pregnancy of a female partner should not impact the study status of a male subject during his participation in the study.
06 September 2017	To change the study design to include a separate washout period prior to the open-label run-in period during which no pain medications are allowed. The taper and washout periods were added to the screening period for a total duration of up to 6 weeks.
06 June 2018	To update the diagnostic criteria for small fiber neuropathy (SFN) in the inclusion criteria.
23 July 2019	To update the details of the interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Sponsor decision to close study early; not due to safety concerns.

Notes: