Clinical trial results:
A Phase 2, Randomized, Double-Blind, Multiple-Dose, Placebo-Controlled Study to Evaluate the Safety and Efficacy of BIIB104 in Subjects With Cognitive Impairment Associated With Schizophrenia (CIAS)

Summary

EudraCT number	2018-003825-27
Trial protocol	DE GB
Global end of trial date	07 April 2022

Results information

Result version number	v1 (current)
This version publication date	14 April 2023
First version publication date	14 April 2023

Trial information

Trial identification

Sponsor protocol code	263CS201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03745820
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 Binney Street, Cambridge, United States, 02142
Public contact	Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	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	07 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of BIIB104 in subjects with CIAS, using the Working Memory Domain of the MATRICS Consensus Cognitive Battery (MCCB).

Protection of trial subjects:

Written informed consent was obtained from each subject or subject's legally authorized representative (e.g., 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	15 November 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	United States: 143
Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	195
EEA total number of subjects	27

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)	195
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 53 investigative sites in the United States, Japan, Spain, Germany, and the United Kingdom from 15 Nov 2018 to 07 April 2022.

Pre-assignment

Screening details:

A total of 554 participants were screened out of which, 195 participants were randomised and dosed to receive BIIB104 or placebo.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received BIIB104 matching placebo capsules, twice a day (BID), orally for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	BIIB104 0.15 mg

Arm description:

Participants received 0.15 milligrams (mg) capsules of BIIB104, BID, orally for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BIIB104 0.15 mg
Investigational medicinal product code	
Other name	PF-04958242
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as specified in the treatment arm.

Arm title	BIIB104 0.5 mg

Arm description:

Participants received 0.5 mg capsules of BIIB104, BID, orally for 12 weeks.

Arm type	Experimental

Investigational medicinal product name	BIIB104 0.5 mg
Investigational medicinal product code	
Other name	PF-04958242
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered as specified in the treatment arm.

Number of subjects in period 1	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg
Started	64	66	65
Completed	52	52	51
Not completed	12	14	14
Consent withdrawn by subject	4	4	4
Non-Compliance with Study Drug	4	3	-
Adverse events	-	-	2
Adverse event	-	3	-
Lost to follow-up	2	-	3
Physician decision unrelated to safety/efficacy	-	-	4
Reason not Specified	2	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received BIIB104 matching placebo capsules, twice a day (BID), orally for 12 weeks.	
Reporting group title	BIIB104 0.15 mg
Reporting group description:	
Participants received 0.15 milligrams (mg) capsules of BIIB104, BID, orally for 12 weeks.	
Reporting group title	BIIB104 0.5 mg
Reporting group description:	
Participants received 0.5 mg capsules of BIIB104, BID, orally for 12 weeks.	

Reporting group values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg
Number of subjects	64	66	65
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40.6	37.7	41.3
standard deviation	± 9.47	± 9.41	± 9.63
Gender categorical Units: Subjects			
Female	20	21	18
Male	44	45	47
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	9	6
Not Hispanic or Latino	45	47	49
Unknown or Not Reported	9	10	10
Race/Ethnicity, Customized Units: Subjects			
Asian	10	8	13
Black or African American	29	27	26
Native Hawaiian or Other Pacific Islander	1	0	1
White	15	19	15
Other	0	2	0
Unknown	9	10	10
MATRICS Consensus Cognitive Battery (MCCB) Working Memory Domain Score			
The MCCB is a cognitive battery that assesses 7 domains recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (i.e., Working Memory, Verbal Learning, Speed of Processing, Attention/Vigilance, Visual Learning, Social Cognition, and Reasoning and Problem Solving). MCCB was administered via laptop computer and paper-and-pencil assessments. MCCB composite T scores are between 40 and 60 (normal range). Higher scores indicate better cognitive functioning. The working memory domain score of the MCCB is reported.			
Units: score on a scale			
arithmetic mean	39.6	38.5	39.8
full range (min-max)	17 to 70	12 to 60	17 to 58

Reporting group values	Total		
Number of subjects	195		
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	--		
Gender categorical Units: Subjects			
Female	59		
Male	136		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	25		
Not Hispanic or Latino	141		
Unknown or Not Reported	29		
Race/Ethnicity, Customized Units: Subjects			
Asian	31		
Black or African American	82		
Native Hawaiian or Other Pacific Islander	2		
White	49		
Other	2		
Unknown	29		
MATRICS Consensus Cognitive Battery (MCCB) Working Memory Domain Score			
The MCCB is a cognitive battery that assesses 7 domains recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (i.e., Working Memory, Verbal Learning, Speed of Processing, Attention/Vigilance, Visual Learning, Social Cognition, and Reasoning and Problem Solving). MCCB was administered via laptop computer and paper-and-pencil assessments. MCCB composite T scores are between 40 and 60 (normal range). Higher scores indicate better cognitive functioning. The working memory domain score of the MCCB is reported.			
Units: score on a scale arithmetic mean full range (min-max)	--		

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received BIIB104 matching placebo capsules, BID, orally for 12 weeks.	
Subject analysis set title	BIIB104 0.15 mg
Subject analysis set type	Safety analysis
Subject analysis set description: Participants received 0.15 mg capsules of BIIB104, BID, orally for 12 weeks.	
Subject analysis set title	BIIB104 0.5 mg
Subject analysis set type	Safety analysis

Subject analysis set description:
Participants received 0.5 mg capsules of BIIB104, BID, orally for 12 weeks.

Reporting group values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg
Number of subjects	63	66	66
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	0	0	0
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female	0	0	0
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	0	0	0
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	0	0	0
Other	0	0	0
Unknown	0	0	0
MATRICS Consensus Cognitive Battery (MCCB) Working Memory Domain Score			
The MCCB is a cognitive battery that assesses 7 domains recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (i.e., Working Memory, Verbal Learning, Speed of Processing, Attention/Vigilance, Visual Learning, Social Cognition, and Reasoning and Problem Solving). MCCB was administered via laptop computer and paper-and-pencil assessments. MCCB composite T scores are between 40 and 60 (normal range). Higher scores indicate better cognitive functioning. The working memory domain score of the MCCB is reported.			
Units: score on a scale			
arithmetic mean	0	0	0
full range (min-max)			

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received BIIB104 matching placebo capsules, twice a day (BID), orally for 12 weeks.	
Reporting group title	BIIB104 0.15 mg
Reporting group description:	
Participants received 0.15 milligrams (mg) capsules of BIIB104, BID, orally for 12 weeks.	
Reporting group title	BIIB104 0.5 mg
Reporting group description:	
Participants received 0.5 mg capsules of BIIB104, BID, orally for 12 weeks.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received BIIB104 matching placebo capsules, BID, orally for 12 weeks.	
Subject analysis set title	BIIB104 0.15 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received 0.15 mg capsules of BIIB104, BID, orally for 12 weeks.	
Subject analysis set title	BIIB104 0.5 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received 0.5 mg capsules of BIIB104, BID, orally for 12 weeks.	

Primary: Change From Baseline in Change From Baseline in Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Working Memory Domain Score at Week 12

End point title	Change From Baseline in Change From Baseline in Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) Working Memory Domain Score at Week 12

End point description:

The MCCB is a cognitive battery that assesses 7 domains recommended by the MATRICS initiative (i.e., Working Memory, Verbal Learning, Speed of Processing, Attention/Vigilance, Visual Learning, Social Cognition, and Reasoning and Problem Solving). MCCB was administered via laptop computer and paper-and-pencil assessments. T-scores for the individual tests were calculated according to the developer's recommended scoring algorithms. MCCB composite T scores are between 40 and 60 (normal range). Higher scores indicate better cognitive functioning. The working memory domain score of the MCCB is reported in this outcome measure. ITT population included all randomised participants who received at least one dose of study treatment (BIIB104 or placebo). Here, "Overall Number of Participants Analysed" signifies the number of participants analysed in this outcome measure.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	50	49	
Units: score on a scale				
least squares mean (standard error)	1.17 (± 0.939)	0.91 (± 0.936)	0.84 (± 0.934)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Mixed Model Repeated Measures(MMRM)model was used to analyse change from baseline of outcome measure(OM)using fixed effects of treatment group,region,study visit,study visit-by-treatment interaction,baseline value of OM,baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8053
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.94
upper limit	2.29
Variability estimate	Standard error of the mean
Dispersion value	1.323

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8472
Method	MMRM
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.88
upper limit	2.37

Variability estimate	Standard error of the mean
Dispersion value	1.328

Secondary: Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An SAE is any untoward medical occurrence that at any dose results in death, places the participant at immediate risk of death, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in a congenital anomaly/birth defect, or is a medically important event. The safety population included all randomised participants who received at least 1 dose of study treatment (BIIB104 or placebo).

End point type	Secondary

End point timeframe:

From first dose of study drug through end of the study (up to Week 14)

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	63	66	66	
Units: participants				
AEs	28	32	28	
SAEs	1	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Total Score Assessed by Scale for the Assessment and Rating of Ataxia (SARA)

End point title	Mean Total Score Assessed by Scale for the Assessment and Rating of Ataxia (SARA)

End point description:

The SARA is a clinical scale that is based on a semiquantitative assessment of cerebellar ataxia on an impairment level and complements the brief neurological examination. The SARA scale is an eight-item clinical rating scale (gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test) with a total score range of 0-40, where 0 is the best neurological status and 40 is the worst neurological status. The safety population included all randomised participants who received at least 1 dose of study treatment (BIIB104 or placebo). Here, "Overall number of participants analysed" signifies the number of participants analysed in this outcome measure and "number analysed" signifies the number of participants analysed at specified time-point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 2, 6, 12 and safety follow-up (Week 14)

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	64	65	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	0.5 (± 1.03)	0.4 (± 1.15)	0.3 (± 0.92)	
Week 2 (n=57,59,62)	0.4 (± 0.85)	0.5 (± 1.10)	0.3 (± 0.68)	
Week 6 (n=52,56,60)	0.4 (± 0.71)	0.3 (± 0.90)	0.2 (± 0.58)	
Week 12 (n=52,51,54)	0.4 (± 0.80)	0.3 (± 0.82)	0.2 (± 0.72)	
Week 14 (n=55,58,57)	0.4 (± 0.85)	0.3 (± 0.91)	0.2 (± 0.69)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in University of California, San Diego Performance Based Skills Assessment-Brief International Version (UPSA-Bi) Assessment at Week 12

End point title	Change From Baseline in University of California, San Diego Performance Based Skills Assessment-Brief International Version (UPSA-Bi) Assessment at Week 12

End point description:

The UPSA-Bi, international version, an abbreviated version of the UPSA-Validation of Intermediate Measures, is a measure of functional capacity and assesses skills used in community tasks. This assessment measures 2 general skills that were previously identified as essential to functioning in the community: financial skills and communication skills. The UPSA-Bi assessment is scored from 0-100, higher scores indicating higher functional status. ITT population included all randomised participants who received at least one dose of study treatment (BIIB104 or placebo). Here, "Overall Number of Participants Analysed" signifies the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	50	49	
Units: score on a scale				
least squares mean (standard error)	2.07 (± 1.303)	5.50 (± 1.292)	5.49 (± 1.305)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB104 0.5 mg
Statistical analysis description:	
An analysis of covariance (ANCOVA) model was applied adjusting for treatment group and baseline value of the OM.	
Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0659
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	7.06
Variability estimate	Standard error of the mean
Dispersion value	1.844

Statistical analysis title	Placebo vs BIIB104 0.15 mg
Statistical analysis description:	
An ANCOVA model was applied adjusting for treatment group and baseline value of the OM.	
Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0637
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	7.06
Variability estimate	Standard error of the mean
Dispersion value	1.835

Secondary: Number of Participants With at Least one Event of Suicidal Ideation and/or Suicidal Behavior as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) Score

End point title	Number of Participants With at Least one Event of Suicidal Ideation and/or Suicidal Behavior as Assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) Score

End point description:

The C-SSRS is an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active

suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). Suicidal behavior is classified on a 6-item scale: 1 (actual attempt), 2 (interrupted attempt), 3 (aborted attempt), 4 (preparatory acts or behavior), 5 (suicidal behavior), and 6 (suicide). The data analysed signifies the participants with at least one event of suicidal ideation and/or suicidal behavior.The safety population included all randomised participants who received at least 1 dose of study treatment (BIIB104 or placebo).Here, "Overall Number of Participants Analysed" signifies the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Up to Week 14

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	65	65	
Units: participants	3	4	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Schizophrenia Cognition Rating Scale (SCoRS) Assessment Score at Week 12

End point title	Change From Baseline in Schizophrenia Cognition Rating Scale (SCoRS) Assessment Score at Week 12

End point description:

The SCoRS is an interview-based assessment of cognition that involves interviews with participants and informants. The SCoRS includes 20 items designed to specifically assess aspects of cognitive functioning found in each of the seven MCCB cognitive domains including the following: Memory: 4 items; Learning: 2 items; Attention: 3 items; Working memory: 2 items; Problem solving: 3 items; Processing/motor speed: 2 items; Social cognition: 3 items; Language: 1 item. Total score range is 20-80, lower scores indicating higher functional status. The data reported in this outcome measure are for global rating score. ITT population included all randomised participants who received at least one dose of study treatment (BIIB104 or placebo). Here, "Overall Number of Participants Analysed" signifies the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	48	50	
Units: score on a scale				
least squares mean (standard error)	-0.51 (± 0.146)	-0.42 (± 0.148)	-0.41 (± 0.145)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB104 0.5 mg
Statistical analysis description: An ANCOVA model was applied adjusting for treatment group and baseline value of the OM.	
Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.614
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.51
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Placebo vs BIIB104 0.15 mg
Statistical analysis description: An ANCOVA model was applied adjusting for treatment group and baseline value of the OM.	
Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6653
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Change From Baseline in MCCB Neurocognitive Composite Scores at Week 12

End point title	Change From Baseline in MCCB Neurocognitive Composite Scores at Week 12

End point description:

The MCCB is a cognitive battery that assesses 7 domains recommended by the MATRICS initiative (i.e., Working Memory, Verbal Learning, Speed of Processing, Attention/Vigilance, Visual Learning, Social Cognition, and Reasoning and Problem Solving). MCCB was administered via laptop computer and paper-and-pencil assessments. T-scores for the individual tests were calculated according to the developer's recommended scoring algorithms. MCCB composite T scores are between 40 and 60 (normal range). Higher scores indicate better cognitive functioning. The MCCB composite score contains all of the tests and domains of the MCCB. ITT population included all randomised participants who received at least one dose of study treatment (BIIB104 or placebo). Here, "Overall Number of Participants Analysed" signifies the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	50	49	
Units: score on a scale				
least squares mean (standard error)	2.90 (± 0.733)	1.80 (± 0.728)	3.39 (± 0.727)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6349
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.55
upper limit	2.53
Variability estimate	Standard error of the mean
Dispersion value	1.032

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2886
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	0.94
Variability estimate	Standard error of the mean
Dispersion value	1.033

Secondary: Change From Baseline in MCCB Individual Domain Scores (Excluding Working Memory Domain) at Week 12

End point title	Change From Baseline in MCCB Individual Domain Scores (Excluding Working Memory Domain) at Week 12

End point description:

The MCCB is a cognitive battery that assesses 7 domains recommended by the MATRICS initiative (i.e., working memory, verbal learning, speed of processing, attention/vigilance, visual learning, social cognition, and reasoning and problem solving). MCCB was administered via laptop computer and paper-and-pencil assessments. T-scores for the individual tests were calculated according to the developer's recommended scoring algorithms. MCCB composite T scores are between 40 and 60 (normal range). Higher scores indicate better cognitive functioning. All the domain scores of the MCCB are reported in this outcome measure with the exception of working memory domain. ITT population included all randomised participants who received at least one dose of study treatment (BIIB104 or placebo). Here, “Overall Number of Participants Analysed” signifies the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	50	49	
Units: score on a scale				
least squares mean (standard error)				
Verbal Learning: Change at Week 12	0.95 (± 0.951)	1.41 (± 0.946)	0.41 (± 0.950)	
Speed of Processing: Change at Week 12	4.42 (± 0.824)	2.28 (± 0.819)	3.99 (± 0.817)	
Attention/Vigilance: Change at Week 12	0.62 (± 0.852)	0.53 (± 0.848)	1.55 (± 0.848)	
Visual Learning: Change at Week 12	1.70 (± 1.131)	0.19 (± 1.125)	1.77 (± 1.125)	
Social Cognition: Change at Week 12	-0.13 (± 0.959)	1.06 (± 0.953)	0.95 (± 0.955)	
Reasoning and Problem Solving: Change at Week 12	2.81 (± 1.019)	2.10 (± 1.1014)	4.40 (± 1.011)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Verbal Learning: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7372
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.21
upper limit	3.11
Variability estimate	Standard error of the mean
Dispersion value	1.345

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Verbal Learning: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6894
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	2.12
Variability estimate	Standard error of the mean
Dispersion value	1.346

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Speed of Processing: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0674
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-2.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.44
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	1.162

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Speed of Processing: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7132
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.72
upper limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	1.161

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Attention/Vigilance: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9428
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.46
upper limit	2.29
Variability estimate	Standard error of the mean
Dispersion value	1.203

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Attention/Vigilance: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4425
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	1.202

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Visual Learning: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3455
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.66
upper limit	1.64
Variability estimate	Standard error of the mean
Dispersion value	1.597

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Visual Learning: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9686
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.09
upper limit	3.21
Variability estimate	Standard error of the mean
Dispersion value	1.595

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Social Cognition: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3832
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.49
upper limit	3.85
Variability estimate	Standard error of the mean
Dispersion value	1.351

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Social Cognition: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4297
Method	MMRM
Parameter estimate	LS Mean DIfference
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	3.75
Variability estimate	Standard error of the mean
Dispersion value	1.357

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Reasoning and Problem Solving: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6245
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.55
upper limit	2.14
Variability estimate	Standard error of the mean
Dispersion value	1.438

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Reasoning and Problem Solving: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg

Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2698
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.25
upper limit	4.43
Variability estimate	Standard error of the mean
Dispersion value	1.436

Secondary: Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score, Positive Subscale, and Negative Subscale Scores at Week 12

End point title	Change From Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score, Positive Subscale, and Negative Subscale Scores at Week 12

End point description:

PANSS includes 3 subscales,30 items:7 items=Positive subscale (e.g., delusions, conceptual disorganization, hallucinatory behaviour);7 items=Negative subscales (e.g., blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal);16 items=General Psychopathology subscale (e.g., somatic concern, anxiety, guilt feelings, mannerisms and posturing, motor retardation, uncooperativeness, disorientation, poor impulse control, preoccupation). Each item on these subscales is rated: 1 (absent) and -7(extreme). The score range is 7-49 for positive and negative subscales, score range is 16-112 for general psychopathology subscale. Total PANSS score (positive + negative + general psychopathology subscale scores) range from 30-210. Higher scores represent more severity in symptoms. ITT population. "Overall Number of Participants Analysed" = the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	51	50	
Units: score on a scale				
least squares mean (standard error)				
Positive Symptoms Scale: Change at Week 12	-0.65 (± 0.431)	-1.09 (± 0.430)	-0.98 (± 0.429)	
Negative Symptoms Scale: Change at Week 12	-0.90 (± 0.461)	-0.98 (± 0.461)	-1.40 (± 0.460)	
Total Score: Change at Week 12	-3.06 (± 1.429)	-4.26 (± 1.421)	-5.03 (± 1.427)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Positive Symptoms Subscale: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4654
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	0.76
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Positive Symptoms Subscale: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5886
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	0.87
Variability estimate	Standard error of the mean
Dispersion value	0.608

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Negative Symptoms Subscale: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment

interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9079
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	1.22
Variability estimate	Standard error of the mean
Dispersion value	0.655

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Negative Symptoms Subscale: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4441
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	0.79
Variability estimate	Standard error of the mean
Dispersion value	0.65

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

Total Score: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5537
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.18
upper limit	2.79
Variability estimate	Standard error of the mean
Dispersion value	2.017

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

Total Score: A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.332
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	-1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.95
upper limit	2.02
Variability estimate	Standard error of the mean
Dispersion value	2.018

Secondary: Change From Baseline in Clinical Global Impression-Severity (CGI-S) Scores at Week 12

End point title	Change From Baseline in Clinical Global Impression-Severity (CGI-S) Scores at Week 12

End point description:

The CGI-S consists of a single 7-point rating score of illness severity. The following question: "Considering your total clinical experience with this particular population, how mentally ill is your participant at this time?" is rated with a score from 1 to 7- 1: Normal, not ill at all; 2: Borderline mentally ill; 3: Mildly ill; 4: Moderately ill; 5: Markedly ill; 6: Severely ill; or 7: Among the most severely ill participants. Lower scores indicate less severity of illness. ITT population included all randomised participants who received at least one dose of study treatment (BIIB104 or placebo). Here, "Overall Number of Participants Analysed" signifies the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	50	50	
Units: score on a scale				
least squares mean (standard error)	-0.19 (± 0.091)	-0.16 (± 0.091)	-0.19 (± 0.091)	

Statistical analyses

Statistical analysis title	Placebo vs BIIB104 0.5 mg

Statistical analysis description:

A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.5 mg
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9952
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.128

Statistical analysis title	Placebo vs BIIB104 0.15 mg

Statistical analysis description:

A MMRM model was used to analyse the change from baseline of the OM of interest, using fixed effects of treatment group, region, study visit, study visit-by-treatment interaction, baseline value of OM, baseline-by-visit interaction.

Comparison groups	Placebo v BIIB104 0.15 mg

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8517
Method	MMRM
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.128

Secondary: Number of Participants With Response on Clinical Global Impression-Improvement (CGI-I) Scale at Week 12

End point title	Number of Participants With Response on Clinical Global Impression-Improvement (CGI-I) Scale at Week 12

End point description:

The CGI-I consists of a single 7-point rating score total improvement, regardless of whether or not the change is due entirely to drug treatment. The following question: "Compared to your participant's condition at the beginning of treatment, how much has your participant changed?" is rated with a score from 1 to 7- 1: Very much improved; 2: Much improved; 3: Minimally improved; 4: No change; 5: Minimally worse; 6: Much worse; or 7: Very much worse. Lower scores indicate greater improvement. ITT population included all randomised participants who received at least one dose of study treatment (BIIB104 or placebo). Here, "Overall Number of Participants Analysed" signifies the number of participants analysed in this outcome measure.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	BIIB104 0.15 mg	BIIB104 0.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	51	50	50	
Units: participants				
Very Much Improved	1	1	0	
Much Improved	11	4	4	
Minimally Improved	13	18	18	
No Change	22	26	26	
Minimally worse	2	1	2	
Much Worse	2	0	0	
Very Much Worse	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug through end of the study (up to Week 14)	
Adverse event reporting additional description:	
Safety population. One participant randomised to placebo, inadvertently received one or more doses of active treatment. For participants affected, a participant was counted only once within each system organ class/preferred term/study period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received BIIB104 matching placebo capsules, BID, orally for 12 weeks.	
Reporting group title	BIIB104 0.5 mg
Reporting group description:	
Participants received 0.5 mg capsules of BIIB104, BID, orally for 12 weeks.	
Reporting group title	BIIB104 0.15 mg
Reporting group description:	
Participants received 0.15 mg capsules of BIIB104, BID, orally for 12 weeks.	

Serious adverse events	Placebo	BIIB104 0.5 mg	BIIB104 0.15 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 63 (1.59%)	2 / 66 (3.03%)	1 / 66 (1.52%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 66 (1.52%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric decompensation			
subjects affected / exposed	0 / 63 (0.00%)	1 / 66 (1.52%)	0 / 66 (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
Infections and infestations			
Appendicitis			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 63 (1.59%)	0 / 66 (0.00%)	0 / 66 (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

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

Non-serious adverse events	Placebo	BIIB104 0.5 mg	BIIB104 0.15 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 63 (3.17%)	8 / 66 (12.12%)	2 / 66 (3.03%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 63 (1.59%)	4 / 66 (6.06%)	1 / 66 (1.52%)
occurrences (all)	1	4	1
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	1 / 63 (1.59%)	4 / 66 (6.06%)	1 / 66 (1.52%)
occurrences (all)	1	4	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 August 2018	The duration of the study treatment period was decreased from 24 weeks to 12 weeks and the duration of the safety follow-up period from 4 weeks to 2 weeks.
12 June 2019	The number of study sites were expanded from approximately 40 to approximately 80 and the inclusion of participants in Japan and possibly other countries.
29 October 2019	The study eligibility criteria was updated: 1) increased the maximum age for participants from 50 to 55 years, 2) the requirements for the identified informants were revised to reduce the burden on participants and informants, and 3) the requirements for oral fluency and reading assessment were revised to standardize test scoring across geographic regions. In addition, the changes for the Japan-specific protocol amendment (Version 3.1) were incorporated into this global version of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported