Clinical trial results:
A Phase II, 6-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial with a quetiapine arm to evaluate the efficacy, tolerability and safety of oral BI 1358894 in patients with Major Depressive Disorder with inadequate response to antidepressants

Summary

EudraCT number	2019-004264-21
Trial protocol	PL CZ SK DE HU BG
Global end of trial date	02 February 2024

Results information

Result version number	v2 (current)
This version publication date	29 March 2025
First version publication date	15 February 2025
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	1402-0011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04521478
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2024
Global end of trial reached?	Yes
Global end of trial date	02 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 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: 51
Country: Number of subjects enrolled	Australia: 51
Country: Number of subjects enrolled	Bulgaria: 7
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 64
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Japan: 95
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Slovakia: 31
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	United States: 460
Worldwide total number of subjects	940
EEA total number of subjects	250

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)	932
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase II, 6-week parallel-group multicenter, randomized, double blind, doubledummy, placebo-controlled trial with a Quetiapine arm in participants with MDD with inadequate response to ongoing treatment with a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor or bupropion.

Pre-assignment

Screening details:

All patients were screened for eligibility prior to participation in the trial, to ensure that they met all inclusion and none of the exclusion criteria. One subject was randomized to the placebo arm but treated with 125 mg BI 1358894, and is shown here in the 125 mg arm. One subject was randomized to the Quetiapine arm, but not treated.

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, Data analyst, Subject

Blinding implementation details:

Participants, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants with an established diagnosis of Major Depressive Disorder (MDD) administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their Ongoing Antidepressants (OAD).

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

Dosage and administration details:

one daily dose of placebo matching quetiapine in the evening for 6 weeks

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

Dosage and administration details:

one daily dose of placebo matching BI 1358894 in the morning for 6 weeks

Arm title	5 mg BI 1358894

Arm description:

Participants with an established diagnosis of MDD administered one 5 milligram (mg) dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

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

Dosage and administration details:

one daily dose of placebo matching quetiapine in the evening for 6 weeks

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:

one daily 5 mg dose of BI 1358894 in the morning for 6 weeks

Arm title	25 mg BI 1358894

Arm description:

Participants with an established diagnosis of MDD administered one 25 mg dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

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

Dosage and administration details:

one daily dose of placebo matching quetiapine in the evening for 6 weeks

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:

one daily 25 mg dose of BI 1358894 in the morning for 6 weeks

Arm title	75 mg BI 1358894

Arm description:

Participants with an established diagnosis of MDD administered one 75 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

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

Dosage and administration details:

one daily dose of placebo matching quetiapine in the evening for 6 weeks

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:

one daily 75 mg dose of BI 1358894 in the morning for 6 weeks

Arm title	125 mg BI 1358894

Arm description:

Participants with an established diagnosis of MDD administered one 125 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

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

Dosage and administration details:

one daily dose of placebo matching quetiapine in the evening for 6 weeks

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:

one daily 125 mg dose of BI 1358894 in the morning for 6 weeks

Arm title	Quetiapine

Arm description:

Participants with an established diagnosis of MDD administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one 150 or 300 mg dose of quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. The daily active dose at the start of therapy was 50 mg on Day 1, 100 mg at Day 2 and 150 mg on Day 3 and 4. Beginning with Day 5, the recommended daily dose of 300 mg was taken. If not tolerated by a participant, the dose was reduced to 150 mg in Week 1. Thereafter, this finally chosen dose had to be stable until end of treatment at Week 6. During the trial, participants also continued treatment with their OAD.

Arm type	Active comparator
Investigational medicinal product name	Quetiapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

one daily 150 or 300 mg dose of quetiapine in the evening for 6 weeks

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

Dosage and administration details:

one daily dose of placebo matching BI 1358894 in the morning for 6 weeks

Number of subjects in period 1[1]	Placebo	5 mg BI 1358894	25 mg BI 1358894
Started	128	36	39
Treated	128	36	39
Completed	115	31	33
Not completed	13	5	6
Adverse event, non-fatal	7	-	2
Technical Problems	-	-	-
Burden of Study Procedures	1	-	-
No Reason Available	-	2	-
Other than listed	3	3	3
Protocol deviation	2	-	1
Lack of efficacy	-	-	-

Number of subjects in period 1[1]	75 mg BI 1358894	125 mg BI 1358894	Quetiapine
Started	39	75	71
Treated	39	75	71
Completed	34	68	59
Not completed	5	7	12
Adverse event, non-fatal	1	2	7
Technical Problems	1	-	-
Burden of Study Procedures	1	-	1
No Reason Available	-	1	-
Other than listed	2	3	3
Protocol deviation	-	-	-
Lack of efficacy	-	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of the 940 enrolled subjects, only 388 were treated.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants with an established diagnosis of Major Depressive Disorder (MDD) administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their Ongoing Antidepressants (OAD).	
Reporting group title	5 mg BI 1358894
Reporting group description:	
Participants with an established diagnosis of MDD administered one 5 milligram (mg) dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.	
Reporting group title	25 mg BI 1358894
Reporting group description:	
Participants with an established diagnosis of MDD administered one 25 mg dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.	
Reporting group title	75 mg BI 1358894
Reporting group description:	
Participants with an established diagnosis of MDD administered one 75 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.	
Reporting group title	125 mg BI 1358894
Reporting group description:	
Participants with an established diagnosis of MDD administered one 125 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.	
Reporting group title	Quetiapine
Reporting group description:	
Participants with an established diagnosis of MDD administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one 150 or 300 mg dose of quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. The daily active dose at the start of therapy was 50 mg on Day 1, 100 mg at Day 2 and 150 mg on Day 3 and 4. Beginning with Day 5, the recommended daily dose of 300 mg was taken. If not tolerated by a participant, the dose was reduced to 150 mg in Week 1. Thereafter, this finally chosen dose had to be stable until end of treatment at Week 6. During the trial, participants also continued treatment with their OAD.	

Reporting group values	Placebo	5 mg BI 1358894	25 mg BI 1358894
Number of subjects	128	36	39
Age categorical			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
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)	125	36	39
From 65-84 years	3	0	0
85 years and over	0	0	0
Age Continuous			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: years			
arithmetic mean	42.9	39.7	44.7
standard deviation	± 13.0	± 13.8	± 12.1
Sex: Female, Male			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
Female	82	27	28
Male	46	9	11
Race (NIH/OMB)			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	24	5	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	2	3
White	98	29	30
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
Hispanic or Latino	19	5	2
Not Hispanic or Latino	109	31	37
Unknown or Not Reported	0	0	0
Montgomery-Åsberg Depression Rating Scale (MADRS) total score			
The MADRS evaluates core symptoms of depression and consists of 10 items. Nine of them are based upon participant reports, and one is on the rater's observation (apparent sadness) during the rating interview. MADRS items are rated on a 0–6 continuum (0=no abnormality, 6=severe). The possible total score could range from 0 (normal with absence of symptoms) to 60 (severe depression). Baseline MADRS total score is the last non-missing value recorded prior to first dose of trial medication. Treated Set (TS).			
Units: Score on a scale			
arithmetic mean	32.0	34.0	34.1
standard deviation	± 6.4	± 4.8	± 5.6

Reporting group values	75 mg BI 1358894	125 mg BI 1358894	Quetiapine
Number of subjects	39	75	71
Age categorical			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
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)	39	73	71
From 65-84 years	0	2	0
85 years and over	0	0	0
Age Continuous			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: years			
arithmetic mean	42.7	47.7	43.6
standard deviation	± 12.2	± 11.7	± 12.4
Sex: Female, Male			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
Female	26	51	49
Male	13	24	22
Race (NIH/OMB)			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	15	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	7	6
White	32	53	53
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
Hispanic or Latino	5	8	12
Not Hispanic or Latino	34	67	59
Unknown or Not Reported	0	0	0
Montgomery-Åsberg Depression Rating Scale (MADRS) total score			
The MADRS evaluates core symptoms of depression and consists of 10 items. Nine of them are based upon participant reports, and one is on the rater's observation (apparent sadness) during the rating interview. MADRS items are rated on a 0–6 continuum (0=no abnormality, 6=severe). The possible total score could range from 0 (normal with absence of symptoms) to 60 (severe depression). Baseline MADRS total score is the last non-missing value recorded prior to first dose of trial medication. Treated Set (TS).			
Units: Score on a scale			
arithmetic mean	32.1	33.1	33.6
standard deviation	± 6.4	± 6.0	± 5.6

Reporting group values	Total		
Number of subjects	388		

Age categorical			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	383		
From 65-84 years	5		
85 years and over	0		
Age Continuous			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
Female	263		
Male	125		
Race (NIH/OMB)			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	68		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	25		
White	295		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.			
Units: Subjects			
Hispanic or Latino	51		
Not Hispanic or Latino	337		
Unknown or Not Reported	0		
Montgomery-Åsberg Depression Rating Scale (MADRS) total score			
The MADRS evaluates core symptoms of depression and consists of 10 items. Nine of them are based upon participant reports, and one is on the rater's observation (apparent sadness) during the rating interview. MADRS items are rated on a 0–6 continuum (0=no abnormality, 6=severe). The possible total score could range from 0 (normal with absence of symptoms) to 60 (severe depression). Baseline MADRS total score is the last non-missing value recorded prior to first dose of trial medication. Treated Set (TS).			
Units: Score on a scale			
arithmetic mean			

standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants with an established diagnosis of Major Depressive Disorder (MDD) administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their Ongoing Antidepressants (OAD).

Reporting group title	5 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 5 milligram (mg) dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

Reporting group title	25 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 25 mg dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

Reporting group title	75 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 75 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

Reporting group title	125 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 125 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. During the trial, participants also continued treatment with their OAD.

Reporting group title	Quetiapine

Reporting group description:

Participants with an established diagnosis of MDD administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one 150 or 300 mg dose of quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks. The daily active dose at the start of therapy was 50 mg on Day 1, 100 mg at Day 2 and 150 mg on Day 3 and 4. Beginning with Day 5, the recommended daily dose of 300 mg was taken. If not tolerated by a participant, the dose was reduced to 150 mg in Week 1. Thereafter, this finally chosen dose had to be stable until end of treatment at Week 6. During the trial, participants also continued treatment with their OAD.

Primary: Change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6

End point title	Change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6[1]

End point description:

Change from baseline in MADRS total score at Week 6 is reported.
Adjusted mean and standard error (SE) were estimated by Restricted Maximum Likelihood (REML)−based Mixed effects model for repeated measures (MMRM) including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline MADRS total score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.
Full analysis set (FAS): all participants in TS that have a baseline and at least one evaluable post-

baseline measurement. As per protocol, data from participants assigned to the quetiapine arm were not included in the primary endpoint.

End point type	Primary

End point timeframe:

MMRM included measurements from baseline (Week 0) and at Weeks 1, 2, 4 and 6 after first drug administration. MMRM estimates of change from baseline to Week 6 is reported.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per protocol, the endpoint applies only to placebo and BI-treated arms.

End point values	Placebo	5 mg BI 1358894	25 mg BI 1358894	75 mg BI 1358894
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	36	39	39
Units: Units on a scale				
least squares mean (standard error)	-13.0 (± 1.0)	-12.4 (± 2.0)	-10.8 (± 1.9)	-10.8 (± 1.9)

End point values	125 mg BI 1358894			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Units on a scale				
least squares mean (standard error)	-11.5 (± 1.4)			

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline MADRS total score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 5 mg BI 1358894
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.7636
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[2] - Difference = (adjusted mean 5 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline MADRS total score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 25 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.304
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.4
upper limit	5.9
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[3] - Difference = (adjusted mean 25 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline MADRS total score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 75 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.309
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.4
upper limit	5.7
Variability estimate	Standard error of the mean
Dispersion value	2.2

Notes:

[4] - Difference = (adjusted mean 75 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline MADRS total score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 125 mg BI 1358894
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.3694
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.5
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.3
upper limit	4.4
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[5] - Difference = (adjusted mean 125 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 5

Statistical analysis description:

The Multiple Comparison Procedures and Modeling (MCPMod) procedure used the estimated values from an MMRM model as input and allowed for simultaneous evaluation of different potential dose response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax), while protecting the overall false positive rate (probability of Type I error) using a one-sided, nominal α level of 10 %.

Comparison groups	Placebo v 5 mg BI 1358894 v 25 mg BI 1358894 v 75 mg BI 1358894 v 125 mg BI 1358894
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.9158
Method	MCPMod Linear model

Notes:

[6] - MCPMod Linear model assumption: no parameter assumptions required. Corresponding dose response is linear

Statistical analysis title	Statistical analysis 6

Statistical analysis description:

The Multiple Comparison Procedures and Modeling (MCPMod) procedure used the estimated values from an MMRM model as input and allowed for simultaneous evaluation of different potential dose response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax), while protecting the overall false positive rate (probability of Type I error) using a one-sided, nominal α level of 10 %.

Comparison groups	Placebo v 5 mg BI 1358894 v 25 mg BI 1358894 v 75 mg BI 1358894 v 125 mg BI 1358894

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.8676
Method	MCPMod Exponential model

Notes:

[7] - MCPMod Exponential model assumption: 5% of the maximum effect is achieved at 25 mg; corresponding to a drug effect achieved mainly at higher doses

Statistical analysis title	Statistical analysis 7

Statistical analysis description:

The Multiple Comparison Procedures and Modeling (MCPMod) procedure used the estimated values from an MMRM model as input and allowed for simultaneous evaluation of different potential dose response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax), while protecting the overall false positive rate (probability of Type I error) using a one-sided, nominal α level of 10 %.

Comparison groups	Placebo v 5 mg BI 1358894 v 25 mg BI 1358894 v 75 mg BI 1358894 v 125 mg BI 1358894
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.9552
Method	MCPMod Emax1 model

Notes:

[8] - MCPMod Emax1 model assumption: 50% of the maximum effect is achieved at 25 mg; corresponding to the assumed true median effective dose (ED50) = 25 mg

Statistical analysis title	Statistical analysis 8

Statistical analysis description:

The Multiple Comparison Procedures and Modeling (MCPMod) procedure used the estimated values from an MMRM model as input and allowed for simultaneous evaluation of different potential dose response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax), while protecting the overall false positive rate (probability of Type I error) using a one-sided, nominal α level of 10 %.

Comparison groups	Placebo v 5 mg BI 1358894 v 25 mg BI 1358894 v 75 mg BI 1358894 v 125 mg BI 1358894
Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.9619
Method	MCPMod Emax2 model

Notes:

[9] - MCPMod Emax2 model assumption: 70% of the maximum effect is achieved at 5 mg; corresponding to a drug effect achieved mainly with low doses, ED50 = 2.14 mg

Statistical analysis title	Statistical analysis 9

Statistical analysis description:

The Multiple Comparison Procedures and Modeling (MCPMod) procedure used the estimated values from an MMRM model as input and allowed for simultaneous evaluation of different potential dose response patterns (Linear, Exponential, Emax1, Emax2, Sigmoid Emax), while protecting the overall false positive rate (probability of Type I error) using a one-sided, nominal α level of 10 %.

Comparison groups	Placebo v 5 mg BI 1358894 v 25 mg BI 1358894 v 75 mg BI 1358894 v 125 mg BI 1358894

Number of subjects included in analysis	312
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.9507
Method	MCPMod Sigmoid Emax model

Notes:

[10] - MCPMod Sigmoid Emax model assumption: 50% of the maximum effect is achieved at 25 mg, 90% 75 mg; corresponding to a more flexible model of the assumed true ED50 = 25 mg

Secondary: Number of participants with response defined as ≥ 50% Montgomery-Åsberg Depression Rating Scale (MADRS) reduction from baseline at Week 6

End point title	Number of participants with response defined as ≥ 50% Montgomery-Åsberg Depression Rating Scale (MADRS) reduction from baseline at Week 6[11]

End point description:

Number of participants with response defined as ≥ 50% MADRS reduction from baseline at Week 6 is reported. Percent reduction from baseline was calculated as follows: [(MADRS total score at baseline - MADRS total score at week 6)/ MADRS total score at baseline] *100.
Full analysis set (FAS): all participants in TS that have a baseline and at least one evaluable post-baseline measurement. As per protocol, data from participants assigned to the quetiapine arm were not included in the secondary endpoints.

End point type	Secondary

End point timeframe:

Prior to the first intake of the trial medication (week 0, baseline) and after 6 weeks of treatment.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per protocol, the endpoint applies only to placebo and BI-treated arms.

End point values	Placebo	5 mg BI 1358894	25 mg BI 1358894	75 mg BI 1358894
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	36	39	39
Units: Participants	40	10	9	12

End point values	125 mg BI 1358894			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants	23			

Statistical analyses

Statistical analysis title	Statistical analysis 10

Statistical analysis description:

Logistic regression model, including the fixed categorical effects of treatment and baseline MDD severity.

Comparison groups	Placebo v 5 mg BI 1358894

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.8889
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.9427
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.4709
upper limit	1.8873

Notes:

[12] - Odds Ratio of 5 mg BI 1358894 vs Placebo

Statistical analysis title	Statistical analysis 12

Statistical analysis description:

Logistic regression model, including the fixed categorical effects of treatment and baseline MDD severity.

Comparison groups	Placebo v 75 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.8048
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.1026
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5757
upper limit	2.1114

Notes:

[13] - Odds Ratio of 75 mg BI 1358894 vs Placebo

Statistical analysis title	Statistical analysis 13

Statistical analysis description:

Logistic regression model, including the fixed categorical effects of treatment and baseline MDD severity.

Comparison groups	Placebo v 125 mg BI 1358894
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.982
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.0072
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5968
upper limit	1.6999

Notes:

[14] - Odds Ratio of 125 mg BI 1358894 vs Placebo

Statistical analysis title	Statistical analysis 11

Statistical analysis description:

Logistic regression model, including the fixed categorical effects of treatment and baseline MDD severity.

Comparison groups	Placebo v 25 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.3284
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.6581
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.3255
upper limit	1.3307

Notes:

[15] - Odds Ratio of 25 mg BI 1358894 vs Placebo

Secondary: Change from baseline in State-Trait Anxiety Inventory (STAI) State and Trait version scores at Week 6

End point title	Change from baseline in State-Trait Anxiety Inventory (STAI) State and Trait version scores at Week 6[16]

End point description:

Change from baseline in STAI State and Trait version scores at Week 6 is reported. The STAI comprises separate self-report scales consisting of 20 statements for measuring state and trait anxiety. The S-Anxiety scale evaluates how respondents feel “right now, at this moment.” The T-Anxiety scale assesses how people generally feel. Each STAI item is given a score of 1 to 4. Scores for both scales can vary from 20 to 80. Higher scores indicate greater anxiety.
Adjusted mean and SE were estimated by REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors. FAS. As per protocol, data from participants assigned to the quetiapine arm were not included in the secondary endpoints.

End point type	Secondary

End point timeframe:

MMRM included measurements from baseline (Week 0) and at Weeks 1, 2, 4 and 6 after first drug administration. MMRM estimates of change from baseline to Week 6 is reported.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per protocol, the endpoint applies only to placebo and BI-treated arms.

End point values	Placebo	5 mg BI 1358894	25 mg BI 1358894	75 mg BI 1358894
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	36	39	39
Units: Units on a scale				
least squares mean (standard error)				
S-Anxiety	-11.3 (± 1.2)	-7.0 (± 2.3)	-8.9 (± 2.3)	-12.3 (± 2.2)

T-Anxiety	-11.0 (± 1.1)	-6.9 (± 2.1)	-10.2 (± 2.1)	-9.9 (± 2.1)

End point values	125 mg BI 1358894			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Units on a scale				
least squares mean (standard error)				
S-Anxiety T-Anxiety	-8.6 (± 1.6) -7.2 (± 1.5)			

Statistical analyses

Statistical analysis title	Statistical analysis 14

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (S-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 5 mg BI 1358894
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.1013
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	8.6
Variability estimate	Standard error of the mean
Dispersion value	2.6

Notes:

[17] - Difference = (adjusted mean 5 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 15

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (S-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 25 mg BI 1358894

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.3596
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.9
upper limit	6.6
Variability estimate	Standard error of the mean
Dispersion value	2.6

Notes:

[18] - Difference = (adjusted mean 25 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 16

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (S-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 75 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.6745
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.2
upper limit	3.1
Variability estimate	Standard error of the mean
Dispersion value	2.5

Notes:

[19] - Difference = (adjusted mean 75 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 17

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (S-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 125 mg BI 1358894

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.187
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.7
upper limit	6
Variability estimate	Standard error of the mean
Dispersion value	2

Notes:

[20] - Difference = (adjusted mean 125 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 18

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (T-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 5 mg BI 1358894
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.0921
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.1
upper limit	8.1
Variability estimate	Standard error of the mean
Dispersion value	2.4

Notes:

[21] - Difference = (adjusted mean 5 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 19

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (T-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 25 mg BI 1358894

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.7395
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.2
upper limit	4.8
Variability estimate	Standard error of the mean
Dispersion value	2.4

Notes:

[22] - Difference = (adjusted mean 25 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 20

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (T-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 75 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.6296
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.7
upper limit	5
Variability estimate	Standard error of the mean
Dispersion value	2.4

Notes:

[23] - Difference = (adjusted mean 75 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 21

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of baseline score (T-Anxiety scale). Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 125 mg BI 1358894

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.0429
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	6.9
Variability estimate	Standard error of the mean
Dispersion value	1.9

Notes:

[24] - Difference = (adjusted mean 125 mg BI 1358894) - (adjusted mean Placebo)

Secondary: Change from baseline in Clinical Global Impression Severity Scale (CGI-S) score at Week 6

End point title	Change from baseline in Clinical Global Impression Severity Scale (CGI-S) score at Week 6[25]

End point description:

Change from baseline in CGI-S score at Week 6 is reported. The CGI-S rating scale evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience with the depression population, a participant is assessed on severity of illness at the time of rating according to: 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 participants.
Adjusted mean and SE were estimated by REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors. FAS. As per protocol, data from participants assigned to the quetiapine arm were not included in the secondary endpoints.

End point type	Secondary

End point timeframe:

MMRM included measurements from baseline (Week 0) and at Weeks 1, 2, 4 and 6 after first drug administration. MMRM estimates of change from baseline to Week 6 is reported.

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per protocol, the endpoint applies only to placebo and BI-treated arms.

End point values	Placebo	5 mg BI 1358894	25 mg BI 1358894	75 mg BI 1358894
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	36	39	39
Units: Units on a scale				
least squares mean (standard error)	-1.3 (± 0.1)	-1.2 (± 0.2)	-1.2 (± 0.2)	-1.1 (± 0.2)

End point values	125 mg BI 1358894			

Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Units on a scale				
least squares mean (standard error)	-1.1 (± 0.2)			

Statistical analyses

Statistical analysis title	Statistical analysis 22

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 5 mg BI 1358894
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.6211
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.3
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[26] - Difference = (adjusted mean 5 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 23

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 25 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.5158
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.2
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[27] - Difference = (adjusted mean 25 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 24

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 75 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.4518
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.2
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[28] - Difference = (adjusted mean 75 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 25

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 125 mg BI 1358894
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.2347
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.2

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.1
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[29] - Difference = (adjusted mean 125 mg BI 1358894) - (adjusted mean Placebo)

Secondary: Change from baseline in Symptoms of Major Depressive Disorder Scale (SMDDS) total score at Week 6

End point title	Change from baseline in Symptoms of Major Depressive Disorder Scale (SMDDS) total score at Week 6[30]

End point description:

Change from baseline in SMDDS total score at Week 6 is reported. The SMDDS is a 16-item, patient-reported outcome measure developed to capture the core symptoms of MDD. The SMDDS uses a recall of "over the past 7 days" and participants respond to each question using a rating scale between 0 ("Not at all" or "Never") to 4 ("Extremely" or "Always"). The total score ranges from 0 to 60 with a higher score indicating more severe depressive symptomatology.
Adjusted mean and SE were estimated by REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors. FAS. As per protocol, data from participants assigned to the quetiapine arm were not included in the secondary endpoints.

End point type	Secondary

End point timeframe:

MMRM included measurements from baseline (Week 0) and at Weeks 1, 2, 4 and 6 after first drug administration. MMRM estimates of change from baseline to Week 6 is reported.

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As per protocol, the endpoint applies only to placebo and BI-treated arms.

End point values	Placebo	5 mg BI 1358894	25 mg BI 1358894	75 mg BI 1358894
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	126	36	39	39
Units: Units on a scale				
least squares mean (standard error)	-13.3 (± 1.2)	-9.9 (± 2.2)	-8.9 (± 2.2)	-12.3 (± 2.1)

End point values	125 mg BI 1358894			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Units on a scale				
least squares mean (standard error)	-10.5 (± 1.6)			

Statistical analyses

Statistical analysis title	Statistical analysis 26

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 5 mg BI 1358894
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.1723
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.7
upper limit	7.6
Variability estimate	Standard error of the mean
Dispersion value	2.5

Notes:

[31] - Difference = (adjusted mean 5 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 28

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 75 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.6864
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3
upper limit	5
Variability estimate	Standard error of the mean
Dispersion value	2.4

Notes:

[32] - Difference = (adjusted mean 75 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 29

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 125 mg BI 1358894
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	= 0.1585
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.8
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.5
upper limit	6
Variability estimate	Standard error of the mean
Dispersion value	1.9

Notes:

[33] - Difference = (adjusted mean 125 mg BI 1358894) - (adjusted mean Placebo)

Statistical analysis title	Statistical analysis 27

Statistical analysis description:

Adjusted means and confidence intervals were estimated using REML−based MMRM including the fixed categorical effects of treatment, concomitant psychotherapy use (yes vs. no), and the fixed continuous effect of the baseline score. Visit was treated as a repeated measure with an unstructured covariance matrix. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom and adjust standard errors.

Comparison groups	Placebo v 25 mg BI 1358894
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.0757
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.3
upper limit	8.5
Variability estimate	Standard error of the mean
Dispersion value	2.5

Notes:

[34] - Difference = (adjusted mean 25 mg BI 1358894) - (adjusted mean Placebo)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first treatment administration until last treatment administration + 28 days, up to approximately 11 weeks.

Adverse event reporting additional description:

Treated Set (TS): all participants that have been randomized and that received at least one administration of study drug. Participants are analysed according to the actual received treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants with an established diagnosis of Major Depressive Disorder (MDD) administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks.
During the trial, participants also continued treatment with their Ongoing Antidepressants (OAD).

Reporting group title	5 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 5 milligram (mg) dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks.
During the trial, participants also continued treatment with their OAD.

Reporting group title	Quetiapine

Reporting group description:

Participants with an established diagnosis of MDD administered one dose of placebo matching BI 1358894 in the morning as film-coated tablets, and one 150 or 300 mg dose of quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks.
The daily active dose at the start of therapy was 50 mg on Day 1, 100 mg at Day 2 and 150 mg on Day 3 and 4. Beginning with Day 5, the recommended daily dose of 300 mg was taken. If not tolerated by a participant, the dose was reduced to 150 mg in Week 1. Thereafter, this finally chosen dose had to be stable until end of treatment at Week 6.
During the trial, participants also continued treatment with their OAD.

Reporting group title	75 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 75 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks.
During the trial, participants also continued treatment with their OAD.

Reporting group title	125 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 125 mg dose of BI 1358894 in the morning as film-coated tablets, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks.
During the trial, participants also continued treatment with their OAD.

Reporting group title	25 mg BI 1358894

Reporting group description:

Participants with an established diagnosis of MDD administered one 25 mg dose of BI 1358894 in the morning as film-coated tablet, and one dose of placebo matching quetiapine in the evening as tablets. Each administration was performed orally once daily, for 6 weeks.
During the trial, participants also continued treatment with their OAD.

Serious adverse events	Placebo	5 mg BI 1358894	Quetiapine
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 128 (5.47%)	0 / 36 (0.00%)	1 / 71 (1.41%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 128 (0.78%)	0 / 36 (0.00%)	0 / 71 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (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
Psychiatric disorders			
Emotional distress			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (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	6 / 128 (4.69%)	0 / 36 (0.00%)	1 / 71 (1.41%)
occurrences causally related to treatment / all	1 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Genital herpes			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (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	75 mg BI 1358894	125 mg BI 1358894	25 mg BI 1358894
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 39 (5.13%)	1 / 75 (1.33%)	2 / 39 (5.13%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	0 / 39 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 39 (0.00%)	1 / 75 (1.33%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary fibrosis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Emotional distress			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	2 / 39 (5.13%)	0 / 75 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Genital herpes			
subjects affected / exposed	1 / 39 (2.56%)	0 / 75 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	5 mg BI 1358894	Quetiapine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 128 (25.00%)	16 / 36 (44.44%)	43 / 71 (60.56%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	3 / 128 (2.34%)	2 / 36 (5.56%)	6 / 71 (8.45%)
occurrences (all)	3	2	6
Somnolence			
subjects affected / exposed	4 / 128 (3.13%)	1 / 36 (2.78%)	24 / 71 (33.80%)
occurrences (all)	6	1	28
Sedation			
subjects affected / exposed	1 / 128 (0.78%)	0 / 36 (0.00%)	6 / 71 (8.45%)
occurrences (all)	1	0	6
Headache			
subjects affected / exposed	13 / 128 (10.16%)	9 / 36 (25.00%)	2 / 71 (2.82%)
occurrences (all)	13	12	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 128 (3.13%)	5 / 36 (13.89%)	7 / 71 (9.86%)
occurrences (all)	6	5	9
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 128 (0.78%)	0 / 36 (0.00%)	1 / 71 (1.41%)
occurrences (all)	1	0	1
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	1 / 71 (1.41%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	4 / 128 (3.13%)	0 / 36 (0.00%)	4 / 71 (5.63%)
occurrences (all)	5	0	4
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 128 (0.00%)	1 / 36 (2.78%)	1 / 71 (1.41%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 128 (0.78%)	2 / 36 (5.56%)	1 / 71 (1.41%)
occurrences (all)	2	2	1
Aggression			
subjects affected / exposed	0 / 128 (0.00%)	2 / 36 (5.56%)	0 / 71 (0.00%)
occurrences (all)	0	2	0
Sleep disorder			
subjects affected / exposed	2 / 128 (1.56%)	0 / 36 (0.00%)	0 / 71 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	1 / 128 (0.78%)	0 / 36 (0.00%)	6 / 71 (8.45%)
occurrences (all)	1	0	6
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	0 / 128 (0.00%)	0 / 36 (0.00%)	0 / 71 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 128 (1.56%)	1 / 36 (2.78%)	2 / 71 (2.82%)
occurrences (all)	2	1	2
Respiratory tract infection			
subjects affected / exposed	0 / 128 (0.00%)	2 / 36 (5.56%)	3 / 71 (4.23%)
occurrences (all)	0	2	3
Nasopharyngitis			
subjects affected / exposed	2 / 128 (1.56%)	0 / 36 (0.00%)	3 / 71 (4.23%)
occurrences (all)	2	0	3
COVID-19			
subjects affected / exposed	5 / 128 (3.91%)	1 / 36 (2.78%)	0 / 71 (0.00%)
occurrences (all)	5	1	0

Non-serious adverse events	75 mg BI 1358894	125 mg BI 1358894	25 mg BI 1358894
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 39 (61.54%)	34 / 75 (45.33%)	22 / 39 (56.41%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 39 (2.56%)	0 / 75 (0.00%)	2 / 39 (5.13%)
occurrences (all)	1	0	5
Dizziness			
subjects affected / exposed	2 / 39 (5.13%)	4 / 75 (5.33%)	6 / 39 (15.38%)
occurrences (all)	2	5	11
Somnolence			
subjects affected / exposed	7 / 39 (17.95%)	5 / 75 (6.67%)	1 / 39 (2.56%)
occurrences (all)	7	6	1
Sedation			
subjects affected / exposed	2 / 39 (5.13%)	2 / 75 (2.67%)	1 / 39 (2.56%)
occurrences (all)	2	2	1

Headache			
subjects affected / exposed	4 / 39 (10.26%)	13 / 75 (17.33%)	4 / 39 (10.26%)
occurrences (all)	5	15	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 39 (5.13%)	4 / 75 (5.33%)	3 / 39 (7.69%)
occurrences (all)	2	4	6
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 39 (0.00%)	3 / 75 (4.00%)	2 / 39 (5.13%)
occurrences (all)	0	4	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 39 (5.13%)	0 / 75 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
Abdominal pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
Dry mouth			
subjects affected / exposed	1 / 39 (2.56%)	1 / 75 (1.33%)	2 / 39 (5.13%)
occurrences (all)	1	1	2
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 39 (2.56%)	1 / 75 (1.33%)	2 / 39 (5.13%)
occurrences (all)	1	1	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 39 (5.13%)	1 / 75 (1.33%)	1 / 39 (2.56%)
occurrences (all)	3	1	1
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 39 (0.00%)	2 / 75 (2.67%)	0 / 39 (0.00%)
occurrences (all)	0	3	0
Aggression			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	0 / 39 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 39 (0.00%)	1 / 75 (1.33%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Insomnia			
subjects affected / exposed	1 / 39 (2.56%)	2 / 75 (2.67%)	2 / 39 (5.13%)
occurrences (all)	1	2	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 39 (0.00%)	1 / 75 (1.33%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 39 (5.13%)	3 / 75 (4.00%)	2 / 39 (5.13%)
occurrences (all)	2	3	3
Respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	0 / 75 (0.00%)	0 / 39 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 39 (5.13%)	2 / 75 (2.67%)	2 / 39 (5.13%)
occurrences (all)	3	2	2
COVID-19			
subjects affected / exposed	3 / 39 (7.69%)	1 / 75 (1.33%)	1 / 39 (2.56%)
occurrences (all)	3	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2020	Global amendment 2 was issued on 7-Jul-2020 and included the following changes: addition of backup procedures to cover for potential impact of coronavirus disease (COVID-19) during trial conduct; removal of restriction for "combined cytochrome P450 (CYP) 3A4 and Uridine diphosphate (UDP)-Glucuronosyltransferase (UGT) inhibitors" as co-meds; addition of speech recording collection; change of inclusionary MADRS entry score from ≥22 to ≥26; addition of exclusion criteria #24 and #25; addition of a description of the role of the external vendor responsible for confirmation of eligibility; addition of Erythrocyte Sedimentation Rate (ESR) test to Haematology; addition of information and rational that drug screen results will be included in the clinical database.
07 September 2020	Global amendment 3 was issued on 7-Sep-2020 and included the following changes: addition of the specification on how to split the screening visit on separate days, if needed; restrictions of strong or moderate CYP3A inhibitors according to the Summary of Product Characteristics (SmPC) of quetiapine; addition of an additional manufacturer of the placebos; definition of Patient Reported Outcomes (PROs) data as source documents; clarification that the investigator must adhere to the global Clinical Trial Protocol (CTP) and referring local amendments, where applicable; definition of minimum required laboratory parameters in case a local laboratory is needed due to restrictions due to COVID-19.
03 March 2021	Global amendment 4 was issued on 3-Mar-2021 and included the following changes: addition of Verification of duplicate participants (VCT); inclusion of optional participant's feedback questionnaire at End of Treatment (EOT); revision of Urinalysis test to align with Central lab testing standards; addition of Norfluoxetine to Fluoxetine.
28 June 2021	Global Amendment 5 was issued on 28-Jun-2021 and included the following changes: woman of childbearing potential (WOCBP) who were sexually abstinent were considered to fulfil the requirements of safe contraception; an option to extend the screening period by 7 days (i.e. to 28 days) was added, to allow for administrative issues such as late reporting of Selective Serotonin Reuptake Inhibitor (SSRI) / Serotonin Norepinephrine Reuptake Inhibitor (SNRI) blood levels.
28 September 2021	Global Amendment 6 was issued on 28-Sep-2021 and included the following changes: the duration of the current depressive episode was extended from 12 months to 18 months; the MADRS score required for entry was changed from ≥ 26 to ≥ 24; the minimum required duration of ongoing SSRI/SNRI monotherapy at screening was reduced from 8 weeks to 6 weeks; confirmation of SSRI/SNRI levels in urine at screening was added to analysis in serum; background SSRI/SNRI could optionally be stopped at EOT, and not only after the end of the trial; other antidepressants were permitted (excluding bupropion) if less than the lowest dose indicated for MDD, e.g., for treatment of anxiety or sleep disorder.
27 April 2022	Global Amendment 7 was issued on 27-Apr-2022 and included the following changes: counseling about the need of contraception at Visit 1 during Informed Consent (IC); reiteration of adherence to contraception at all visits; removal of onsite ESR; confirmation of SSRI/SNRI exposure can be done either in urine or serum under conditions as described; new data added from preclinical trials showing teratogenicity potential in animals; renaming of Visits; update of the Seroquel Summary of Product Characteritics reference.

26 September 2022	Global Amendment 8 was issued on 26-Sep-2022 and included the following changes: investigators were required to ensure that participants understood the contraception requirements, and were to confirm that participants were willing to abide by these; counselling on contraception was to be provided at all visits.
26 October 2022	Global Amendment 9 was issued on 26-Oct-2022 and included the following changes: the duration of the current depressive episode was extended from 18 months to 24 months; Bupropion (Selective Norepinephrine Dopamine Reuptake Inhibitor) was added as an acceptable antidepressant background treatment; the restriction on sensitive CYP2B6 concomitant medications was lifted; the minimal needed duration of ongoing monotherapy with an SSRI/SNRI/bupropion was reduced from 6 to 4 weeks; lifetime usage of transcranial magnetic stimulation (TMS) was changed to only exclude TMS if used during the current depressive episode, or within 12 months prior to screening;´ the customized Antidepressant Treatment Response Questionnaire (ATRQ) defining the minimal required duration for stable antidepressant therapy at screening was changed from 6 to 4 weeks; it was recommended to use different raters for the Columbia Suicide Severity Rating Scale (C-SSRS) scale and adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported