



Clinical trial results:

A phase II randomized, double-blinded, placebo-controlled, parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12-week treatment period in patients with borderline personality disorder

Summary

EudraCT number	2020-000078-12
Trial protocol	SE FR PL DE BG DK CZ BE IT RO
Global end of trial date	25 January 2023

Results information

Result version number	v1 (current)
This version publication date	07 February 2024
First version publication date	07 February 2024

Trial information

Trial identification

Sponsor protocol code	1402-0012
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04566601
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, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, 001 18002430127, clintriage.rdg@boehringer-ingelheim.co

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	10 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2022
Global end of trial reached?	Yes
Global end of trial date	25 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were to provide proof of concept (PoC) and dose-ranging data of BI 1358894 compared to placebo in patients with borderline personality disorder (BPD) to support dose selection for pivotal studies.

Protection of trial subjects:

A log of all patients enrolled into the trial (i.e. who had signed informed consent) was maintained in the Investigator site file (ISF) irrespective of whether they have been treated with investigational medication or not. If a patient was enrolled in error (did not meet all inclusion criteria or met one or more exclusion criteria on the day of enrolment), the sponsor was to be contacted immediately.

After premature trial medication discontinuation, patients were to be asked to further attend scheduled trial visits unless they withdrew consent to participate in the trial. If it was not possible to attend all visits, at least phone contacts were to occur at the scheduled visit time points. It was vital to explain to patients the importance of continuing trial participation and the value of collecting data for all randomised patients. This text was added in Global Amendment 1 of the clinical trial protocol (CTP).

If new efficacy or safety information became available, Boehringer Ingelheim was to review the benefit-risk-assessment and, if needed, pause or discontinue the trial medication for all patients or take any other appropriate action to guarantee the safety of the trial patients. Even if the trial medication was discontinued, the patients were asked to remain in the trial and, given their agreement, underwent the procedures for early treatment discontinuation and follow-up as outlined in the CTP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2020
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	Argentina: 82
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Bulgaria: 17
Country: Number of subjects enrolled	Czechia: 27
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Mexico: 64

Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	United States: 283
Worldwide total number of subjects	655
EEA total number of subjects	176

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)	654
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients with BPD were randomised to receive either BI 1358894 or placebo in a 2.5:1:1:1:2 ratio (placebo or BI 1358894 5 milligram (mg), 25 mg, 75 mg, or 125 mg), for 12 weeks.

This trial included a screening period, a 12-week randomised treatment period, and a 4-week follow-up period.

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	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Blinding implementation details:

Study medications were administered double-blinded. In order to maintain blinding in regard to each treatment, each dose contained 4 tablets in a double-dummy design. Double-dummy design was required since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes. Placebo tablets were identical in size and appearance to the corresponding active tablet and were combined with active tablets as needed in each dose group to maintain the blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 milligram (mg), one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Arm type	Placebo
Investigational medicinal product name	Placebo matching BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 milligram (mg), one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Arm title	BI 1358894 5mg
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Arm description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 5 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Arm type	Experimental
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Investigational medicinal product name	Placebo matching BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Investigational medicinal product name	BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 5 milligram (mg) of BI 1358894.

Arm title	BI 1358894 25mg
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Arm description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Arm type	Experimental
Investigational medicinal product name	Placebo matching BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Investigational medicinal product name	BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894.

Arm title	BI 1358894 75mg
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Arm description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and one film-coated tablet of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=75 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and one film-coated tablet of placebo matching BI 1358894 50 mg.

Arm type	Experimental
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Investigational medicinal product name	Placebo matching BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and one film-coated tablet of placebo matching BI 1358894 50 mg.

Investigational medicinal product name	BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and one film-coated tablet of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=75 mg).

Arm title	BI 1358894 125mg
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Arm description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and two film-coated tablets of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=125 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg.

Arm type	Experimental
Investigational medicinal product name	Placebo matching BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg.

Investigational medicinal product name	BI 1358894
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and two film-coated tablets of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=125 mg).

Number of subjects in period 1^[1]	Placebo	BI 1358894 5mg	BI 1358894 25mg
Started	128	52	53
Completed	95	40	35
Not completed	33	12	18
Adverse event, non-fatal	7	4	6
Technical problems	-	-	1
Perceived lack of efficacy	2	-	1
Protocol deviation	3	-	1
No reason available	3	2	7
Burden of study procedures	3	-	-
Change of residence	2	2	-
Other than listed	13	4	2

Number of subjects in period 1^[1]	BI 1358894 75mg	BI 1358894 125mg
Started	53	104
Completed	40	77
Not completed	13	27
Adverse event, non-fatal	5	12
Technical problems	-	-
Perceived lack of efficacy	1	2
Protocol deviation	1	1
No reason available	1	5
Burden of study procedures	3	1
Change of residence	1	2
Other than listed	1	4

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: Out of 655 enrolled subjects only 390 were randomized.

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 milligram (mg), one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.	
Reporting group title	BI 1358894 5mg
Reporting group description:	
Patients were administered for 12 weeks once daily, orally one film-coated tablet of 5 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.	
Reporting group title	BI 1358894 25mg
Reporting group description:	
Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.	
Reporting group title	BI 1358894 75mg
Reporting group description:	
Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and one film-coated tablet of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=75 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and one film-coated tablet of placebo matching BI 1358894 50 mg.	
Reporting group title	BI 1358894 125mg
Reporting group description:	
Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and two film-coated tablets of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=125 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg.	

Reporting group values	Placebo	BI 1358894 5mg	BI 1358894 25mg
Number of subjects	128	52	53
Age categorical			
Treated Set (TS).			
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)	128	52	53
From 65-84 years	0	0	0
85 years and over	0	0	0

Age Continuous			
Treated Set (TS).			
Units: years			
arithmetic mean	30.4	29.2	31.0
standard deviation	± 9.9	± 9.6	± 11.1
Sex: Female, Male			
Treated Set (TS).			
Units: Participants			
Female	107	50	48
Male	21	2	5
Race (NIH/OMB)			
Treated Set (TS).			
Units: Subjects			
American Indian or Alaska Native	5	2	1
Asian	2	3	2
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	8	3	3
White	112	44	46
More than one race	0	0	1
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated Set (TS).			
Units: Subjects			
Hispanic or Latino	50	17	25
Not Hispanic or Latino	78	35	28
Unknown or Not Reported	0	0	0
ZAN-BPD total score at Baseline			
<p>The ZANarini rating scale for Borderline Personality Disorder (ZAN-BPD) reflects the nine DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) criteria and the scale has 4 domain scores that reveal core areas of BPD (i.e., affective, cognitive, impulsive and interpersonal symptoms). The ZAN-BPD scale includes a 5-point rating scale (i.e., 0 = no symptoms to 4 = severe symptoms) for each criterion. The total ZAN-BPD score is the sum of the 4 domain scores and ranges from 0 to 36 where higher scores mean severe symptoms.</p>			
Treated Set (TS).			
Units: score on a scale			
arithmetic mean	16.6	15.7	15.8
standard deviation	± 5.0	± 5.4	± 4.8

Reporting group values	BI 1358894 75mg	BI 1358894 125mg	Total
Number of subjects	53	104	390
Age categorical			
Treated Set (TS).			
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)	53	103	389
From 65-84 years	0	1	1

85 years and over	0	0	0
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Age Continuous			
Treated Set (TS).			
Units: years			
arithmetic mean	30.6	29.9	
standard deviation	± 9.7	± 11.2	-
Sex: Female, Male			
Treated Set (TS).			
Units: Participants			
Female	48	83	336
Male	5	21	54
Race (NIH/OMB)			
Treated Set (TS).			
Units: Subjects			
American Indian or Alaska Native	1	6	15
Asian	4	7	18
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	1	4	19
White	46	85	333
More than one race	1	2	4
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated Set (TS).			
Units: Subjects			
Hispanic or Latino	20	34	146
Not Hispanic or Latino	33	70	244
Unknown or Not Reported	0	0	0
ZAN–BPD total score at Baseline			
The ZANarini rating scale for Borderline Personality Disorder (ZAN-BPD) reflects the nine DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) criteria and the scale has 4 domain scores that reveal core areas of BPD (i.e., affective, cognitive, impulsive and interpersonal symptoms). The ZAN-BPD scale includes a 5-point rating scale (i.e., 0 = no symptoms to 4 = severe symptoms) for each criterion. The total ZAN-BPD score is the sum of the 4 domain scores and ranges from 0 to 36 where higher scores mean severe symptoms.			
Treated Set (TS).			
Units: score on a scale			
arithmetic mean	16.1	16.4	
standard deviation	± 4.6	± 5.2	-

End points

End points reporting groups

Reporting group title	Placebo
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Reporting group description:

In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 milligram (mg), one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Reporting group title	BI 1358894 5mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 5 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Reporting group title	BI 1358894 25mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Reporting group title	BI 1358894 75mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and one film-coated tablet of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=75 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and one film-coated tablet of placebo matching BI 1358894 50 mg.

Reporting group title	BI 1358894 125mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and two film-coated tablets of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=125 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg.

Subject analysis set title	Full analysis set (FAS)
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Subject analysis set type	Full analysis
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Subject analysis set description:

FAS consisted of all patients in TS who had a baseline and at least 1 evaluable post-baseline measurement for the primary endpoint. This was the main analysis set for the evaluation of efficacy data.

Subject analysis set title	Treated set (TS)
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Subject analysis set type	Per protocol
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Subject analysis set description:

TS) consisted of all patients who were randomised and that received at least 1 administration of trial medication. The TS was the main analysis set for the evaluation of safety. Patients were analysed according to the actual received treatment.

Primary: Change from baseline in Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) total score at Week 10

End point title	Change from baseline in Zanarini rating scale for Borderline Personality Disorder (ZAN-BPD) total score at Week 10
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End point description:

The ZAN-BPD scale reflects the nine DSM-5 criteria and the scale has 4 domain scores that reflect core areas of BPD (i.e., affective, cognitive, impulsive and interpersonal symptoms). The ZAN-BPD scale

includes a 5-point rating scale (i.e., 0 = no symptoms to 4 = severe symptoms) for each criterion. The total ZAN-BPD score is the sum of the 4 domain scores and ranges from 0 to 36 where higher scores mean severe symptoms.

Least squares means and 95% confidence intervals were estimated by restricted maximum likelihood-based mixed effects mixed repeated measures (REML-based MMRM). LS mean (standard error) for Week 10 are reported.

Since the MMRM included the measurements from baseline, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10, number of participants analyzed for the primary endpoint for each arm are the participants who had a ZAN-BPD score value at baseline and one ZAN-BPD score value at one of the post-baseline timepoints up to Week 10.

End point type	Primary
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End point timeframe:

The change from baseline at Week 10 in the total ZAN-BPD score was calculated using the MMRM model which is a longitudinal analyses and it incorporates ZAN-BPD measurements from baseline, Weeks 1, 2, 4, 6, 8 and Week 10.

End point values	Placebo	BI 1358894 5mg	BI 1358894 25mg	BI 1358894 75mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124 ^[1]	52 ^[2]	52 ^[3]	52 ^[4]
Units: units on a scale				
least squares mean (standard error)	-8.7 (± 0.5)	-8.0 (± 0.9)	-9.2 (± 0.9)	-8.9 (± 0.8)

Notes:

[1] - Full analysis set (FAS).

[2] - Full analysis set (FAS).

[3] - Full analysis set (FAS).

[4] - Full analysis set (FAS).

End point values	BI 1358894 125mg			
Subject group type	Reporting group			
Number of subjects analysed	102 ^[5]			
Units: units on a scale				
least squares mean (standard error)	-9.0 (± 0.6)			

Notes:

[5] - Full analysis set (FAS).

Statistical analyses

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 5mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95 % confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. LS means differences (95 % confidence intervals) for Week 10 are reported.

Comparison groups	BI 1358894 5mg v Placebo
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Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	= 0.4994 ^[7]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	2.69

Notes:

[6] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 5mg" - Least Squares Mean of "Placebo".

[7] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 75mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95 % confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. LS means differences (95 % confidence intervals) for Week 10 are reported.

Comparison groups	Placebo v BI 1358894 75mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	= 0.8166 ^[9]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	1.72

Notes:

[8] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 75mg" - Least Squares Mean of "Placebo".

[9] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 125mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95 % confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. LS means differences (95 % confidence intervals) for Week 10 are reported.

Comparison groups	Placebo v BI 1358894 125mg
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Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other ^[10]
P-value	= 0.6588 ^[11]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.96
upper limit	1.24

Notes:

[10] - No formal hypotheses were tested.

Mean Difference (Net)=Least Squares Mean of "BI 1358894 125mg" - Least Squares Mean of "Placebo".

[11] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 25mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95 % confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. LS means differences (95 % confidence intervals) for Week 10 are reported.

Comparison groups	Placebo v BI 1358894 25mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[12]
P-value	= 0.6014 ^[13]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	1.51

Notes:

[12] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 25mg" - Least Squares Mean of "Placebo".

[13] - P-value is considered nominal.

Statistical analysis title	MCP-Mod sigmoid Emax model fit
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Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 1358894 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.100).

Comparison groups	Placebo v BI 1358894 5mg v BI 1358894 25mg v BI 1358894 75mg v BI 1358894 125mg
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Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	other ^[14]
P-value	= 0.3914
Method	MCP-Mod sigmoid Emax model fit

Notes:

[14] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed categorical covariates of treatment, visit (baseline, Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction.

Sigmoid Emax model assumption: 50% of the maximum effect is achieved at 25 mg, and 90% of the maximum effect is achieved at 75 mg.

Statistical analysis title	MCP-Mod Emax1 model fit
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Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 1358894 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.100).

Comparison groups	Placebo v BI 1358894 5mg v BI 1358894 25mg v BI 1358894 75mg v BI 1358894 125mg
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	other ^[15]
P-value	= 0.4104
Method	MCP-Mod Emax1 model fit

Notes:

[15] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10 and 12) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction.

Emax1 model assumption: 50% of the maximum effect is achieved at 25 mg.

Statistical analysis title	MCP-Mod linear model fit
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Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 1358894 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.100).

Comparison groups	Placebo v BI 1358894 5mg v BI 1358894 25mg v BI 1358894 75mg v BI 1358894 125mg
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	other ^[16]
P-value	= 0.456
Method	MCP-Mod linear model fit

Notes:

[16] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction.

Linear model assumption: No parameter assumptions required.

Statistical analysis title	MCP-Mod exponential model fit
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Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 1358894 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.100).

Comparison groups	Placebo v BI 1358894 5mg v BI 1358894 25mg v BI 1358894 75mg v BI 1358894 125mg
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	other ^[17]
P-value	= 0.4908
Method	MCP-Mod exponential model fit

Notes:

[17] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction.

Exponential model assumption: 5% of the maximum effect is achieved at 25 mg.

Statistical analysis title	MCP-Mod Emax2 model fit
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Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 4 doses of BI 1358894 and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 5 different plausible dose-response patterns (linear, exponential, Emax 1, Emax 2 and Sigmoid Emax) while protecting the overall probability of type I error (one-sided alpha of 0.100).

Comparison groups	Placebo v BI 1358894 5mg v BI 1358894 25mg v BI 1358894 75mg v BI 1358894 125mg
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	other ^[18]
P-value	= 0.4974
Method	MCP-Mod Emax2 model fit

Notes:

[18] - MMRM estimates were used as input for the MCP-Mod. MMRM included the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the baseline ZAN-BPD total score strata indicator (≤ 18 vs. ≥ 19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction.

Emax2 model assumption: 70% of the maximum effect is achieved at 5 mg.

Secondary: Zanarini rating scale for borderline personality disorder (ZAN-BPD) response: defined as $\geq 30\%$ ZAN-BPD reduction from baseline at Week 10

End point title	Zanarini rating scale for borderline personality disorder (ZAN-BPD) response: defined as $\geq 30\%$ ZAN-BPD reduction from baseline at Week 10
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End point description:

Number of participants with ZAN-BPD response is reported. ZAN-BPD response was defined as $\geq 30\%$ ZAN-BPD reduction from baseline at Week 10.

The ZAN-BPD scale reflects the nine DSM-5 criteria and the scale has 4 domain scores that reflect core areas of BPD (i.e., affective, cognitive, impulsive and interpersonal symptoms). The ZAN-BPD scale includes a 5-point rating scale (i.e., 0 = no symptoms to 4 = severe symptoms) for each criterion. The total ZAN-BPD score is the sum of the 4 domain scores and ranges from 0 to 36 where higher scores mean severe symptoms.

End point type	Secondary
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End point timeframe:

Baseline and at Week 10

End point values	Placebo	BI 1358894 5mg	BI 1358894 25mg	BI 1358894 75mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92 ^[19]	37 ^[20]	33 ^[21]	41 ^[22]
Units: Participants	68	22	28	34

Notes:

[19] - FAS. Only participants with ZAN BPD total score data at Week 10 are reported.

[20] - FAS. Only participants with ZAN BPD total score data at Week 10 are reported.

[21] - FAS. Only participants with ZAN BPD total score data at Week 10 are reported.

[22] - FAS. Only participants with ZAN BPD total score data at Week 10 are reported.

End point values	BI 1358894 125mg			
Subject group type	Reporting group			
Number of subjects analysed	74 ^[23]			
Units: Participants	59			

Notes:

[23] - FAS. Only participants with ZAN BPD total score data at Week 10 are reported.

Statistical analyses

Statistical analysis title	Logistic regression "Placebo" vs "BI 1358894 5mg"
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Statistical analysis description:

Logistic regression included treatment, baseline ZAN–BPD score and baseline ZAN–BPD strata indicator as covariates.

Comparison groups	Placebo v BI 1358894 5mg
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other ^[24]
Parameter estimate	Odds ratio (OR)
Point estimate	0.486
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.207
upper limit	1.14

Notes:

[24] - Odds Ratio was calculated as: BI 1358894 5mg/Placebo.

Statistical analysis title	Logistic regression "Placebo" vs "BI1358894 125mg"
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Statistical analysis description:

Logistic regression included treatment, baseline ZAN–BPD score and baseline ZAN–BPD strata indicator as covariates.

Comparison groups	Placebo v BI 1358894 125mg
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	other ^[25]
Parameter estimate	Odds ratio (OR)
Point estimate	1.352

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.642
upper limit	2.913

Notes:

[25] - Odds Ratio was calculated as: BI 1358894 125mg/Placebo.

Statistical analysis title	Logistic regression "Placebo" vs "BI 1358894 75mg"
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Statistical analysis description:

Logistic regression included treatment, baseline ZAN–BPD score and baseline ZAN–BPD strata indicator as covariates.

Comparison groups	Placebo v BI 1358894 75mg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other ^[26]
Parameter estimate	Odds ratio (OR)
Point estimate	1.753

Confidence interval

level	95 %
sides	2-sided
lower limit	0.698
upper limit	4.861

Notes:

[26] - Odds Ratio was calculated as: BI 1358894 75mg/Placebo.

Statistical analysis title	Logistic regression "Placebo" vs "BI 1358894 25mg"
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Statistical analysis description:

Logistic regression included treatment, baseline ZAN–BPD score and baseline ZAN–BPD strata indicator as covariates.

Comparison groups	Placebo v BI 1358894 25mg
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	other ^[27]
Parameter estimate	Odds ratio (OR)
Point estimate	2.294

Confidence interval

level	95 %
sides	2-sided
lower limit	0.829
upper limit	7.48

Notes:

[27] - Odds Ratio was calculated as: BI 1358894 25mg/Placebo.

Secondary: Change from baseline in Difficulties in Emotion Regulation Scale (DERS-16) total score at Week 10

End point title	Change from baseline in Difficulties in Emotion Regulation Scale (DERS-16) total score at Week 10
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End point description:

The DERS is a self-report measure of emotion regulation difficulties. It consists of 16 items that assess non-acceptance of negative emotions, inability to engage in goal-directed behaviors when distressed,

difficulties controlling impulsive behaviors when distressed, limited access to emotion regulation strategies perceived as effective, and lack of emotional clarity. Each item is scored from 1 (almost never (0-10%)) to 5 (almost always (91-100%)). Total DERS-16 can range from 16 to 80, with higher scores reflecting greater levels of emotion dysregulation.

Least squares means and 95% confidence intervals were estimated by restricted maximum likelihood-based mixed effects mixed repeated measures (REML-based MMRM). LS mean (standard error) for Week 10 are reported.

For this endpoint were analyzed participants who had a DERS-16 total score value at baseline and a DERS-16 total score value at one of the post-baseline timepoints up to Week 10.

End point type	Secondary
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End point timeframe:

Change from baseline in DERS-16 total score at Week 10 was calculated using the MMRM model which is a longitudinal analyses and it incorporates DERS-16 measurements from baseline, Weeks 1, 2, 4, 6, 8 and Week 10.

End point values	Placebo	BI 1358894 5mg	BI 1358894 25mg	BI 1358894 75mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124 ^[28]	52 ^[29]	52 ^[30]	52 ^[31]
Units: units on a scale				
least squares mean (standard error)	-9.77 (± 1.4)	-9.87 (± 2.1)	-9.76 (± 2.2)	-10.56 (± 2.1)

Notes:

[28] - Full analysis set (FAS).

[29] - Full analysis set (FAS).

[30] - Full analysis set (FAS).

[31] - Full analysis set (FAS).

End point values	BI 1358894 125mg			
Subject group type	Reporting group			
Number of subjects analysed	102 ^[32]			
Units: units on a scale				
least squares mean (standard error)	-8.60 (± 1.5)			

Notes:

[32] - Full analysis set (FAS).

Statistical analyses

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 5mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline DERS-16 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 5mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[33]
P-value	= 0.9675 ^[34]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.11
upper limit	4.9

Notes:

[33] - No formal hypotheses were tested.

Mean Difference (Net): Least Squares Mean of "BI 1358894 5mg" - Least Squares Mean of "Placebo".

[34] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 25mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline DERS-16 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 25mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[35]
P-value	= 0.9969 ^[36]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.08
upper limit	5.1

Notes:

[35] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 25mg" - Least Squares Mean of "Placebo".

[36] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 75mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline DERS-16 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 75mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[37]
P-value	= 0.7542 ^[38]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.73
upper limit	4.15

Notes:

[37] - No formal hypotheses were tested.

No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 75mg" - Least Squares Mean of "Placebo".

[38] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 125mg"
Statistical analysis description:	
Least Squares (LS) mean difference and 95% confidence interval were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline DERS-16 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.	
Comparison groups	Placebo v BI 1358894 125mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other ^[39]
P-value	= 0.5683 ^[40]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.86
upper limit	5.19

Notes:

[39] - No formal hypotheses were tested.

No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 125mg" - Least Squares Mean of "Placebo".

[40] - P-value is considered nominal.

Secondary: Change from baseline in State-Trait Anxiety Inventory (STAI-S) total score at Week 10

End point title	Change from baseline in State-Trait Anxiety Inventory (STAI-S) total score at Week 10
End point description:	
The STAI-S consists of 20 item state anxiety questions that evaluate how respondents feel "right now, at this moment". All items are rated on a weighted score of 1 to 4 scale (e.g. from 'Almost Never to 'Almost Always'). STAI-S score ranges from 20 to 80 where higher scores indicate greater anxiety. Least squares means and 95% confidence intervals were estimated by restricted maximum likelihood-based mixed effects mixed repeated measures (REML-based MMRM). LS mean (standard error) for Week 10 are reported. Since the MMRM included the measurements from baseline, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10, number of participants analyzed for the primary endpoint for each arm are the participants who had a STAI-S total score value at baseline and a STAI-S total score value at one of the post-baseline timepoints up to Week 10.	
End point type	Secondary

End point timeframe:

Change from baseline in STAI-S total score at Week 10 was calculated using the MMRM model which is a longitudinal analyses and it incorporates STAI-S measurements from baseline, Weeks 1, 2, 4, 6, 8 and Week 10.

End point values	Placebo	BI 1358894 5mg	BI 1358894 25mg	BI 1358894 75mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124 ^[41]	52 ^[42]	52 ^[43]	52 ^[44]
Units: units on a scale				
least squares mean (standard error)	-6.64 (± 1.2)	-8.71 (± 1.9)	-5.43 (± 2.0)	-7.00 (± 1.8)

Notes:

[41] - Full analysis set (FAS).

[42] - Full analysis set (FAS).

[43] - Full analysis set (FAS).

[44] - Full analysis set (FAS).

End point values	BI 1358894 125mg			
Subject group type	Reporting group			
Number of subjects analysed	102 ^[45]			
Units: units on a scale				
least squares mean (standard error)	-5.49 (± 1.3)			

Notes:

[45] - Full analysis set (FAS).

Statistical analyses

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 25mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline STAI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 25mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[46]
P-value	= 0.6009 ^[47]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.33
upper limit	5.75

Notes:

[46] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 25mg" - Least Squares Mean of "Placebo".

[47] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 5mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline STAI-S total score, and treatment-by-visit interaction, as well as

baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 5mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[48]
P-value	= 0.3568 ^[49]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-2.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.49
upper limit	2.35

Notes:

[48] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 5mg" - Least Squares Mean of "Placebo".

[49] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 125mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline STAI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 125mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other ^[50]
P-value	= 0.5262 ^[51]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	4.71

Notes:

[50] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 125mg" - Least Squares Mean of "Placebo".

[51] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 75mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline STAI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 75mg
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Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[52]
P-value	= 0.8705 ^[53]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	3.98

Notes:

[52] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 75mg" - Least Squares Mean of "Placebo".

[53] - P-value is considered nominal.

Secondary: Change from baseline in Patient Health Questionnaire (PHQ-9) total score at Week 10

End point title	Change from baseline in Patient Health Questionnaire (PHQ-9) total score at Week 10
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End point description:

The PHQ-9 is a 9-item brief self-reported tool used for screening and assessing the severity of depression. PHQ-9 has a maximum total score of 27. Depression Severity is assessed as: none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), or severe (20-27).

Least squares means and 95% confidence intervals were estimated by restricted maximum likelihood-based mixed effects mixed repeated measures (REML-based MMRM).

LS mean (standard error) for Week 10 are reported.

Since the MMRM included the measurements from baseline, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10, number of participants analyzed for the primary endpoint for each arm are the participants who had a PHQ-9 total score value at baseline and a PHQ-9 total score value at one of the post-baseline timepoints up to Week 10.

End point type	Secondary
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End point timeframe:

Change from baseline in PHQ-9 total score at Week 10 was calculated using the MMRM model which is a longitudinal analyses and it incorporates PHQ-9 measurements from baseline, Weeks 1, 2, 4, 6, 8 and Week 10.

End point values	Placebo	BI 1358894 5mg	BI 1358894 25mg	BI 1358894 75mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124 ^[54]	52 ^[55]	52 ^[56]	52 ^[57]
Units: units on a scale				
least squares mean (standard error)	-1.30 (± 0.6)	-3.13 (± 0.9)	-1.07 (± 0.9)	-1.57 (± 0.9)

Notes:

[54] - Full analysis set (FAS).

[55] - Full analysis set (FAS).

[56] - Full analysis set (FAS).

[57] - Full analysis set (FAS).

End point values	BI 1358894 125mg			
Subject group type	Reporting group			
Number of subjects analysed	102 ^[58]			

Units: units on a scale				
least squares mean (standard error)	-1.43 (± 0.6)			

Notes:

[58] - Full analysis set (FAS).

Statistical analyses

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 5mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PHQ-9 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 5mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[59]
P-value	= 0.0782 ^[60]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.87
upper limit	0.21

Notes:

[59] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 5mg" - Least Squares Mean of "Placebo".

[60] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 125mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PHQ-9 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 125mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other ^[61]
P-value	= 0.8743 ^[62]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	1.51

Notes:

[61] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 125mg" - Least Squares Mean of "Placebo".

[62] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 75mg"
Statistical analysis description:	
Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PHQ-9 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.	
Comparison groups	Placebo v BI 1358894 75mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[63]
P-value	= 0.791 ^[64]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	1.74

Notes:

[63] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 75mg" - Least Squares Mean of "Placebo".

[64] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 25mg"
Statistical analysis description:	
Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PHQ-9 total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.	
Comparison groups	Placebo v BI 1358894 25mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[65]
P-value	= 0.8266 ^[66]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	2.32

Notes:

[65] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 25mg" - Least Squares Mean of "Placebo".

[66] - P-value is considered nominal.

Secondary: Change from baseline in Clinical Global Impression Severity scale (CGI-S) at Week 10

End point title	Change from baseline in Clinical Global Impression Severity scale (CGI-S) at Week 10
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End point description:

The CGI-S rating scale measures the clinician's impression of the severity of illness exhibited by a participant. The CGI-S only question states "Considering your total clinical experience with this particular population, please choose the response below that best describes how mentally ill the patient was over the past week?", and is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients.

Least squares means and 95% confidence intervals were estimated by restricted maximum likelihood-based mixed effects mixed repeated measures (REML-based MMRM).

LS mean (standard error) for Week 10 are reported.

For this endpoint were analyzed participants who had a CGI-S scale value at baseline and a CGI-S scale value at one of the post-baseline timepoints up to Week 10.

End point type	Secondary
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End point timeframe:

Change from baseline in CGI-S scale at Week 10 was calculated using the MMRM model which is a longitudinal analyses and it incorporates CGI-S measurements from baseline, Weeks 1, 2, 4, 6, 8 and Week 10.

End point values	Placebo	BI 1358894 5mg	BI 1358894 25mg	BI 1358894 75mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124 ^[67]	52 ^[68]	51 ^[69]	51 ^[70]
Units: units on a scale				
least squares mean (standard error)	-1.23 (± 0.1)	-1.29 (± 0.2)	-1.47 (± 0.2)	-1.24 (± 0.2)

Notes:

[67] - Full analysis set (FAS).

[68] - Full analysis set (FAS).

[69] - Full analysis set (FAS).

[70] - Full analysis set (FAS).

End point values	BI 1358894 125mg			
Subject group type	Reporting group			
Number of subjects analysed	102 ^[71]			
Units: units on a scale				
least squares mean (standard error)	-1.42 (± 0.1)			

Notes:

[71] - Full analysis set (FAS).

Statistical analyses

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 5mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the

fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline CGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 5mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[72]
P-value	= 0.8016 ^[73]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.37

Notes:

[72] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 5mg" - Least Squares Mean of "Placebo".

[73] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 25mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline CGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 25mg
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other ^[74]
P-value	= 0.2929 ^[75]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.2

Notes:

[74] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 25mg" - Least Squares Mean of "Placebo".

[75] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 75mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline CGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 75mg
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other ^[76]
P-value	= 0.9666 ^[77]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.4

Notes:

[76] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 75mg" - Least Squares Mean of "Placebo".

[77] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 125mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline CGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 125mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other ^[78]
P-value	= 0.2833 ^[79]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.15

Notes:

[78] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 125mg" - Least Squares Mean of "Placebo".

[79] - P-value is considered nominal.

Secondary: Change from baseline in Patient Global Impression Severity scale (PGI-S) at Week 10

End point title	Change from baseline in Patient Global Impression Severity scale (PGI-S) at Week 10
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End point description:

The PGI-S measures the patient's impression of the severity of their illness. It is a single item 5-point scale that asks patients to rate the severity of their illness. The PGI-S question states "Please choose the response below that best describes the overall severity of your symptoms of Borderline Personality Disorder at this time. (Select one response)": 1=No symptoms; 2=Mild; 3=Moderate; 4=Severe; 5=Very severe.

Least squares means and 95% confidence intervals were estimated by restricted maximum likelihood-based mixed effects mixed repeated measures (REML-based MMRM).

LS means (standard error) for Week 10 are reported.
 Since the MMRM included the measurements from baseline, Week 1, Week 2, Week 4, Week 6, Week 8 and Week 10, number of participants analyzed for the primary endpoint for each arm are the participants who had a PGI-S scale value at baseline and a PGI-S scale value at one of the post-baseline timepoints up to Week 10.

End point type	Secondary
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End point timeframe:

Change from baseline in PGI-S scale at Week 10 was calculated using the MMRM model which is a longitudinal analyses and it incorporates PGI-S measurements from baseline, Weeks 1, 2, 4, 6, 8 and Week 10.

End point values	Placebo	BI 1358894 5mg	BI 1358894 25mg	BI 1358894 75mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	124 ^[80]	52 ^[81]	50 ^[82]	52 ^[83]
Units: units on a scale				
least squares mean (standard error)	-0.61 (± 0.1)	-0.73 (± 0.1)	-0.73 (± 0.2)	-0.64 (± 0.1)

Notes:

[80] - Full analysis set (FAS).

[81] - Full analysis set (FAS).

[82] - Full analysis set (FAS).

[83] - Full analysis set (FAS).

End point values	BI 1358894 125mg			
Subject group type	Reporting group			
Number of subjects analysed	102 ^[84]			
Units: units on a scale				
least squares mean (standard error)	-0.69 (± 0.1)			

Notes:

[84] - Full analysis set (FAS).

Statistical analyses

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 5mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 5mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[85]
P-value	= 0.4552 ^[86]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.2

Notes:

[85] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 5mg" - Least Squares Mean of "Placebo".

[86] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 125mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 125mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other ^[87]
P-value	= 0.554 ^[88]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.19

Notes:

[87] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 125mg" - Least Squares Mean of "Placebo".

[88] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 75mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 75mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	other ^[89]
P-value	= 0.8388 ^[90]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.29

Notes:

[89] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 75mg" - Least Squares Mean of "Placebo".

[90] - P-value is considered nominal.

Statistical analysis title	MMRM "Placebo" vs. "BI 1358894 25mg"
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Statistical analysis description:

Least Squares (LS) mean difference and 95% confidence interval were estimated by restricted maximum likelihood-based mixed effects model repeated measures (REML-based MMRM) including the fixed categorical covariates of treatment, visit (baseline and Week 1, 2, 4, 6, 8, 10) and the continuous fixed covariate of baseline PGI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used.

Comparison groups	Placebo v BI 1358894 25mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other ^[91]
P-value	= 0.4734 ^[92]
Method	Mixed effects model repeated measures
Parameter estimate	Mean difference (net)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.22

Notes:

[91] - No formal hypotheses were tested.

Mean Difference (Net) = Least Squares Mean of "BI 1358894 25mg" - Least Squares Mean of "Placebo".

[92] - P-value is considered nominal.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug administration until the last dose of study drug administration + 4 weeks of residual effect period, up to 17 weeks.

Adverse event reporting additional description:

Treated set (TS) consisted of all patients who were randomised and that received at least 1 administration of trial medication. Patients were analysed according to the actual received treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 milligram (mg), one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Reporting group title	BI 1358894 5mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 5 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 25 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Reporting group title	BI 1358894 125mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and two film-coated tablets of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=125 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg.

Reporting group title	BI 1358894 75mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894 and one film-coated tablet of 50 milligram (mg) of BI 1358894 (total BI 1358894 dose=75 mg). In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and one film-coated tablet of placebo matching BI 1358894 50 mg.

Reporting group title	BI 1358894 25mg
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Reporting group description:

Patients were administered for 12 weeks once daily, orally one film-coated tablet of 25 milligram (mg) of BI 1358894. In order to maintain blinding in regard to each treatment group since BI 1358894 tablets (5 mg, 25 mg, 50 mg) are different sizes, patients were also administered for 12 weeks once daily, orally one film-coated tablet of placebo matching BI 1358894 5 mg and two film-coated tablets of placebo matching BI 1358894 50 mg.

Serious adverse events	Placebo	BI 1358894 5mg	BI 1358894 125mg
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 128 (8.59%)	4 / 52 (7.69%)	16 / 104 (15.38%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 128 (0.00%)	1 / 52 (1.92%)	0 / 104 (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			
Aggression			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Drug abuse			

subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal behaviour			
subjects affected / exposed	0 / 128 (0.00%)	1 / 52 (1.92%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic stress disorder			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Suicidal ideation			
subjects affected / exposed	8 / 128 (6.25%)	3 / 52 (5.77%)	6 / 104 (5.77%)
occurrences causally related to treatment / all	2 / 9	0 / 9	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Comminuted fracture			
subjects affected / exposed	1 / 128 (0.78%)	0 / 52 (0.00%)	0 / 104 (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
Forearm fracture			

subjects affected / exposed	1 / 128 (0.78%)	0 / 52 (0.00%)	0 / 104 (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 disorders			
Myocardial infarction			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Nausea			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cannabinoid hyperemesis syndrome			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Vomiting			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Jaundice cholestatic			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
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			
Calculus urinary			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 128 (0.78%)	0 / 52 (0.00%)	0 / 104 (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
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Hepatitis A			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Wound abscess			
subjects affected / exposed	1 / 128 (0.78%)	0 / 52 (0.00%)	0 / 104 (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
Pneumonia			

subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (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
Metabolic acidosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 52 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BI 1358894 75mg	BI 1358894 25mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 53 (7.55%)	3 / 53 (5.66%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal behaviour			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic stress disorder			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			

subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Comminuted fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cannabinoid hyperemesis syndrome			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			

subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis A			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	BI 1358894 5mg	BI 1358894 125mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 128 (58.59%)	32 / 52 (61.54%)	61 / 104 (58.65%)
Investigations			
Weight increased			
subjects affected / exposed	0 / 128 (0.00%)	1 / 52 (1.92%)	5 / 104 (4.81%)
occurrences (all)	0	1	6
Nervous system disorders			

Somnolence subjects affected / exposed occurrences (all)	4 / 128 (3.13%) 4	3 / 52 (5.77%) 5	4 / 104 (3.85%) 5
Headache subjects affected / exposed occurrences (all)	32 / 128 (25.00%) 86	18 / 52 (34.62%) 27	33 / 104 (31.73%) 94
Dizziness subjects affected / exposed occurrences (all)	9 / 128 (7.03%) 10	6 / 52 (11.54%) 7	8 / 104 (7.69%) 11
Disturbance in attention subjects affected / exposed occurrences (all)	5 / 128 (3.91%) 5	3 / 52 (5.77%) 3	0 / 104 (0.00%) 0
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 128 (1.56%) 3	4 / 52 (7.69%) 6	1 / 104 (0.96%) 1
Fatigue subjects affected / exposed occurrences (all)	11 / 128 (8.59%) 13	6 / 52 (11.54%) 8	9 / 104 (8.65%) 14
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	2 / 128 (1.56%) 3	2 / 52 (3.85%) 2	1 / 104 (0.96%) 1
Diarrhoea subjects affected / exposed occurrences (all)	10 / 128 (7.81%) 11	4 / 52 (7.69%) 5	4 / 104 (3.85%) 4
Nausea subjects affected / exposed occurrences (all)	17 / 128 (13.28%) 28	5 / 52 (9.62%) 7	7 / 104 (6.73%) 11
Dyspepsia subjects affected / exposed occurrences (all)	1 / 128 (0.78%) 1	2 / 52 (3.85%) 2	0 / 104 (0.00%) 0
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	3 / 128 (2.34%) 3	0 / 52 (0.00%) 0	4 / 104 (3.85%) 5

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 128 (5.47%)	0 / 52 (0.00%)	2 / 104 (1.92%)
occurrences (all)	7	0	2
Oropharyngeal pain			
subjects affected / exposed	9 / 128 (7.03%)	3 / 52 (5.77%)	4 / 104 (3.85%)
occurrences (all)	10	3	6
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 128 (7.03%)	6 / 52 (11.54%)	3 / 104 (2.88%)
occurrences (all)	12	8	3
Intentional self-injury			
subjects affected / exposed	7 / 128 (5.47%)	2 / 52 (3.85%)	3 / 104 (2.88%)
occurrences (all)	10	2	4
Insomnia			
subjects affected / exposed	10 / 128 (7.81%)	5 / 52 (9.62%)	6 / 104 (5.77%)
occurrences (all)	15	6	7
Initial insomnia			
subjects affected / exposed	5 / 128 (3.91%)	1 / 52 (1.92%)	0 / 104 (0.00%)
occurrences (all)	6	1	0
Infections and infestations			
Pharyngitis			
subjects affected / exposed	2 / 128 (1.56%)	3 / 52 (5.77%)	0 / 104 (0.00%)
occurrences (all)	2	3	0
COVID-19			
subjects affected / exposed	16 / 128 (12.50%)	3 / 52 (5.77%)	7 / 104 (6.73%)
occurrences (all)	17	3	10
Influenza			
subjects affected / exposed	8 / 128 (6.25%)	3 / 52 (5.77%)	7 / 104 (6.73%)
occurrences (all)	8	3	7
Nasopharyngitis			
subjects affected / exposed	10 / 128 (7.81%)	3 / 52 (5.77%)	9 / 104 (8.65%)
occurrences (all)	11	4	12
Metabolism and nutrition disorders			
Hyperinsulinaemia			

subjects affected / exposed	1 / 128 (0.78%)	0 / 52 (0.00%)	0 / 104 (0.00%)
occurrences (all)	1	0	0
Increased appetite			
subjects affected / exposed	4 / 128 (3.13%)	1 / 52 (1.92%)	8 / 104 (7.69%)
occurrences (all)	5	2	13

Non-serious adverse events	BI 1358894 75mg	BI 1358894 25mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 53 (64.15%)	40 / 53 (75.47%)	
Investigations			
Weight increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Nervous system disorders			
Somnolence			
subjects affected / exposed	6 / 53 (11.32%)	5 / 53 (9.43%)	
occurrences (all)	7	6	
Headache			
subjects affected / exposed	15 / 53 (28.30%)	23 / 53 (43.40%)	
occurrences (all)	38	32	
Dizziness			
subjects affected / exposed	7 / 53 (13.21%)	5 / 53 (9.43%)	
occurrences (all)	11	5	
Disturbance in attention			
subjects affected / exposed	4 / 53 (7.55%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 53 (3.77%)	3 / 53 (5.66%)	
occurrences (all)	2	4	
Fatigue			
subjects affected / exposed	6 / 53 (11.32%)	1 / 53 (1.89%)	
occurrences (all)	6	4	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 53 (1.89%)	5 / 53 (9.43%)	
occurrences (all)	1	5	

Diarrhoea			
subjects affected / exposed	3 / 53 (5.66%)	3 / 53 (5.66%)	
occurrences (all)	3	3	
Nausea			
subjects affected / exposed	2 / 53 (3.77%)	5 / 53 (9.43%)	
occurrences (all)	3	6	
Dyspepsia			
subjects affected / exposed	3 / 53 (5.66%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	5 / 53 (9.43%)	1 / 53 (1.89%)	
occurrences (all)	9	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences (all)	2	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 53 (3.77%)	0 / 53 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 53 (5.66%)	3 / 53 (5.66%)	
occurrences (all)	5	3	
Intentional self-injury			
subjects affected / exposed	2 / 53 (3.77%)	1 / 53 (1.89%)	
occurrences (all)	3	1	
Insomnia			
subjects affected / exposed	4 / 53 (7.55%)	5 / 53 (9.43%)	
occurrences (all)	4	5	
Initial insomnia			
subjects affected / exposed	3 / 53 (5.66%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Pharyngitis			

subjects affected / exposed occurrences (all)	0 / 53 (0.00%) 0	0 / 53 (0.00%) 0	
COVID-19 subjects affected / exposed occurrences (all)	6 / 53 (11.32%) 6	1 / 53 (1.89%) 1	
Influenza subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	1 / 53 (1.89%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 53 (13.21%) 10	3 / 53 (5.66%) 3	
Metabolism and nutrition disorders Hyperinsulinaemia subjects affected / exposed occurrences (all)	3 / 53 (5.66%) 3	1 / 53 (1.89%) 1	
Increased appetite subjects affected / exposed occurrences (all)	1 / 53 (1.89%) 1	1 / 53 (1.89%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2020	Global Amendment 1 - Update of the term 'End of Treatment (EoT) Visit' to 'Visit 9 or End of Treatment (EoT) Visit' to distinguish patients who discontinue trial medication prematurely and continue with trial visits when they reach Week 12 (Visit 9) and patients completing the 12-week treatment (EoT). Addition of "the patient shows disease progression/worsening that precludes further participation in the trial per investigator's clinical judgement" as another reason for individual patient treatment discontinuation. Addition of "an unexpected and unusual high dropout rate" as a reason for discontinuation of the trial by the sponsor. Addition of erythrocyte sedimentation rate (ESR) in the haematology tests. Correction to urinalysis specifications to align with laboratory terminology. Addition of alternate trial procedures in case of COVID-19 restriction. Removing inhibitors of uridine glucuronyl transferases (UGT) enzymes from restricted medications. Patient Eligibility Review.
28 June 2021	Global Amendment 2 - The following main changes were implemented: Addition of telemedicine visits and the use of local laboratory in case of COVID-19-related kit shortage. Addition of patient global impressions of impact (PGI-I) assessment. Correction of "Initiation or change in any type or frequency of psychotherapy for BPD within the last 3 months prior to randomisation" to "(...) prior to screening". Clarification of the 7-day recall period for clinical global impression severity scale (CGI-S). Addition of participant check for multiple trial participation.
27 April 2022	Global Amendment 3 - The following main changes were implemented: Addition of new safety information on embryo-foetal development toxicity data, which suggests that a risk for teratogenicity in humans cannot be excluded. Addition of sexual abstinence as a non-allowed method of contraception for women of child bearing potential (WOCBP) who are heterosexually active. Addition of pregnancy test at Visits 3, 4, 6, and 8, and follow-up (FUP) Visit 1. Addition of contraception counselling for WOCBP.
23 September 2022	Global Amendment 4: The following main changes were implemented: Addition of confirmation by the investigator and the patient about the use of contraception. Removal of sensitive substrates of CYP2B6 from restricted medications based on the information from a clinical drug-drug interaction (DDI) study with bupropion. Addition of the possibility to perform ESR analysis locally at sites with an ongoing inability to obtain ESR result from the central laboratory.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported