Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Intravenously Administered BIIB092 in Participants with Progressive Supranuclear Palsy

Summary

EudraCT number	2016-002554-21
Trial protocol	GB DE AT ES GR FR IT
Global end of trial date	07 February 2020

Results information

Result version number	v2 (current)
This version publication date	31 March 2021
First version publication date	24 September 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	251PP301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03068468
WHO universal trial number (UTN)	-
Other trial identifiers	Bristol-Myers Squibb: CN002-012

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	250 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	07 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of BIIB092, compared to placebo, as measured by a change from baseline in the PSP Rating Scale (PSPRS) at Week 52 and to assess the safety and tolerability of BIIB092, relative to placebo, by measuring the frequency of deaths, SAEs, and AEs leading to discontinuation, and Grade 3 & 4 laboratory abnormalities.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 129
Country: Number of subjects enrolled	Germany: 81
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Japan: 39
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Australia: 1
Worldwide total number of subjects	490
EEA total number of subjects	255

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)	119
From 65 to 84 years	371
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 89 investigative sites in the United States, Australia, Austria, Canada, France, Germany, Greece, Italy, Japan, Republic of Korea, Russia Federation, Spain and United Kingdom from June 01, 2017 to February 07, 2020.

Pre-assignment

Screening details:

A total of 490 subjects with Progressive Supranuclear Palsy disease were enrolled and randomised in the study. Of these, 486 subjects received the study drug in PC period. After completing PC period, 416 subjects entered and dosed in OLE period and no subjects completed the study due to early termination of the study.

Period 1

Period 1 title	Placebo-Controlled (PC) 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 (PC Period)

Arm description:

Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind PC period and receive only placebo.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects assigned to BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks.

Arm title	BIIB092 2000 mg (PC Period)

Arm description:

Subjects who received at least one dose of BIIB092 2000 mg and were either assigned to BIIB092 2000 milligrams (mg) IV infusion or BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks in double blind PC period.

Arm type	Experimental
Investigational medicinal product name	BIIB092
Investigational medicinal product code	BIIB092
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects who received at least one dose of BIIB092 2000 mg, once every 4 weeks for 48 weeks in double blind PC period.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Subjects who received BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks in double blind PC period.

Number of subjects in period 1[1]	Placebo (PC Period)	BIIB092 2000 mg (PC Period)
Started	165	321
Completed	144	279
Not completed	21	42
Consent withdrawn by subject	3	11
Adverse Event	16	21
Death	-	1
Withdrawal by Parent/Guardian	1	2
Reason not specified	1	6
Lack of efficacy	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects who started the baseline period are the subjects who were treated in the study.

Period 2

Period 2 title	Open-Label Extension (OLE) Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BIIB092 Late Start (OLE Period)

Arm description:

Late start subjects received only placebo in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.

Arm type	Experimental
Investigational medicinal product name	BIIB092
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Late start subjects received only placebo in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52.

Arm title	BIIB092 Early Start (OLE Period)

Arm description:

Early start subjects are those who received BIIB092 2000 mg in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.

Arm type	Experimental
Investigational medicinal product name	BIIB092
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Early start subjects are those who received BIIB092 2000 mg in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52.

Number of subjects in period 2[2]	BIIB092 Late Start (OLE Period)	BIIB092 Early Start (OLE Period)
Started	140	276
Completed	0	0
Not completed	140	276
Consent withdrawn by subject	7	20
Failure to meet randomization criteria	2	-
Adverse Event	13	17
Death	-	1
Withdrawal by Parent/Guardian	-	4
Lost to follow-up	1	-
Reason not specified	1	4
Withdrawal by sponsor	115	228
Lack of efficacy	1	2

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The number of subjects starting the open-label extension period is not the same as the number of subjects who completed the placebo-controlled period because few of the subjects did not enter the open-label extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (PC Period)
Reporting group description:	
Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind PC period and receive only placebo.	
Reporting group title	BIIB092 2000 mg (PC Period)
Reporting group description:	
Subjects who received at least one dose of BIIB092 2000 mg and were either assigned to BIIB092 2000 milligrams (mg) IV infusion or BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks in double blind PC period.	

Reporting group values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)	Total
Number of subjects	165	321	486
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	68.9	68.7	
standard deviation	± 6.57	± 7.02	-
Sex: Female, Male Units: subjects			
Female	74	136	210
Male	91	185	276
Race Units: Subjects			
White	138	281	419
Black or African American	1	1	2
Asian Indian	3	3	6
Chinese	0	1	1
Japanese	16	23	39
Asian Other	4	10	14
Unknown	3	2	5
Ethnicity Units: Subjects			
Hispanic or Latino	5	7	12
Not Hispanic or Latino	117	242	359
Unknown or Not Reported	43	72	115

End points

End points reporting groups

Reporting group title	Placebo (PC Period)
Reporting group description:	
Subjects assigned to BIIB092 matching placebo intravenous (IV) infusion once every 4 weeks for 48 weeks in double blind PC period and receive only placebo.	
Reporting group title	BIIB092 2000 mg (PC Period)
Reporting group description:	
Subjects who received at least one dose of BIIB092 2000 mg and were either assigned to BIIB092 2000 milligrams (mg) IV infusion or BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks in double blind PC period.	
Reporting group title	BIIB092 Late Start (OLE Period)
Reporting group description:	
Late start subjects received only placebo in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.	
Reporting group title	BIIB092 Early Start (OLE Period)
Reporting group description:	
Early start subjects are those who received BIIB092 2000 mg in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.	
Subject analysis set title	BIIB092 Late Start
Subject analysis set type	Safety analysis
Subject analysis set description:	
Late start subjects received only placebo in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.	
Subject analysis set title	BIIB092 Early Start
Subject analysis set type	Safety analysis
Subject analysis set description:	
Early start subjects are those who received BIIB092 2000 mg in the placebo-controlled period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.	

Primary: Change From Baseline in Progressive Supranuclear Palsy Rating Scale (PSPRS) at Week 52

End point title	Change From Baseline in Progressive Supranuclear Palsy Rating Scale (PSPRS) at Week 52
End point description:	
The PSPRS is a quantitative measure of disability in participants with PSP. The PSPRS comprises 28 items in 6 areas. Six items are rated on a 3-point scale (0-2) and 22 are rated on a 5-point scale (0-4). The 6 areas are the History/Daily Activities, Mentation, Bulbar, Ocular Motor, Limb Motor, and Gait. The 28-item PSPRS total score ranges from 0 (normal) to 100. Fifteen items are selected to form a 15-item PSPRS and three domains are identified: Gait/Limb function, Ocular Motor, and Bulbar. The total 15-item PSPRS score ranges from 0 (normal) to 52. A positive change from baseline indicates worsening. Intent-to-Treat (ITT) population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139[1]	278[2]		
Units: Score on a scale				
arithmetic mean (standard error)				
PSPRS: 28 items	10.6 (± 0.8)	10.4 (± 0.6)		
PSPRS: 15 items	7.57 (± 0.52)	7.29 (± 0.38)		

Notes:

[1] - 'Number of Subjects Analysed' signifies number of subjects who had response on Week 52.

[2] - 'Number of Subjects Analysed' signifies number of subjects who had response on Week 52.

Statistical analyses

Statistical analysis title	28-items

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo,95% confidence interval and p-value at each time point were based on a mixed model for repeated measures model (MMRM), with change from baseline in 28-item PSPRS total score as dependent variable and with fixed effects of treatment group, time(categorical), treatment group-by-time interaction, baseline 28-item PSPRS, baseline 28-item PSPRS by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8483
Method	Mixed model for repeated measures (MMRM)
Parameter estimate	Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1.6

Statistical analysis title	15-items

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in 15-item PSPRS total score as dependent variable and with fixed effects of treatment group, time (categorical), treatment group by-time interaction, baseline 15-item PSPRS, baseline 15-item PSPRS by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6503
Method	MMRM
Parameter estimate	Difference
Point estimate	-0.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.94

Primary: Percentage of Subjects with Death, Serious Adverse Events (SAEs), Adverse Events (AEs) and Adverse Events (AEs) Leading to Discontinuation of Drug

End point title	Percentage of Subjects with Death, Serious Adverse Events (SAEs), Adverse Events (AEs) and Adverse Events (AEs) Leading to Discontinuation of Drug[3]

End point description:

AEs: any sign, symptom, or diagnosis/disease that is unfavorable or unintended, that is new, or if pre-existing, worsens in subjects administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. SAEs: an event that results in death; an event that, in the view of the investigator, places the subject at immediate risk of death (a life-threatening event); an outcome that results in a congenital anomaly/birth defect diagnosed in a child of a subject; an event that requires or prolongs inpatient hospitalization; an event that results in persistent or significant disability/incapacity. Safety population. Subjects randomised to Placebo that received at least one dose of BIIB092 2000 mg during the PC period was counted in the BIIB092 2000 mg group for the safety population. Three subjects who received BIIB092 in Placebo group were counted in BIIB092 200 mg group.

End point type	Primary

End point timeframe:

up to 52 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistical analysis was planned to be reported for this endpoint.

End point values	BIIB092 Late Start	BIIB092 Early Start		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	162	324		
Units: Percentage of subjects				
number (not applicable)				
Death	4.9	4.9		
SAEs	32.1	27.2		
AEs	93.2	92.9		
AEs Leading to Discontinuation of Drug	11.1	7.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Movement Disorder Society (MDS)-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II at Week 52

End point title	Change From Baseline in Movement Disorder Society (MDS)-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II at Week 52

End point description:

The MDS-UPRDRS Part 2 includes 13 items assessing motor aspects of experiences of daily living (M-EDL) these include speech, saliva and drooling, chewing and swallowing, handwriting, doing hobbies and other activities, eating tasks, tremor, dressing, hygiene, turning in bed, getting out of bed, walking and balance, and freezing. All items have 5 responses with uniform anchors of 0= normal, 1= slight, 2= mild, 3= moderate, and 4= severe. Total score ranges from 0 to 52, higher score indicating severe conditions. A positive change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143[4]	270[5]		
Units: Score on a scale				
arithmetic mean (standard error)	6.7 (± 0.6)	7.0 (± 0.4)		

Notes:

[4] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[5] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MDS-UPDRS as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline MDS-UPDRS, baseline MDS-UPDRS by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6031
Method	MMRM
Parameter estimate	Difference
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.7

Secondary: Clinical Global Impression of Change (CGI-C) Scale Score

End point title	Clinical Global Impression of Change (CGI-C) Scale Score

End point description:

The CGI-C scale measures the change in the patient's clinical status from a specific point in time. Using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4

indicating no change. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Week 52

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138[6]	271[7]		
Units: Score on a scale				
arithmetic mean (standard error)	5.3 (± 0.1)	5.2 (± 0.1)		

Notes:

[6] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[7] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with CGI-C as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline CGI-S, baseline CGI-S by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7743
Method	MMRM
Parameter estimate	Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Secondary: Change From Baseline in Progressive Supranuclear Palsy (PSP)-Cognitive Composite Battery Z-Score at Week 52

End point title	Change From Baseline in Progressive Supranuclear Palsy (PSP)-Cognitive Composite Battery Z-Score at Week 52

End point description:

The PSP cognitive composite battery is used to identify and characterize abnormal cognitive decline in PSP subjects. The PSP cognitive composite battery includes 13 sub-tests in total: 11 tests from the RBANS (only the picture naming is excluded), letter number sequencing test, and phonemic fluency test. Three domains are identified: Memory and learning, Visual-Motor function, and Working memory and Executive. A z-score transformation is applied for each component test at each visit, and the final total composite z-score is the average of the three-domain z-scores. A z-score of 0 is equal to the estimated mean adjusted by age and is considered average for this study population. Lower values are indicative

of cognitive decline. A negative change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134[8]	249[9]		
Units: z-score				
arithmetic mean (standard error)	-0.283 (± 0.032)	-0.245 (± 0.024)		

Notes:

[8] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[9] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSP-cognitive composite battery as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline PSP-cognitive composite battery, baseline PSP-cognitive composite battery by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	383
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.318
Method	MMRM
Parameter estimate	Difference
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.112

Secondary: Change From Baseline in Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS) Scale at Week 52

End point title	Change From Baseline in Repeatable Battery for the Assessment of Neuropsychological Disease Severity (RBANS) Scale at Week 52

End point description:

The RBANS provides both a total scale score and scores for 5 different cognitive domains. Specifically, the test measures immediate memory, visuospatial/constructional ability, language, attention, and delayed memory. Scores from all subtests are aggregated into a total composite score. RBANS data were age-normed and analysed as index scores (also referred to as standard scores), which have a mean of 100 and a standard deviation of 15. Higher scores on each sub measure and index better

performance. A negative change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111[10]	222[11]		
Units: Score on a scale				
arithmetic mean (standard error)	-3.1 (± 0.7)	-3.2 (± 0.5)		

Notes:

[10] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[11] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in RBANS as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline RBANS , baseline RBANS by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.827
Method	MMRM
Parameter estimate	Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.4

Secondary: Change From Baseline in Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL) Score

End point title	Change From Baseline in Progressive Supranuclear Palsy Quality of Life Scale (PSP-QoL) Score

End point description:

The PSP-QoL is a patient-reported outcome measure specifically for assessing the health-related quality of life in people living with PSP.It is validated 45-item questionnaire and visual analog scale(VAS)that is comprised of 2 subscales:physical health state (22 items), which covers mobility,dysarthria,dysphagia,visual disturbances,self-care and activities of daily living,and mental health state (23 items),which covers emotional,cognitive and social functioning.Items are given a 6-reponse option format (No Problem,Slight Problem,Moderate Problem,Marked Problem,Extreme Problem and Not Applicable).The

subscale results are derived by summing the respective items for that subscale and transforming the scores into a range of 0 to 100, the higher the scores=greater impact of the disease. The PSP-QoL also comprises of a Life Satisfaction rating gauge, which is a VAS with a range of 0 (worst) to 100 (best). ITT population. Here, 'n'=number of subjects analysed for each parameter.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142[12]	264[13]		
Units: Score on a scale				
arithmetic mean (standard error)				
Physical Scale Score (n=142, 264)	11.3 (± 1.5)	11.2 (± 1.1)		
Mental Scale Score (n=140, 264)	5.6 (± 1.4)	6.1 (± 1.0)		
Satisfaction With Your Life Today(n=141,264)	-3.7 (± 1.8)	-5.4 (± 1.3)		

Notes:

[12] - 'Number of Subjects Analysed' signifies number of subjects who had response on Week 52.

[13] - 'Number of Subjects Analysed' signifies number of subjects who had response on Week 52.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Physical scale score: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSP-QoL as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for PSP-QoL, baseline PSP-QoL by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9304
Method	MMRM
Parameter estimate	Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	3.3

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Mental scale score: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSPQoL as dependent variable and with fixed effects of treatment group, time (categorical), treatment

group-bytime interaction, baseline for PSP-QoL, baseline PSP-QoL by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7859
Method	MMRM
Parameter estimate	Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	3.7

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Satisfaction With Your Life Today: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in PSPQoL as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-bytime interaction, baseline for PSP-QoL, baseline PSP-QoL by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4297
Method	MMRM
Parameter estimate	Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	2.5

Secondary: Change From Baseline in Schwab and England Activities of Daily Living (SEADL) Scale Score at Week 48

End point title	Change From Baseline in Schwab and England Activities of Daily Living (SEADL) Scale Score at Week 48

End point description:

The SEADL scale is a means of assessing a person's ability to perform daily activities in terms of speed and independence, with 100% indicating total independence, falling to 0%, which indicates a state of complete dependence. The individual is asked to rate his or her function using an 11-point scale (10% increments), from 100% (completely independent; able to do all chores without slowness, difficulty, or impairment; essentially normal; unaware of any difficulty) to 0% (vegetative functions such as swallowing, bladder and bowels are not functioning; bedridden). A negative change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140[14]	277[15]		
Units: Score on a scale				
arithmetic mean (standard error)	-13.7 (± 1.4)	-11.7 (± 1.0)		

Notes:

[14] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[15] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in SEADL as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for SEADL , baseline SEADL by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2084
Method	MMRM
Parameter estimate	Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	5.2

Secondary: Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Week 52

End point title	Change From Baseline in Clinical Global Impression of Severity (CGI-S) Score at Week 52

End point description:

The Clinical Global Impression of Severity (CGI-S) Rating evaluates the severity of individual symptoms and treatment response in subjects with mental disorders. The CGI-S is a 7-point scale that that requires the clinician to rate the severity of the patient's illness at the time of assessment. A rating of 1 is considered normal, or with the least severe symptoms, a rating of 7 is extremely ill, or the worst symptoms. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140[16]	269[17]		
Units: Score on a scale				
arithmetic mean (standard error)	0.6 (± 0.1)	0.6 (± 0.0)		

Notes:

[16] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[17] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in CGI-S as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for CGI-S, baseline CGI-S by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5701
Method	MMRM
Parameter estimate	Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1

Secondary: Change From Baseline in Phonemic Fluency Test Score at Week 48

End point title	Change From Baseline in Phonemic Fluency Test Score at Week 48

End point description:

Phonemic fluency is a sensitive test for assessing frontal lobe dysfunction. Subjects are given a letter of the alphabet and asked to name as many words as they can that start with that letter in 1 minute. The score for each trial is auto-calculated as follows: Trial 1: Total number of correct responses for the first letter (range 0 to 40); Trial 2: Total number of correct responses for the second letter (range 0 to 40). The total score from the two trials was used for analysis (range 0 to 80). More number of words correlates to better phonemic fluency. A negative change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141[18]	273[19]		
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.9 (± 0.4)	0.0 (± 0.3)		

Notes:

[18] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[19] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092(Late Start Vs Early Start)

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Phonemic Fluency Test as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline Phonemic Fluency Test, baseline Phonemic Fluency Test by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0517
Method	MMRM
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.8

Secondary: Change From Baseline in Letter-Number Sequencing Test at Week 48

End point title	Change From Baseline in Letter-Number Sequencing Test at Week 48

End point description:

Letter number is a test of working memory which involves ordering a series of up to 8 letters and numbers in which the numbers are repeated back first in order starting with the lowest number, then followed by the letters in alphabetical order. LNS consists of 10 items and each item has 3 trials rated as Incorrect (0) or Correct (1). The LNS total raw score (range 0 to 30) is auto-calculated by summing the 10 individual item scores (range 0 to 3 for each item). Higher number of correct items correlated to better performance and a negative change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139[20]	271[21]		
Units: Score on a scale				
arithmetic mean (standard error)	-1.9 (± 0.4)	-1.1 (± 0.3)		

Notes:

[20] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[21] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Letter Number Sequence as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline Letter Number Sequence, baseline Letter Number Sequence by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	410
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0387
Method	MMRM
Parameter estimate	Difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.7

Secondary: Change From Baseline in Color Trails at Week 48

End point title	Change From Baseline in Color Trails at Week 48

End point description:

The Color Trails test is a language free version of the Trail Making Test and was developed to allow for broader cross-cultural assessment. For Part 1 (color trails test 1), the respondent uses a pencil to rapidly connect circles numbered 1-25 in sequence. For Part 2 (color trails test 2), the respondent rapidly connects number circles in sequence, but alternates between pink and yellow background. The length of time to complete each trial is recorded, along with qualitative features of performance indicative of brain dysfunction, such as near-misses, prompts, number sequence errors, and color sequence errors. Less time indicates better performance. A positive change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143[22]	279[23]		
Units: Seconds				
arithmetic mean (standard error)				
Color Trails Test 1	16.8 (± 3.6)	16.9 (± 2.7)		
Color Trails Test 2	10.6 (± 2.4)	10.5 (± 1.8)		

Notes:

[22] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[23] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Color Trails Test 1: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Color trails Test 1 as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for Color Trails Test 1, baseline Color Trails Test 1 by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9815
Method	MMRM
Parameter estimate	Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	8.3

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Color Trails Test 2: Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in Color Trails Test 2 as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for Color Trails Test 2, baseline Color Trails Test 2 by time interaction, and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)

Number of subjects included in analysis	422
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9869
Method	MMRM
Parameter estimate	Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	5.6

Secondary: Change From Baseline in Montreal Cognitive Assessment (MoCA) Score at Week 48

End point title	Change From Baseline in Montreal Cognitive Assessment (MoCA) Score at Week 48

End point description:

The MOCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Scores on the MOCA range from 0-30, with higher score being better performance. A negative change from baseline indicates worsening. ITT population included randomised subjects who had received at least 1 dose of blinded study treatment (BII092 or Placebo).

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136[24]	264[25]		
Units: Score on a scale				
arithmetic mean (standard error)	-1.0 (± 0.3)	-0.5 (± 0.2)		

Notes:

[24] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

[25] - 'Number of Subjects Analysed' signifies the total number of subjects analysed in this endpoint.

Statistical analyses

Statistical analysis title	BIIB092 Late Start vs BIIB092 Early Start

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MoCA as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MoCA, baseline MoCA by time interaction,baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)

Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1763
Method	MMRM
Parameter estimate	Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.2

Secondary: Number of Participants with Treatment Emergent Antibodies (anti-BIIB092) Positive Results in Serum

End point title	Number of Participants with Treatment Emergent Antibodies (anti-BIIB092) Positive Results in Serum

End point description:

ADA population – subset of the safety population with at least one evaluable post-baseline evaluable ADA samples.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	BIIB092 Late Start	BIIB092 Early Start		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	162	323		
Units: Subjects	7	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Brain Volumes as Determined by MRI at Week 52

End point title	Change From Baseline of Brain Volumes as Determined by MRI at Week 52

End point description:

A 3 dimension (3D) T1-weighted MRI was performed to estimate brain volumes (e.g., ventricles, whole brain, midbrain, pons, superior cerebellar peduncle, third ventricle, and frontal lobes). Efficacy MRI population is the subset of the ITT population who had a least one measurable brain volumetric measurement. Here, 'n' signifies the number of subjects analysed for each parameter.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Placebo (PC Period)	BIIB092 2000 mg (PC Period)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114[26]	238[27]		
Units: Cubic centimeter (cm^3)				
arithmetic mean (standard error)				
Ventricles Volume: Change at Week 52 (n =103,222)	3.823 (± 0.302)	3.802 (± 0.216)		
Whole Brain Volume: Change at Week 52(n =101,210)	-18.612 (± 1.296)	-19.126 (± 0.950)		
Midbrain Volume: Change at Week 52 (n =108, 224)	-0.116 (± 0.008)	-0.120 (± 0.006)		
Pons Volume: Change at Week 52 (n =100, 223)	-0.198 (± 0.017)	-0.198 (± 0.012)		
Cerebellar Peduncle Volume:ChangeWeek52(n=101,216)	-0.005 (± 0.002)	-0.004 (± 0.002)		
Third Ventricle Volume:Change at Week52(n=114,238)	0.140 (± 0.014)	0.146 (± 0.010)		
Frontal Lobe Volume: Change at Week 52 (n =89,178)	1.184 (± 0.279)	1.143 (± 0.205)		

Notes:

[26] - 'Number of Subjects Analysed' signifies number of subjects who had response on Week 52.

[27] - 'Number of Subjects Analysed' signifies number of subjects who had response on Week 52.

Statistical analyses

Statistical analysis title	Ventricles Volume

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9527
Method	MMRM
Parameter estimate	Difference
Point estimate	-0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.726
upper limit	0.684

Statistical analysis title	Whole Brain Volume

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7357
Method	MMRM
Parameter estimate	Difference
Point estimate	-0.514
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.506
upper limit	2.478

Statistical analysis title	Midbrain Volume

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6439
Method	MMRM
Parameter estimate	Difference
Point estimate	-0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.023
upper limit	0.014

Statistical analysis title	Pons Volume

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9864
Method	MMRM
Parameter estimate	Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.04

Statistical analysis title	Cerebellar Peduncle Volume

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7529
Method	MMRM
Parameter estimate	Difference
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.006

Statistical analysis title	Third Ventricle Volume

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.685
Method	MMRM
Parameter estimate	Difference
Point estimate	0.006

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.038

Statistical analysis title	Frontal Lobe Volume

Statistical analysis description:

Adjusted mean for each treatment group, difference with Placebo, 95% confidence interval and p-value at each time point were based on an MMRM model, with change from baseline in MRI region as dependent variable and with fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline for MRI region, baseline MRI region by time interaction, baseline Color Trails 2 test (<=170 or >170 seconds) and region.

Comparison groups	Placebo (PC Period) v BIIB092 2000 mg (PC Period)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	MMRM
Parameter estimate	Difference
Point estimate	-0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	0.598

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to 140 weeks

Adverse event reporting additional description:

Subjects randomised to Placebo that received at least 1 dose of BIIB092 2000 mg during the PC period was counted in the BIIB092 2000 mg group for the safety population. Subjects exposed are subjects who received drug in respective study periods. Subjects affected were counted only once within each system organ class/preferred term/study period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo (PC Period)

Reporting group description:

Subjects assigned to BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks in double-blind PC period and received only placebo.

Reporting group title	BIIB092 2000 mg (PC Period)

Reporting group description:

Subjects who received at least one dose of BIIB092 2000 mg and were either assigned to BIIB092 2000 mg IV infusion or BIIB092 matching placebo IV infusion once every 4 weeks for 48 weeks in double blind PC period.

Reporting group title	BIIB092 late start (OLE Period)

Reporting group description:

Late start subjects received only placebo in the PC period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.

Reporting group title	BIIB092 early start (OLE Period)

Reporting group description:

Early start subjects are those who received BIIB092 2000 mg in the PC period and assigned to BIIB092 2000 mg IV infusion once every 4 weeks starting at Week 52 in the OLE period.

Serious adverse events	Placebo (PC Period)	BIIB092 2000 mg (PC Period)	BIIB092 late start (OLE Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 162 (32.10%)	88 / 324 (27.16%)	40 / 137 (29.20%)
number of deaths (all causes)	8	16	10
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Breast neoplasm			

subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Colorectal cancer			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Malignant melanoma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Malignant melanoma in situ			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Metastatic gastric cancer			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pituitary tumour benign			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Prostate cancer			

subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Death			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Drowning			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Euthanasia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Gait disturbance			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait inability			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
General physical health deterioration			
subjects affected / exposed	1 / 162 (0.62%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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

Prostatitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Aspiration			
subjects affected / exposed	3 / 162 (1.85%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Choking			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 162 (1.23%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	8 / 162 (4.94%)	6 / 324 (1.85%)	5 / 137 (3.65%)
occurrences causally related to treatment / all	0 / 9	0 / 6	0 / 6
deaths causally related to treatment / all	0 / 4	0 / 2	0 / 1

Pneumothorax			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Pulmonary embolism			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Respiratory arrest			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Respiratory depression			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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 distress			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Respiratory failure			
subjects affected / exposed	3 / 162 (1.85%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Anxiety			

subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Assisted suicide			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Confusional state			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Hallucination			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Mental status changes			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Suicidal ideation			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Liver function test increased			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Lumbar puncture			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 162 (0.00%)	3 / 324 (0.93%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Concussion			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Contusion			

subjects affected / exposed	1 / 162 (0.62%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Fall			
subjects affected / exposed	10 / 162 (6.17%)	41 / 324 (12.65%)	8 / 137 (5.84%)
occurrences causally related to treatment / all	0 / 11	0 / 45	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 162 (0.62%)	3 / 324 (0.93%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Fracture			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Hip fracture			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human bite			

subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Humerus fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Joint dislocation			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal foreign body			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Open globe injury			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Periprosthetic fracture			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Radius fracture			

subjects affected / exposed	0 / 162 (0.00%)	3 / 324 (0.93%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 162 (0.62%)	4 / 324 (1.23%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Scapula fracture			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Skin laceration			
subjects affected / exposed	1 / 162 (0.62%)	4 / 324 (1.23%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 162 (0.62%)	2 / 324 (0.62%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			

subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Tendon rupture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Thermal burn			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Tibia fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Traumatic haematoma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Wrist fracture			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Wrong dose			

subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Atrioventricular block second degree			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Cardiac arrest			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
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 failure			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypertensive heart disease			

subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Akathisia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Cerebral disorder			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Dyskinesia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Encephalopathy			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Epilepsy			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbosacral radiculopathy			

subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Metabolic encephalopathy			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Monoparesis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Movement disorder			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Noninfective encephalitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Peroneal nerve palsy			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Progressive supranuclear palsy			
subjects affected / exposed	3 / 162 (1.85%)	6 / 324 (1.85%)	5 / 137 (3.65%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 3
Seizure			

subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Somnolence			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Syncope			
subjects affected / exposed	1 / 162 (0.62%)	2 / 324 (0.62%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Iron deficiency anaemia			
subjects affected / exposed	1 / 162 (0.62%)	1 / 324 (0.31%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Colitis microscopic			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 162 (0.62%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Dysphagia			
subjects affected / exposed	5 / 162 (3.09%)	3 / 324 (0.93%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	1 / 5	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Femoral hernia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Gastritis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Hernial eventration			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Hiatus hernia			

subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Large intestine polyp			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Melaena			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Umbilical hernia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Volvulus			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Skin and subcutaneous tissue disorders			

Dermal cyst			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Hydronephrosis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Nephrolithiasis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Renal impairment			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Ureterolithiasis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Urge incontinence			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Urinary retention			

subjects affected / exposed	1 / 162 (0.62%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondrocalcinosis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Haematoma muscle			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Muscle rigidity			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Osteitis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Osteoarthritis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Pain in extremity			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Abscess neck			
subjects affected / exposed	1 / 162 (0.62%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Bacterial infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Bronchitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Cystitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Diverticulitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Gastroenteritis			

subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 162 (0.62%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Pneumonia			
subjects affected / exposed	0 / 162 (0.00%)	10 / 324 (3.09%)	5 / 137 (3.65%)
occurrences causally related to treatment / all	0 / 0	0 / 11	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Respiratory syncytial virus bronchitis			

subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Urinary tract infection			
subjects affected / exposed	3 / 162 (1.85%)	1 / 324 (0.31%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 162 (0.00%)	0 / 324 (0.00%)	0 / 137 (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
Viral infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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
Wound infection staphylococcal			

subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	0 / 137 (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			
Dehydration			
subjects affected / exposed	0 / 162 (0.00%)	1 / 324 (0.31%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 162 (0.62%)	0 / 324 (0.00%)	0 / 137 (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
Failure to thrive			
subjects affected / exposed	0 / 162 (0.00%)	2 / 324 (0.62%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0

Serious adverse events	BIIB092 early start (OLE Period)		
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 279 (22.58%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast neoplasm			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			

subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma in situ				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic gastric cancer				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pituitary tumour benign				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Cyst				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	2 / 279 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Drowning				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Euthanasia				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gait disturbance				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gait inability				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Systemic inflammatory response syndrome				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Acquired phimosis				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Benign prostatic hyperplasia				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostatitis				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal				

disorders				
Acute respiratory failure				
subjects affected / exposed	4 / 279 (1.43%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Choking				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	12 / 279 (4.30%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pulmonary embolism				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary oedema				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory arrest				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory depression				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory distress				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Agitation				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anxiety				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Assisted suicide				

subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Confusional state				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Insomnia				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver function test increased				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar puncture				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	2 / 279 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Clavicle fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	11 / 279 (3.94%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	2 / 279 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Human bite				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				

subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal foreign body				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Open globe injury				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periprosthetic fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Scapula fracture				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	2 / 279 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon injury				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thermal burn				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic haematoma				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Traumatic intracranial haemorrhage				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrong dose				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block second degree				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive heart disease				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				

subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Akathisia			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral disorder			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 279 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyskinesia			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbosacral radiculopathy			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			

subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoparesis				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Movement disorder				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neurological decompensation				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Noninfective encephalitis				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peroneal nerve palsy				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Progressive supranuclear palsy				
subjects affected / exposed	4 / 279 (1.43%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 3			
Seizure				
subjects affected / exposed	2 / 279 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Somnolence				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	2 / 279 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Iron deficiency anaemia				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis microscopic				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				

subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	4 / 279 (1.43%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Faecaloma			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femoral hernia			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hernial eventration			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hiatus hernia			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			

subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Melaena			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermal cyst			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Calculus urinary			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ureterolithiasis			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urge incontinence			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chondrocalcinosis			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematoma muscle			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle rigidity			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteitis			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			

subjects affected / exposed	2 / 279 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Bacterial infection			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	2 / 279 (0.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Parainfluenzae virus infection				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	6 / 279 (2.15%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 2			
Pneumonia influenzal				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary tuberculosis				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus bronchitis				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 279 (0.72%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	4 / 279 (1.43%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 279 (0.36%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Viral infection				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection staphylococcal				
subjects affected / exposed	0 / 279 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				

subjects affected / exposed	1 / 279 (0.36%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 279 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Failure to thrive			
subjects affected / exposed	0 / 279 (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	Placebo (PC Period)	BIIB092 2000 mg (PC Period)	BIIB092 late start (OLE Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 162 (78.40%)	235 / 324 (72.53%)	69 / 137 (50.36%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	24 / 162 (14.81%)	41 / 324 (12.65%)	15 / 137 (10.95%)
occurrences (all)	42	63	19
Fall			
subjects affected / exposed	83 / 162 (51.23%)	174 / 324 (53.70%)	45 / 137 (32.85%)
occurrences (all)	204	359	91
Head injury			
subjects affected / exposed	8 / 162 (4.94%)	21 / 324 (6.48%)	4 / 137 (2.92%)
occurrences (all)	10	24	5
Skin abrasion			
subjects affected / exposed	10 / 162 (6.17%)	28 / 324 (8.64%)	7 / 137 (5.11%)
occurrences (all)	26	46	10
Skin laceration			
subjects affected / exposed	18 / 162 (11.11%)	40 / 324 (12.35%)	8 / 137 (5.84%)
occurrences (all)	26	52	15
Vascular disorders			

Haematoma			
subjects affected / exposed	11 / 162 (6.79%)	24 / 324 (7.41%)	7 / 137 (5.11%)
occurrences (all)	17	35	9
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 162 (8.02%)	18 / 324 (5.56%)	0 / 137 (0.00%)
occurrences (all)	17	20	0
Headache			
subjects affected / exposed	22 / 162 (13.58%)	31 / 324 (9.57%)	3 / 137 (2.19%)
occurrences (all)	31	46	3
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	15 / 162 (9.26%)	36 / 324 (11.11%)	4 / 137 (2.92%)
occurrences (all)	15	38	4
Diarrhoea			
subjects affected / exposed	9 / 162 (5.56%)	23 / 324 (7.10%)	4 / 137 (2.92%)
occurrences (all)	11	26	6
Psychiatric disorders			
Insomnia			
subjects affected / exposed	14 / 162 (8.64%)	16 / 324 (4.94%)	4 / 137 (2.92%)
occurrences (all)	14	18	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 162 (4.32%)	18 / 324 (5.56%)	0 / 137 (0.00%)
occurrences (all)	9	19	0
Back pain			
subjects affected / exposed	9 / 162 (5.56%)	15 / 324 (4.63%)	3 / 137 (2.19%)
occurrences (all)	11	16	8
Musculoskeletal pain			
subjects affected / exposed	6 / 162 (3.70%)	19 / 324 (5.86%)	2 / 137 (1.46%)
occurrences (all)	7	19	2
Pain in extremity			
subjects affected / exposed	7 / 162 (4.32%)	17 / 324 (5.25%)	0 / 137 (0.00%)
occurrences (all)	7	17	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	14 / 162 (8.64%)	28 / 324 (8.64%)	6 / 137 (4.38%)
occurrences (all)	15	32	6
Urinary tract infection			
subjects affected / exposed	31 / 162 (19.14%)	56 / 324 (17.28%)	15 / 137 (10.95%)
occurrences (all)	44	85	18

Non-serious adverse events	BIIB092 early start (OLE Period)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	130 / 279 (46.59%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	24 / 279 (8.60%)		
occurrences (all)	33		
Fall			
subjects affected / exposed	79 / 279 (28.32%)		
occurrences (all)	138		
Head injury			
subjects affected / exposed	8 / 279 (2.87%)		
occurrences (all)	8		
Skin abrasion			
subjects affected / exposed	12 / 279 (4.30%)		
occurrences (all)	18		
Skin laceration			
subjects affected / exposed	14 / 279 (5.02%)		
occurrences (all)	16		
Vascular disorders			
Haematoma			
subjects affected / exposed	11 / 279 (3.94%)		
occurrences (all)	14		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 279 (1.08%)		
occurrences (all)	4		
Headache			

subjects affected / exposed occurrences (all)	13 / 279 (4.66%) 22		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 16 / 279 (5.73%) 19 9 / 279 (3.23%) 9		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 10 / 279 (3.58%) 11		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 3 / 279 (1.08%) 3 11 / 279 (3.94%) 11 3 / 279 (1.08%) 3 5 / 279 (1.79%) 5		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 16 / 279 (5.73%) 19 36 / 279 (12.90%) 40		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 August 2017	Sponsor name from BMS to Biogen. This includes replacing the BMS title page with the Biogen title page, inserting the Biogen Sponsor Signature Page and Biogen Sponsor Information section, changing the compound name from BMS-986168 to BIIB092 throughout the document, and changing the study name from CN002012 to 251PP301.
13 September 2017	Sponsor name changed from BMS to Biogen. This includes replacing the BMS title page with the Biogen title page, inserting the Biogen Sponsor Signature Page and Biogen Sponsor Information section, changing the compound name from BMS-986168 to BIIB092 throughout the document, and changing the study name from CN002012 to 251PP301.
14 November 2017	Missing safety assessment, 12-lead electrocardiogram (ECG), and instruction to the assess infusion site to the double-blind schedule of events was added.
16 May 2018	Increase in the study sample size.
24 May 2018	An error was corrected in the decision criteria that would allow a subject who no longer has an active hepatitis C infection to enroll in the study.
01 February 2019	The study treatment product provided for use in the open-label extension period, to include the 2000 milligram per vial (mg/vial).

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.

Study got terminated as the primary endpoint was not met. PC period was completed at the time of termination. The study was not terminated due to a safety concern.

Notes: