Clinical trial results:
A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered BI 409306 during a 28-week treatment period as adjunctive therapy to antipsychotic treatment for the prevention of relapse in patients with schizophrenia

Summary

EudraCT number	2017-002369-23
Trial protocol	ES
Global end of trial date	31 March 2021

Results information

Result version number	v1
This version publication date	25 March 2022
First version publication date	25 March 2022

Trial information

Trial identification

Sponsor protocol code	1289-0049

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03351244
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 18002430127, clintriage.rdg@boehringer-ingelheim.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	28 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2021
Global end of trial reached?	Yes
Global end of trial date	31 March 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of the trial was to investigate the efficacy, safety, and tolerability of BI 409306 25 mg and 50 mg once daily compared with placebo given for 28 weeks in patients with schizophrenia on antipsychotic treatment. The trial was designed to show superiority of BI 409306 over placebo in preventing relapse of schizophrenia symptoms.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 353
Country: Number of subjects enrolled	Japan: 66
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Spain: 1
Worldwide total number of subjects	470
EEA total number of subjects	19

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)	470
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase II trial aimed to evaluate the impact of 28-week treatment with BI 409306 (added to standard antipsychotic medication) compared with placebo on preventing relapse in patients with schizophrenia.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Subjects attended a specialist site which ensured that they (the subjects) strictly met all inclusion and none of the exclusion criteria. Subjects were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 409306 25 mg

Arm description:

1 film-coated tablet of 25 milligrams (mg) of BI 409306 plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7.

Taper period: 2 tablets of 10 mg BI 409306 and 2 tablets of placebo q.d. on Day 1 of the taper period; 2 tablets of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 2-3 of taper period; 1 tablet of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Arm type	Experimental
Investigational medicinal product name	BI 409306
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 film-coated tablet of 25 milligrams (mg) of BI 409306 plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups. Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7. Taper period: 2 tablets of 10 mg BI 409306 and 2 tablets of placebo q.d. on Day 1 of the taper period; 2 tablets of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 2-3 of taper period; 1 tablet of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Arm title	BI 409306 50 mg

Arm description:

1 film-coated tablet of 50 milligrams (mg) of BI 409306 plus 1 tablet of 25 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period

of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal period.

Taper period: 4 tablets of 10 mg BI 409306 q.d. on Day 1 of taper period; 3 tablets of 10 mg BI 409306 q.d. on Day 2-3 of taper period; 2 tablets of 10 mg BI 409306 q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Arm type	Experimental
Investigational medicinal product name	BI 409306
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 film-coated tablet of 50 milligrams (mg) of BI 409306 plus 1 tablet of 25 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups. Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal period. Taper period: 4 tablets of 10 mg BI 409306 q.d. on Day 1 of taper period; 3 tablets of 10 mg BI 409306 q.d. on Day 2-3 of taper period; 2 tablets of 10 mg BI 409306 q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Arm title	Placebo

Arm description:

1 film-coated tablet of 25 milligrams (mg) of matching Placebo plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Both withdrawal and taper periods: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal/taper period; 3 tablets of 10 mg placebo q.d. on Day 2-3 of withdrawal/taper period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal/taper period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal/taper period.

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

Dosage and administration details:

1 film-coated tablet of 25 milligrams (mg) of matching Placebo plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups. Both withdrawal and taper periods: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal/taper period; 3 tablets of 10 mg placebo q.d. on Day 2-3 of withdrawal/taper period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal/taper period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal/taper period.

Number of subjects in period 1[1]	BI 409306 25 mg	BI 409306 50 mg	Placebo
Started	89	88	87
Completed	62	48	53
Not completed	27	40	34
COVID-19 restrictions	3	-	1
Consent withdrawn by subject	11	16	13
Investigator's decision	-	-	2
System error	-	-	2
Adverse event, non-fatal	7	11	12
Non-compliance	2	5	-
Lost to follow-up	2	6	4
Protocol deviation	2	2	-

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: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	BI 409306 25 mg

Reporting group description:

1 film-coated tablet of 25 milligrams (mg) of BI 409306 plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7.

Taper period: 2 tablets of 10 mg BI 409306 and 2 tablets of placebo q.d. on Day 1 of the taper period; 2 tablets of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 2-3 of taper period; 1 tablet of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Reporting group title	BI 409306 50 mg

Reporting group description:

1 film-coated tablet of 50 milligrams (mg) of BI 409306 plus 1 tablet of 25 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal period.

Taper period: 4 tablets of 10 mg BI 409306 q.d. on Day 1 of taper period; 3 tablets of 10 mg BI 409306 q.d. on Day 2-3 of taper period; 2 tablets of 10 mg BI 409306 q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Reporting group title	Placebo

Reporting group description:

1 film-coated tablet of 25 milligrams (mg) of matching Placebo plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Both withdrawal and taper periods: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal/taper period; 3 tablets of 10 mg placebo q.d. on Day 2-3 of withdrawal/taper period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal/taper period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal/taper period.

Reporting group values	BI 409306 25 mg	BI 409306 50 mg	Placebo
Number of subjects	89	88	87
Age categorical			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

Adults (18-64 years)	89	88	87
From 65-84 years	0	0	0
85 years and over	0	0	0

Age Continuous			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: years			
arithmetic mean	38.4	41.9	40.5
standard deviation	± 9.8	± 9.6	± 9.8

Sex: Female, Male			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Participants			
Female	29	36	32
Male	60	52	55

Race (NIH/OMB)			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	23	20	20
Native Hawaiian or Other Pacific Islander	0	2	0
Black or African American	36	37	32
White	23	24	25
More than one race	1	1	2
Unknown or Not Reported	6	4	8

Ethnicity (NIH/OMB)			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Subjects			
Hispanic or Latino	10	15	15
Not Hispanic or Latino	75	69	68
Unknown or Not Reported	4	4	4

Reporting group values	Total		
Number of subjects	264		
Age categorical			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	264		
From 65-84 years	0		
85 years and over	0		

Age Continuous			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Participants			
Female	97		
Male	167		
Race (NIH/OMB)			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	63		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	105		
White	72		
More than one race	4		
Unknown or Not Reported	18		
Ethnicity (NIH/OMB)			
Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.			
Units: Subjects			
Hispanic or Latino	40		
Not Hispanic or Latino	212		
Unknown or Not Reported	12		

End points

End points reporting groups

Reporting group title	BI 409306 25 mg

Reporting group description:

1 film-coated tablet of 25 milligrams (mg) of BI 409306 plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7.

Taper period: 2 tablets of 10 mg BI 409306 and 2 tablets of placebo q.d. on Day 1 of the taper period; 2 tablets of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 2-3 of taper period; 1 tablet of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Reporting group title	BI 409306 50 mg

Reporting group description:

1 film-coated tablet of 50 milligrams (mg) of BI 409306 plus 1 tablet of 25 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal period.

Taper period: 4 tablets of 10 mg BI 409306 q.d. on Day 1 of taper period; 3 tablets of 10 mg BI 409306 q.d. on Day 2-3 of taper period; 2 tablets of 10 mg BI 409306 q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Reporting group title	Placebo

Reporting group description:

1 film-coated tablet of 25 milligrams (mg) of matching Placebo plus 1 tablet of 50 mg matching placebo were administered orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of treatment groups.

Both withdrawal and taper periods: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal/taper period; 3 tablets of 10 mg placebo q.d. on Day 2-3 of withdrawal/taper period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal/taper period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal/taper period.

Subject analysis set title	BI 409306 pooled
Subject analysis set type	Full analysis

Subject analysis set description:

This group included all participants who administered BI 409306 during the study.

Primary: Incidence rate of first relapse after 28 weeks of treatment

End point title	Incidence rate of first relapse after 28 weeks of treatment

End point description:

The incidence rate of first relapse after 28 weeks of treatment is reported.

Full analysis set (FAS): the FAS includes all patients in the treated set with at least 1 baseline and post-baseline measurement of any type.

End point type	Primary

End point timeframe:

28 weeks

End point values	BI 409306 25 mg	BI 409306 50 mg	Placebo	BI 409306 pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	89	88	87	177
Units: Events per patient-years				
number (not applicable)	0.527	0.434	0.496	0.482

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: The model included the treatment effect as the only covariate and was stratified by country.	
Comparison groups	BI 409306 25 mg v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7735
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.585
upper limit	2.056

Statistical analysis title	Statistical analysis 3
Statistical analysis description: The model included the treatment effect as the only covariate and was stratified by country.	
Comparison groups	Placebo v BI 409306 pooled
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9862
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.576
upper limit	1.753

Statistical analysis title	Statistical analysis 2
Statistical analysis description: The model included the treatment effect as the only covariate and was stratified by country.	
Comparison groups	BI 409306 50 mg v Placebo
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7809
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.468
upper limit	1.77

Secondary: Change from baseline in Positive and Negative Syndrome Scale (PANSS) positive symptoms score after 28 weeks of treatment

End point title	Change from baseline in Positive and Negative Syndrome Scale (PANSS) positive symptoms score after 28 weeks of treatment
End point description: Positive and Negative Syndrome Scale (PANSS): assesses the severity of psychotic symptoms and progression of disease. The PANSS positive symptoms score is the sum of scores from 7 Items where each item has a minimum score 1 (better outcome) and maximum score 7 (worse outcome). The PANSS postive symptoms score ranges from 7 (less severe the disease) to 49 (more severe the disease). Full analysis set (FAS): the FAS includes all patients in the treated set with at least 1 baseline and post-baseline measurement of any type. Only participants with non-missing results were included in the analysis.	
End point type	Secondary
End point timeframe: At baseline and at Week 28.	

End point values	BI 409306 25 mg	BI 409306 50 mg	Placebo	BI 409306 pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	73	55	65	128
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	-0.54 (-1.370 to 0.294)	-0.71 (-1.641 to 0.224)	-0.92 (-1.769 to -0.070)	-0.61 (-1.231 to 0.005)

Statistical analyses

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

A restricted maximum likelihood-based approach using a mixed model with repeated measurements was applied. The analysis included the fixed, categorical effects of treatment at each visit, and the fixed continuous effects of baseline at each visit.

Comparison groups	BI 409306 25 mg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5289
Method	Mixed model with repeated measurements
Parameter estimate	Placebo-corrected adjusted mean
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.809
upper limit	1.57

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

A restricted maximum likelihood-based approach using a mixed model with repeated measurements was applied. The analysis included the fixed, categorical effects of treatment at each visit, and the fixed continuous effects of baseline at each visit.

Comparison groups	BI 409306 50 mg v Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.744
Method	Mixed model with repeated measurements
Parameter estimate	Placebo-corrected adjusted mean
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.055
upper limit	1.475

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

A restricted maximum likelihood-based approach using a mixed model with repeated measurements was applied. The analysis included the fixed, categorical effects of treatment at each visit, and the fixed continuous effects of baseline at each visit.

Comparison groups	Placebo v BI 409306 pooled

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5659
Method	Mixed model with repeated measurements
Parameter estimate	Placebo-corrected adjusted mean
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.745
upper limit	1.358

Secondary: Change from baseline in Clinical Global Impressions–Severity (CGI-S) scale score after 28 weeks of treatment

End point title	Change from baseline in Clinical Global Impressions–Severity (CGI-S) scale score after 28 weeks of treatment

End point description:

Clinical Global Impressions-Severity (CGI-S): One-item evaluation completed by the clinician to measure the severity of psychopathology.
The CGI-S score ranges from 1 (normal) through to 7 (most severely ill). The higher the score, the worse the psychopathology.

Full analysis set (FAS): the FAS includes all patients in the treated set with at least 1 baseline and post-baseline measurement of any type.
Only participants with non-missing results were included in the analysis.

End point type	Secondary

End point timeframe:

At baseline and at Week 28

End point values	BI 409306 25 mg	BI 409306 50 mg	Placebo	BI 409306 pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	73	55	65	128
Units: Score on a scale				
arithmetic mean (standard deviation)	-0.15 (± 0.758)	-0.22 (± 0.839)	-0.22 (± 0.718)	-0.18 (± 0.791)

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impressions-Improvement (PGI-I) scale score after 28 weeks of treatment

End point title	Patient Global Impressions-Improvement (PGI-I) scale score after 28 weeks of treatment

End point description:

Patient Global Impressions-Improvement (PGI-I): One-item evaluation completed by the patient to assess their overall evaluation of his/her status compared to how they felt at randomisation.
The PGI-I score ranges from 1 (Very much better) through to 7 (Very much worse). The higher the score, the worse the improvement.

Full analysis set (FAS): the FAS includes all patients in the treated set with at least 1 baseline and post-baseline measurement of any type.
Only participants with non-missing results were included in the analysis.

End point type	Secondary

End point timeframe:

At Week 28

End point values	BI 409306 25 mg	BI 409306 50 mg	Placebo	BI 409306 pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	54	63	126
Units: Score on a scale				
arithmetic mean (standard deviation)	2.61 (± 1.328)	2.96 (± 1.197)	2.94 (± 1.190)	2.76 (± 1.280)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of suicidal ideation and behaviour (assessed by Columbia Suicide Severity Rating Scale (C-SSRS)) after 28 weeks of treatment

End point title	Incidence rate of suicidal ideation and behaviour (assessed by Columbia Suicide Severity Rating Scale (C-SSRS)) after 28 weeks of treatment

End point description:

Columbia Suicide Severity Rating Scale (C-SSRS): suicide risk assessment. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed.
Suicidal behavior is collected in nominal scale as presence/absence of actual attempts, non-suicidal self-injurious behavior, interrupted attempts, aborted attempts, preparatory acts or behavior, and any suicidal behavior.
Suicidal ideation is rated on a 6-point scale from 0 (No ideation present) to 5 (Active ideation with plan and intent). A score of 4 or 5 on this scale indicates serious suicidal ideation.

The Incidence rate of suicidal ideation and behaviour (assessed by C-SSRS) after 28 weeks of treatment is reported.

Full analysis set (FAS): the FAS includes all patients in the treated set with at least 1 baseline and post-baseline measurement of any type.

End point type	Secondary

End point timeframe:

28 weeks

End point values	BI 409306 25 mg	BI 409306 50 mg	Placebo	BI 409306 pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	89	88	87	177
Units: Events per patient-years				
number (not applicable)	0.070	0.077	0.071	0.073

Statistical analyses

Statistical analysis title	Statistical analysis 7
Statistical analysis description:	
The model included the treatment effect as the only covariate and was stratified by country.	
Comparison groups	BI 409306 25 mg v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9938
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.203
upper limit	4.989

Statistical analysis title	Statistical analysis 8
Statistical analysis description:	
The model included the treatment effect as the only covariate and was stratified by country.	
Comparison groups	BI 409306 50 mg v Placebo
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.893
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.225
upper limit	5.531

Statistical analysis title	Statistical analysis 9

Statistical analysis description:	
The model included the treatment effect as the only covariate and was stratified by country.	
Comparison groups	Placebo v BI 409306 pooled
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.936
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.265
upper limit	4.233

Secondary: Change from baseline in Personal and Social Performance scale (PSP) score after 28 weeks of treatment

End point title	Change from baseline in Personal and Social Performance scale (PSP) score after 28 weeks of treatment

End point description:

Personal and Social Performance scale (PSP): The PSP is a 100-point, single item, clinician rated scale to assess 4 domains of social functioning (Four domains over the past month: (1) socially useful activities, (2) personal and social relationships, (3) self-care and (4) disturbing and aggressive behaviors.) in patients with schizophrenia. The PSP score is a single score ranging from 1 to 100. Higher scores represent better personal and social functioning.

Full analysis set (FAS): the FAS includes all patients in the treated set with at least 1 baseline and post-baseline measurement of any type.
Only participants with non-missing results were included in the analysis.

End point type	Secondary

End point timeframe:

At baseline and at Week 28

End point values	BI 409306 25 mg	BI 409306 50 mg	Placebo	BI 409306 pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	72	54	65	126
Units: Score on a scale				
arithmetic mean (standard deviation)	2.8 (± 8.8)	2.4 (± 9.4)	3.0 (± 10.2)	2.6 (± 9.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rate of new prescription or increase in dose of an ongoing antipsychotic medication

End point title	Incidence rate of new prescription or increase in dose of an ongoing antipsychotic medication

End point description:

The incidence rate of new prescription or increase in dose of an ongoing antipsychotic medication is reported.

Full analysis set (FAS): the FAS includes all patients in the treated set with at least 1 baseline and post-baseline measurement of any type.

End point type	Secondary

End point timeframe:

28 weeks

End point values	BI 409306 25 mg	BI 409306 50 mg	Placebo	BI 409306 pooled
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	89	88	87	177
Units: Events per patient-years				
number (not applicable)	0.168	0.130	0.217	0.149

Statistical analyses

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

The model included the treatment effect as the only covariate and was stratified by country.

Comparison groups	BI 409306 25 mg v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6362
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.788
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.293
upper limit	2.118

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

The model included the treatment effect as the only covariate and was stratified by country.

Comparison groups	Placebo v BI 409306 pooled

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4253
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.703
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.296
upper limit	1.671

Statistical analysis title	Statistical analysis 11
Statistical analysis description:	
The model included the treatment effect as the only covariate and was stratified by country.	
Comparison groups	BI 409306 50 mg v Placebo
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3782
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.612
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.205
upper limit	1.826

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From 1st dose until withdraw or end of 1-week (1W) taper period + 3W follow-up, up to 32W. Serious (non-serious) adverse events: From 1st dose until withdraw or end of 1W taper period + 1W residual effect period, up to 30W.

Adverse event reporting additional description:

Treated set (TS): the TS includes all patients who were randomised and were documented to have taken at least 1 dose of trial drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	BI 409306 25mg

Reporting group description:

1 film-coated tablet of 25 milligrams (mg) of BI 409306 plus 1 tablet of 50 mg matching placebo were administered orally
once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up
period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of
treatment groups. Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets
of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1
tablet of 10mg placebo q.d. on Day 6-7. Taper period: 2 tablets of 10 mg BI 409306 and 2 tablets of placebo q.d. on Day 1 of the taper period; 2 tablets of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 2-3 of taper
period; 1 tablet of 10 mg BI 409306 and 1 tablet of placebo q.d. on Day 4-5 of taper period; 1 tablet of 10 mg BI 409306
q.d. on Day 6-7 of taper period.

Reporting group title	Placebo

Reporting group description:

1 film-coated tablet of 25 milligrams (mg) of matching Placebo plus 1 tablet of 50 mg matching placebo were administered
orally once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a followup
period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization
of treatment groups. Both withdrawal and taper periods: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of
withdrawal/taper period; 3 tablets of 10 mg placebo q.d. on Day 2-3 of withdrawal/taper period; 2 tablets of 10mg placebo
q.d. on Day 4-5 of withdrawal/taper period; 1 tablet of 10mg placebo q.d. on Day 6-7 of withdrawal/taper period.

Reporting group title	BI 409306 50mg

Reporting group description:

1 film-coated tablet of 50 milligrams (mg) of BI 409306 plus 1 tablet of 25 mg matching placebo were administered orally
once daily for a treatment period of 28 weeks, followed by a withdrawal/taper period of 7 days, followed by a follow-up
period of 3 weeks. Participants were randomized to either withdrawal or taper period in 1:1 ratio at the randomization of
treatment groups. Withdrawal period: 4 tablets of 10 mg placebo once daily (q.d.) on Day 1 of withdrawal period; 3 tablets
of 10 mg placebo q.d. on Day2-3 of withdrawal period; 2 tablets of 10mg placebo q.d. on Day 4-5 of withdrawal period; 1
tablet of 10mg placebo q.d. on Day 6-7 of withdrawal period. Taper period: 4 tablets of 10 mg BI 409306 q.d. on Day 1 of

taper period; 3 tablets of 10 mg BI 409306 q.d. on Day 2-3 of taper period; 2 tablets of 10 mg BI 409306 q.d. on Day 4-5
of taper period; 1 tablet of 10 mg BI 409306 q.d. on Day 6-7 of taper period.

Serious adverse events	BI 409306 25mg	Placebo	BI 409306 50mg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 89 (10.11%)	12 / 87 (13.79%)	7 / 88 (7.95%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Myocardial infarction			
subjects affected / exposed	0 / 89 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 89 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Ileus			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	0 / 88 (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, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
Psychiatric disorders			
Acute psychosis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Agitation			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
Anxiety			
subjects affected / exposed	0 / 89 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
Depression suicidal			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	0 / 88 (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

Hallucination, auditory			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Schizophrenia			
subjects affected / exposed	2 / 89 (2.25%)	4 / 87 (4.60%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	1 / 4	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal behaviour			
subjects affected / exposed	0 / 89 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance abuse			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Suicidal ideation			
subjects affected / exposed	3 / 89 (3.37%)	2 / 87 (2.30%)	0 / 88 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 89 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 87 (0.00%)	1 / 88 (1.14%)
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			
Complicated appendicitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 87 (0.00%)	0 / 88 (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
Wound infection			
subjects affected / exposed	0 / 89 (0.00%)	1 / 87 (1.15%)	0 / 88 (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
Pneumonia			
subjects affected / exposed	0 / 89 (0.00%)	3 / 87 (3.45%)	0 / 88 (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

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

Non-serious adverse events	BI 409306 25mg	Placebo	BI 409306 50mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 89 (33.71%)	19 / 87 (21.84%)	25 / 88 (28.41%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 89 (6.74%)	4 / 87 (4.60%)	7 / 88 (7.95%)
occurrences (all)	6	4	13
Somnolence			
subjects affected / exposed	5 / 89 (5.62%)	3 / 87 (3.45%)	3 / 88 (3.41%)
occurrences (all)	5	3	3
Eye disorders			
Photophobia			
subjects affected / exposed	3 / 89 (3.37%)	1 / 87 (1.15%)	8 / 88 (9.09%)
occurrences (all)	3	1	8
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	1 / 89 (1.12%)	5 / 87 (5.75%)	1 / 88 (1.14%)
occurrences (all)	1	6	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 89 (5.62%)	0 / 87 (0.00%)	6 / 88 (6.82%)
occurrences (all)	5	0	6
Schizophrenia			
subjects affected / exposed	6 / 89 (6.74%)	2 / 87 (2.30%)	4 / 88 (4.55%)
occurrences (all)	6	2	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 89 (7.87%)	7 / 87 (8.05%)	5 / 88 (5.68%)
occurrences (all)	7	10	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2017	- The key secondary endpoint, change from baseline in Positive and Negative Syndrome Scale (PANSS) positive symptoms score after 28 weeks of treatment, was added (it was a further endpoint prior to the revision). The key secondary endpoint was added to the hypothesis testing hierarchy. - To ensure clinical stability of patients entering the trial, 2 inclusion criteria were modified: Criterion 3: patients were required to take a stable dose of antipsychotic medication(s) for at least 12 weeks (instead of 8) prior to randomisation; Criterion 6: patients were required to have Clinical Global Impressions-Severity (CGI-S) score ≤4 at both Visits 1 and 2 (instead of only at Visit 1). - Inclusion criteria 4 and 7 were slightly modified. - A Japan-specific requirement for Informed consent form (ICF) signature was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 March 2020	Due to the current COVID-19 pandemic, the recruitment of new subjects was temporarily discontinued. Ongoing, randomised patients were managed per Trial Protocol.	28 April 2020

Notes:

Limitations and caveats

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

The study was terminated due to sponsor decision. The planned number of participants to be recruited was not reached.

Notes: