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Efficacy, Tolerability, and Safety of TRPC4/5 Inhibitor BI 1358894 in Patients With Major Depressive Disorder and Inadequate Response to Antidepressants:

A Phase 2 Randomized, Placebo-Controlled, Parallel Group, Dose-Ranging Trial

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Abstract

Objective: To assess proof-of-concept (PoC) for efficacy, tolerability, and safety of TRPC4/5 inhibitor BI 1358894 vs placebo in patients with major depressive disorder (MDD) with inadequate response to ongoing antidepressants.

Methods: In this phase 2, multicenter, randomized, double-blind, dose-finding trial (December 2020–February 2024), patients with MDD (per *DSM-5*) and current depressive episode of ≥8 weeks and ≤24 months were randomized (3.5:1:1:1:2:2) to receive placebo or BI 1358894 (5 mg, 25 mg, 75 mg, or 125 mg) or quetiapine 150–300 mg orally, once daily for 6 weeks. Primary end point was change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at Week 6. Secondary end points included ≥50% reduction from baseline in MADRS total score at Week 6, change from baseline in State-Trait Anxiety Inventory scores, Clinical Global Impression Severity Scale score, and Symptoms of Major Depressive Disorder Scale total score at Week 6.

Results: Of 940 enrolled patients, 389 were randomized, and 361 (93.0%) completed the trial. No differences were observed between BI 1358894 treatment groups and placebo for primary and secondary end points. Adverse events were slightly more frequent in the BI 1358894-total group (66.7%) vs placebo (53.9%). No worsening of Columbia-Suicide Severity Rating Scale was observed for most patients; serious adverse events of suicidal ideation were reported for 4.7% (placebo), 5.1% (BI 1358894 75 mg group), and 1.4% (quetiapine) of patients.

Conclusion: Although this was a negative trial in MDD with PoC not established, BI 1358894 was well tolerated with no increase in self-harm or suicidality.

Trial Registration: ClinicalTrials.gov identifier: NCT04521478.

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Major depressive disorder (MDD) is a prevalent condition that is challenging to treat despite the availability of a wide variety of antidepressant treatments.[1] Approximately 30% of patients with MDD do not reach remission even after 4 medication steps and continue to experience residual symptoms and poor quality of life.[2,3] Additionally, patients with MDD exhibit a higher mortality rate relative to the general population,[4–6] with an 8.62 times greater likelihood of dying by suicide.[7]

Most clinical guidelines recommend selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or bupropion (norepinephrine-dopamine reuptake inhibitor) as the first-line pharmacologic treatment for MDD.[8–11] When monotherapy with first-line treatments is ineffective, common management strategies involve switching to a different antidepressant within the same or different class, combining antidepressants, or using adjuncts such as lithium or atypical antipsychotics in

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Clinical Points

- Given the limitations of current treatments for major depressive disorder, there is an urgent need for new options. This study explores a new TRPC4/5 inhibitor, BI 1358894, as a potential alternative to existing add-on treatments.
- The trial did not demonstrate efficacy for BI 1358894, but the treatment was well tolerated with no observed increase in self-harm or suicidality.

addition to first-line treatments.[10,12,13] The commonly prescribed adjuncts are associated with an increased side-effect burden, which can restrict their applicability.[10,14] Given the limitations of existing treatments and the high disease burden of MDD, there is a pressing need for new and effective treatments.

A potential pathophysiological mechanism underlying MDD involves an imbalance in the corticolimbic circuitry.[15,16] Transient receptor potential canonical ion channels 4 and 5 (TRPC4/5) are involved in the regulation of neuronal excitability and are primarily expressed in brain areas associated with emotion and mood, including the corticolimbic system including the amygdala.[17,18] BI 1358894 is a TRPC4/5 inhibitor in development for symptomatic treatment of MDD, which is theorized to address symptoms of depression through attenuation of amygdala hyperreactivity.[19] As such, BI 1358894 may represent a potential new alternative to existing adjunctive treatments for MDD. In phase 1 trials of healthy volunteers, BI 1358894 reduced psychological and physiological responses to cholecystokinin-tetrapeptide (CCK-4) induced panic symptoms[20] and was found to be well tolerated with a favorable pharmacokinetic profile.[21,22] The present trial was conducted to provide proof-of-concept (PoC) for TRPC4/5 ion channel inhibition and dose-ranging data for BI 1358894 vs placebo in patients with MDD with inadequate response to ongoing antidepressants, in order to support dose selection for pivotal studies. Additionally, the safety and tolerability of BI 1358894 was assessed.

METHODS

Trial Design, Randomization, and Blinding

This was a phase 2, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial (ClinicalTrials.gov identifier: NCT04521478), with an additional quetiapine group, in patients with MDD with inadequate response to ongoing antidepressants (Figure 1). This trial was conducted in 120 sites in 14 countries between December 21, 2020, and February 2, 2024 (Supplementary Figure 1). Eligible patients with documented ongoing antidepressants (SSRI/SNRI/bupropion) were randomized to receive placebo or BI 1358894 (5 mg, 25 mg, 75 mg, or 125 mg) or quetiapine extended release 150–300 mg orally, once daily in a 3.5:1:1:1:2:2 ratio for 6 weeks. Randomization codes were computer-generated by a specialized randomization group within the sponsor company. Based on these codes, the allocation of patients to treatment was performed using an interactive response technology run by an external vendor. Access to the randomization code was controlled and documented. The clinical trial team remained blinded to the randomized treatment assignments until the final database lock, with one prespecified exception. To facilitate the exclusion of pharmacokinetic (PK) samples from placebo participants in the analyses, randomization codes were provided to the bioanalytics team prior to the last participant completing the trial. However, these randomization codes and the PK results remained undisclosed until the trial was officially unblinded.

Randomization into each treatment group was stratified by baseline severity of MDD (baseline Montgomery-Åsberg Depression Rating Scale [MADRS] score ≤19 vs >19). Randomization occurred up to 3 weeks after screening, and fluctuations in depressive symptoms could be expected; therefore, no MADRS cutoff was imposed at the randomization visit to avoid potential inflation of baseline severity.

Medication kits corresponding to assigned medication numbers were given to patients. Using this procedure, patients and trial staff were blinded to treatment group assignments. BI 1358894 tablets or matching placebos were administered orally every morning. The selection of BI 1358894 doses (5 mg, 25 mg, 75 mg, and 125 mg) was guided by preclinical findings and PK data from prior phase 1 studies.[21,23] The half maximal effective concentration (EC50) from preclinical studies was used to select the target total plasma concentration in humans. Considering the limitations and uncertainties associated with preclinical animal tests in predicting antidepressive efficacy in humans, an adequate multiple above and below this target dose was explored in this clinical dose range finding study, leading to the dose range of 5 mg to 125 mg.

Quetiapine is a commonly recommended adjunctive agent in patients with inadequate response to antidepressant monotherapy.[10,13] Therefore, a quetiapine treatment group was included in this trial for reference. Quetiapine or matching placebo was administered orally every evening. Adherence was measured using the traditional tablet-counting method, plus by video-monitoring using a smartphone application.

Using a multiple comparison procedure with modeling (MCPMod) approach, a total sample size of

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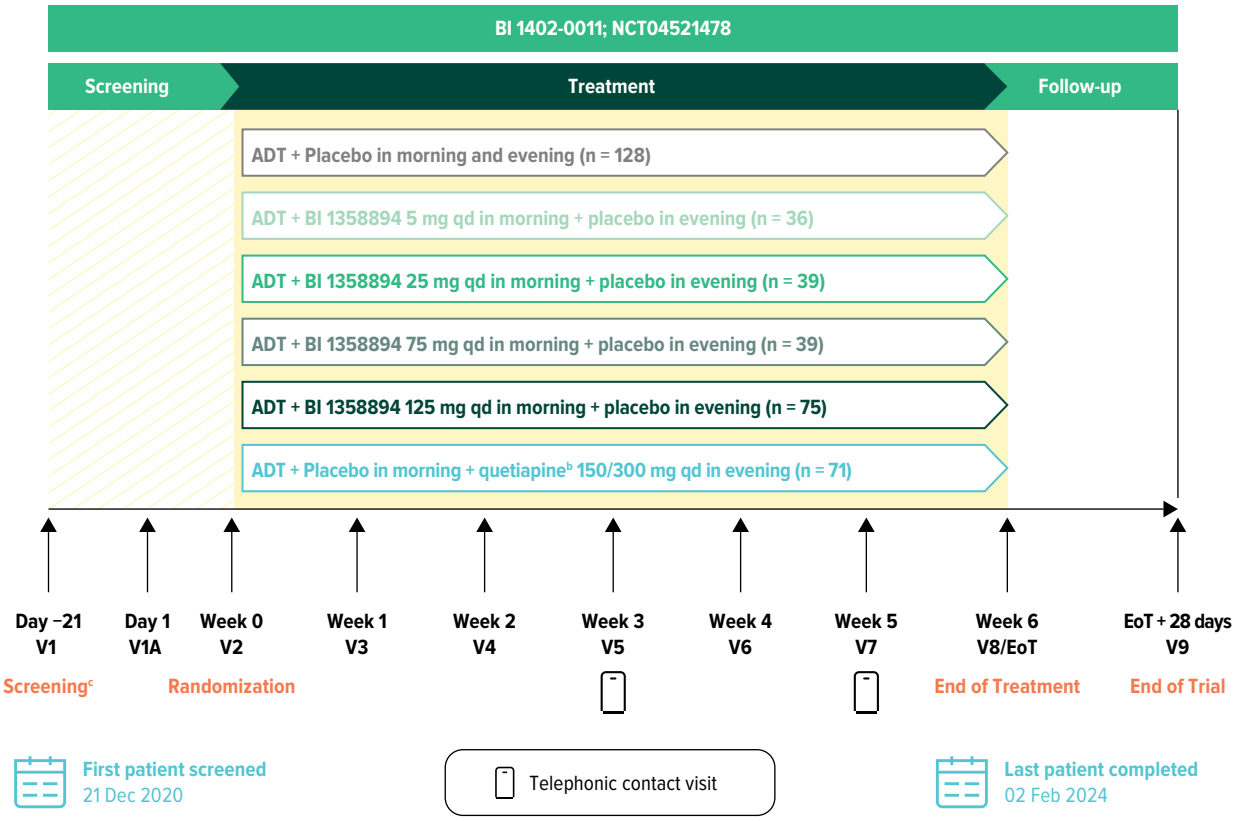
Figure 1.
Trial Design[a]



[a]This trial had 7 outpatient visits (Visits 1 [screening], 2 [randomization], 3 [Week 1], 4 [Week 2], 6 [Week 4], 8 [EoT; Week 6], and 9 or end of study follow-up [EoT + 28 d]) and 2 telephonic contact visits (Visit 5 [Week 3] and 7 [Week 5]).
[b]72 patients were randomized in the quetiapine group, of which 71 received treatment. Quetiapine dosing began at 50 mg on Day 1 and gradually increased to 300 mg by Day 5. If patients had difficulty tolerating the 300 mg dose, it could be lowered to 150 mg per day at the Week 1 visit.
[c]The screening period of 21 days was extendable up to 28 days in case of operational delays, eg, late reporting of SSRI/SNRI/bupropion blood levels.
Abbreviations: ADT = ongoing antidepressant treatment, EoT = end of treatment, n = number of patients randomized in each treatment group, V = visit, qd = once daily.

approximately 431 patients was needed to determine PoC with 81% average power across models, with 1-sided 10% α level, assuming a 30% dropout rate and 281 evaluable patients across the placebo and BI 1358894 treatment groups.

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation of Good Clinical Practice guidelines, applicable regulatory requirements, and Boehringer Ingelheim standard operating procedures. The clinical trial protocol and informed consent form were approved by the Independent Ethics Committees and/or Institutional Review Boards of the participating centers.

Participants

The trial included patients aged 18–65 years, with an established diagnosis of MDD (per Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition) at screening who provided informed consent. In order to exclude chronic forms of depression and ensure a more homogeneous MDD sample, patients were required to be experiencing a current depressive episode of ≥8 weeks and ≤24 months. Eligibility criteria also included a MADRS total score ≥24 (confirmed by a trained site-based rater and computer-administered patient-reported MADRS) and a score ≥3 on the Reported Sadness Item, along with documented ongoing antidepressant monotherapy (protocol specified SSRI or SNRI, or bupropion) of ≥4 weeks at the screening visit as confirmed by detectable drug levels in urine or blood samples. Patients were excluded at screening if they had ever met diagnostic criteria for a psychotic disorder, had a diagnosis of any other psychiatric disorder as the primary focus of treatment within 6 months prior to screening, had a history of major neurological illness, or had a diagnosis of any personality disorder that could impact trial participation, or a substance abuse disorder, within 3 months prior to screening. Patients

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with suicidal behavior 12 months prior to screening or a Columbia-Suicide Severity Rating Scale (C-SSRS) score of 4 or 5 in the 3 months prior to screening or at screening or baseline visit were also excluded. Patients could have no more than two unsuccessful monotherapy treatments with an approved antidepressant (SSRI/SNRI/bupropion) at adequate dose and duration for the current ongoing major depressive episode. The full eligibility criteria and the protocol amendments for the inclusion criteria are presented in the Supplementary Materials.

End Points and Assessments

Primary end point. The primary end point was change from baseline in MADRS total score at Week 6. The MADRS includes 10 items that measure core symptoms of depression. Each item is scored from 0 (indicating no abnormality) to 6 (indicating severe symptoms), with total scores spanning from 0 (no symptoms) to 60 (high severity).[24] Subgroup analyses of the primary end point were conducted for baseline disease severity, demographics (sex, age group, concomitant psychotherapy use, type of background medication, race [White/non-White, Asian/non-Asian], and region), and overall medication adherence.

Secondary end points. Secondary end points were treatment response (defined as ≥50% reduction from baseline in MADRS total score) at Week 6, change from baseline in the State-Trait Anxiety Inventory (STAI) State and Trait version total scores,[25] Clinical Global Impression Severity Scale (CGI-S) score,[26] and Symptoms of Major Depressive Disorder Scale (SMDDS)[27] total score at Week 6.

Exploratory end points. The key exploratory end points included BI 1358894 plasma concentration, relative percent change from baseline in total MADRS score over time, remission defined as MADRS score ≤10 at Week 6, and change from baseline in STAI, CGI-S, and SMDDS scores over time. Other exploratory end points are summarized in the Supplementary Materials.

Safety and Tolerability

The percentages of patients with adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI) were recorded. The prespecified AESI was hepatic injury, which included an elevation of aminotransferase [aspartate transaminase {AST} and/or alanine transaminase {ALT}] ≥3-fold upper limit of normal [ULN] combined with total bilirubin elevation ≥2-fold ULN measured in the same blood sample, or aminotransferase [ALT and/or AST] elevations ≥10-fold ULN), and extrapyramidal AEs were recorded. Suicidal risk was assessed by the C-SSRS. Any clinically significant abnormalities in physical examination, vital signs, 12-lead electrocardiogram (ECG), and laboratory tests were also reported.

Statistical Analysis

Primary analysis of the primary end point used a hypothetical estimand, which focused on the treatment effect assuming that the trial medication was taken as directed and excluding intercurrent events, including all data collected while on treatment from the first dose of trial medication to the last dose plus 7 days. Any data collected after a patient discontinued treatment, regardless of the reason, were not included in the primary analysis. MCPMod was used to evaluate several possible dose-response models to identify the best-fitting model based on BI 1358894 and placebo treatment groups (refer to the Supplementary Materials for details). If at least one dose-response model showed statistical significance, demonstrating a nonflat dose-response curve for change from baseline in MADRS total score at Week 6, indicating a benefit of at least one BI 1358894 dose over placebo, this would establish PoC.

As a basis for the MCPMod analysis and to assess quantitative treatment benefit, a mixed model for repeated measure (MMRM) analysis was used to generate covariate adjusted estimates of mean change from baseline to Week 6 in MADRS total score and associated covariance matrices. The MMRM included discrete fixed effects for baseline MADRS severity level, treatment at each visit, concomitant psychotherapy use, and the continuous effects of baseline. No formal hypothesis tests were performed to compare BI 1358894 and quetiapine or to compare quetiapine and placebo as the trial was not statistically powered for such comparisons. However, an exploratory post hoc MMRM analysis was conducted for the primary end point to assess potential trends in quetiapine treatment effects compared to placebo and all doses of BI 1358894. Descriptive summaries of quetiapine and placebo responses were used to assess the impact of placebo response.

For the secondary end point of treatment response (≥50% reduction in MADRS total score from baseline), the proportion of participants achieving response for each analysis visit up to Week 6 was summarized as the frequency and percentage of participants in each treatment arm. MADRS response up to Week 6 was analyzed using a logistic regression model, including fixed categorical effects of treatment and baseline MDD severity. For the other secondary end points, a similar MMRM approach was used to obtain the adjusted change from baseline at Week 6 for each of the BI treatment groups vs placebo. All end points were summarized descriptively.

Efficacy was assessed for the full analysis set; ie, all randomized patients who received ≥1 dose of trial medication during the trial had a baseline and ≥1 evaluable postbaseline measurement for the primary end point. Safety analyses were conducted on the treated set (TS), ie, all randomized patients who

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Table 1.

Baseline Demographics and Characteristics (Treated Set)

	Placebo n = 128	BI 1358894 5 mg n = 36	BI 1358894 25 mg n = 39	BI 1358894 75 mg n = 39	BI 1358894 125 mg n = 75	Quetiapine 150/300 mg n = 71	Total N = 388
Demographic characteristics							
Age, mean (SD), y	42.9 (13.0)	39.7 (13.8)	44.7 (12.1)	42.7 (12.2)	47.7 (11.7)	43.6 (12.4)	43.8 (12.7)
Female, n (%)	82 (64.1)	27 (75.0)	28 (71.8)	26 (66.7)	51 (68.0)	49 (69.0)	263 (67.8)
BMI, mean (SD) kg/m²	29.6 (8.2)	29.0 (8.7)	29.9 (9.5)	29.8 (7.6)	31.8 (9.3)	29.0 (9.0)	29.9 (8.7)
<30 kg/m², n (%)	78 (60.9)	19 (52.8)	23 (59.0)	25 (64.1)	35 (46.7)	44 (62.0)	224 (57.7)
≥30 kg/m², n (%)	50 (39.1)	17 (47.2)	16 (41.0)	14 (35.9)	40 (53.3)	27 (38.0)	164 (42.3)
Race, n (%)							
Asian	24 (18.8)	5 (13.9)	6 (15.4)	6 (15.4)	15 (20.0)	12 (16.9)	68 (17.5)
Black or African American	6 (4.7)	2 (5.6)	3 (7.7)	1 (2.6)	7 (9.3)	6 (8.5)	25 (6.4)
White	98 (76.6)	29 (80.6)	30 (76.9)	32 (82.1)	53 (70.7)	53 (74.6)	295 (76.0)
Hispanic or Latino ethnicity (yes), n (%)	19 (14.8)	5 (13.9)	2 (5.1)	5 (12.8)	8 (10.7)	12 (16.9)	51 (13.1)
Clinical characteristics							
Time since diagnosis of MDD, mean (SD), y	9.3 (9.0)	8.4 (7.5)	11.0 (9.3)	9.8 (9.1)	12.2 (11.6)	11.2 (12.7)	10.3 (10.3)
MADRS total score[a], mean (SD)	32.0 (6.4)	34.0 (4.8)	34.1 (5.6)	32.1 (6.4)	33.1 (6.0)	33.6 (5.6)	32.9 (6.0)
C-SSRS Lifetime suicidal ideation, n (%)	63 (49.2)	21 (58.3)	19 (48.7)	17 (43.6)	38 (50.7)	32 (45.1)	190 (49.0)
C-SSRS Lifetime suicidal behavior, n (%)	25 (19.5)	10 (27.8)	9 (23.1)	6 (15.4)	10 (13.3)	9 (12.7)	69 (17.8)
Type of background medication, n (%)							
Bupropion	8 (6.3)	1 (2.8)	1 (2.6)	1 (2.6)	5 (6.7)	2 (2.8)	18 (4.6)
SNRI	42 (32.8)	13 (36.1)	18 (46.2)	12 (30.8)	24 (32.0)	22 (31.0)	131 (33.8)
SSRI	77 (60.2)	21 (58.3)	19 (48.7)	26 (66.7)	46 (61.3)	44 (62.0)	233 (60.1)
None	1 (0.8)	1 (2.8)	1 (2.6)	0.0	0.0	3 (4.2)	6 (1.5)

[a]MADRS was administered by a trained site-based rater.

Abbreviations: BMI = body mass index, C-SSRS = Columbia-Suicide Severity Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, n = number of randomized patients, SD = standard deviation, SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin norepinephrine reuptake inhibitor.

received ≥1 dose of the trial medication. BI 1358894 plasma concentration was assessed for all patients in the TS who had ≥1 evaluable PK plasma concentration measurement.

RESULTS

Patient Disposition and Demographics

Of the 940 enrolled patients, 389 were randomized and 340 (87.6%) completed trial treatment. Of the 388 treated patients, 361 (93.0%) completed the trial, including 21 patients who remained in the trial following premature discontinuation of treatment. The patient disposition flowchart is presented in Supplementary Figure 2. Mean (standard deviation [SD]) age was 43.8 (12.7) years, mean (SD) body mass index was 29.9 (8.7) kg/m², and 263 (67.8%) were female. Most patients were White (76.0%), had moderate-to-severe depression (mean [SD] MADRS total score was 32.9 [6.0]), and had a long disease history (mean [SD] time since diagnosis of MDD was 10.3 [10.3] years). Overall, 60.1% of patients were taking background SSRI, 33.8% were taking SNRI, and 4.6% were taking bupropion (Table 1). Use of SSRI/SNRI or bupropion was confirmed by serum testing in 382 (98.5%) patients at baseline and 315 (81.2%) patients at end of treatment. Medication adherence results are included in the Supplementary Materials.

Efficacy

Primary end point. BI 1358894 failed to separate from placebo in the change from baseline in MADRS total score at any dose level or time point (Figure 2A; Supplementary Table 1). None of the models investigated in the MCPMod analysis indicated a nonflat dose-response for BI 1358894 (*P* values were nonsignificant, ie, exceeded 0.85 for all models); therefore, PoC could not be established (Supplementary Table 2). Further, the subgroup analyses did not reveal any differences between the BI 1358894 treatment groups and placebo. The change from baseline in MADRS total score in the quetiapine group showed a small numerical increase compared to placebo and BI 1358894 at all time points (Figure 2B; Supplementary Table 3).

Secondary end points. The treatment response rate (≥50% reduction in MADRS) for patients did not differentiate from placebo in any of the BI 1358894 treatment groups. The mean reductions from baseline in STAI, CGI-S, and SMDDS scores were also similar between the BI 1358894 treatment groups and placebo over the duration of treatment, with no significant differences (Table 2). The descriptive results of change from baseline in STAI, CGI-S,

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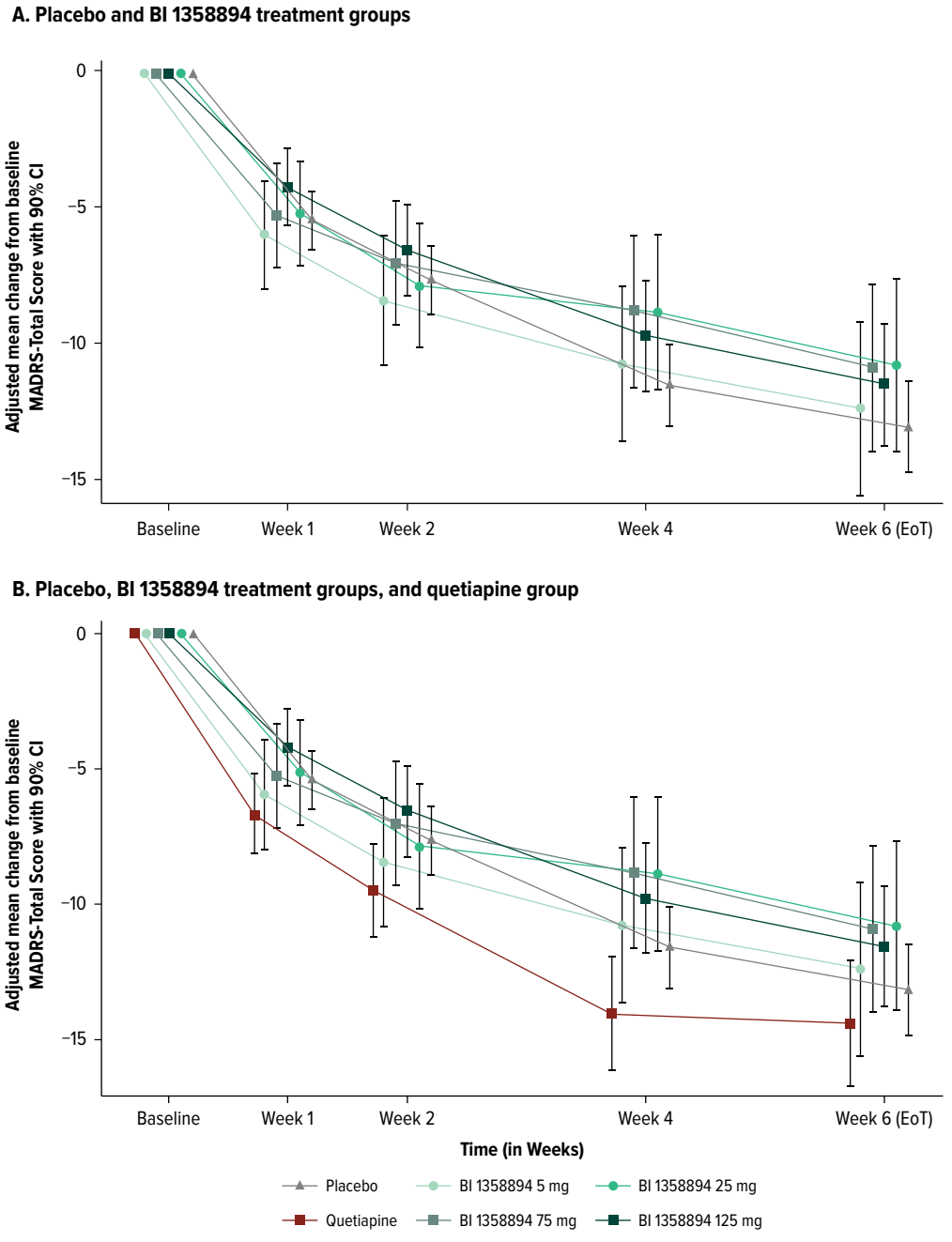
Figure 2.

Change from Baseline in MADRS Total Score up to Week 6 (Full Analysis Set)



Abbreviations: CI = confidence interval, EoT = end of treatment, MADRS = Montgomery-Åsberg Depression Rating Scale.

and SMDDS scores at Week 6 were similar in the quetiapine and placebo groups (Supplementary Table 3).

Exploratory end points. BI 1358894 plasma concentrations increased with increasing dose. Steady state was reached after 2 weeks and was retained until the end of treatment at Week 6 in all BI 1358894 treatment groups (Supplementary Figure 3). Additionally, there was no correlation between plasma concentration of BI 1358894 and change from baseline in MADRS total score at any dose level (Supplementary Figure 4).

There were no significant differences between the BI 1358894 treatment groups and placebo for any of the other exploratory end points (data not shown).

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Table 2.

Secondary End Points (Full Analysis Set)

		BI 1358894			
	Placebo n = 126	5 mg n = 36	25 mg n = 39	75 mg n = 39	125 mg n = 72
n*	112	30	32	33	64
Treatment response (≥50% reduction in MADRS) at Week 6					
Response rate (%)	35.7	33.3	28.1	36.4	35.9
Odds ratio vs placebo [90% CI]	–	0.9 [0.5–1.9]	0.7 [0.3–1.3]	1.1 [0.6–2.1]	1.0 [0.6–1.7]
Change from baseline in STAI State Anxiety total score at Week 6					
Adjusted mean change (SE) [90% CI]	−11.3 (1.2) [−13.3 to −9.3]	−7.0 (2.3) [−10.8 to −3.2]	−8.9 (2.3) [−12.7 to −5.2]	−12.3 (2.2) [−16.0 to −8.7]	−8.6 (1.6) [−11.3 to −5.9]
Change from baseline in STAI Trait Anxiety total score at Week 6					
Adjusted mean change (SE) [90% CI]	−11.0 (1.1) [−12.9 to −9.1]	−6.9 (2.1) [−10.4 to −3.4]	−10.2 (2.1) [−13.7 to −6.7]	−9.9 (2.1) [−13.3 to −6.5]	−7.2 (1.5) [−9.7 to −4.7]
Change from baseline in CGI-S score at Week 6					
Adjusted mean change (SE) [90% CI]	−1.3 (0.1) [−1.5 to −1.1]	−1.2 (0.2) [−1.6 to −0.8]	−1.2 (0.2) [−1.5 to −0.8]	−1.1 (0.2) [−1.5 to −0.8]	−1.1 (0.2) [−1.3 to −0.8]
Change from baseline in SMDDS score at Week 6					
Adjusted mean change (SE) [90% CI]	−13.3 (1.2) [−15.2 to −11.4]	−9.9 (2.2) [−13.5 to −6.2]	−8.9 (2.2) [−12.5 to −5.3]	−12.3 (2.1) [−15.8 to −8.8]	−10.5 (1.6) [−13.1 to −8.0]

Abbreviations: CI = confidence interval, CGI-S = Clinical Global Impression Severity Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, n = number of patients in the full analysis set, n* = number of patients with data available for the respective end point, SE = standard error, SMDDS = Symptoms of Major Depressive Disorder Scale, STAI = State-Trait Anxiety Inventory.

Table 3.

Overall Summary of AEs (Treated Set)[a]

		BI 1358894					
AE type, n (%)	Placebo n = 128	5 mg n = 36	25 mg n = 39	75 mg n = 39	125 mg n = 75	Total n = 189	Quetiapine 300/150 mg n = 71
Any	69 (53.9)	21 (58.3)	24 (61.5)	30 (76.9)	51 (68.0)	126 (66.7)	54 (76.1)
Severe	9 (7.0)	2 (5.6)	4 (10.3)	4 (10.3)	2 (2.7)	12 (6.3)	1 (1.4)
Treatment-related[b]	36 (28.1)	15 (41.7)	16 (41.0)	17 (43.6)	34 (45.3)	82 (43.4)	45 (63.4)
Leading to treatment discontinuation	7 (5.5)	–	2 (5.1)	1 (2.6)	2 (2.7)	5 (2.6)	7 (9.9)
Other significant	9 (7.0)	1 (2.8)	2 (5.1)	2 (5.1)	7 (9.3)	12 (6.3)	26 (36.6)
Serious	7 (5.5)	–	2 (5.1)	2 (5.1)	1 (1.3)	5 (2.6)	1 (1.4)
Life threatening	1 (0.8)	–	-	1 (2.6)	–	1 (0.5)	–
Hospitalization	1 (0.8)	–	1 (2.6)	1 (2.6)	–	2 (1.1)	–
Other	5 (3.9)	–	1 (2.6)	1 (2.6)	1 (2.6)	3 (1.6)	1 (1.4)

[a]AEs were coded using MedDRA version 26.1.
[b]Investigator defined.
Abbreviations: AEs = adverse events, MedDRA = Medical dictionary for drug regulatory activities, n = number of patients in respective treatment group.

Safety

Overall, AEs were reported in all treatment groups, most frequently in the BI 1358894 75 mg group (76.9%), followed by the quetiapine (76.1%) and placebo (53.9%) groups (Table 3). AEs leading to trial medication discontinuation were most frequently reported in the quetiapine group (9.9%) followed by the placebo group (5.5%) while the frequency was lower in the BI 1358894-total group (2.6%; Supplementary Table 4).

The most frequently reported AEs (incidence of ≥5%) in the BI 1358894-total treated group vs placebo were headache (15.9% vs. 10.2%), dizziness (7.4% vs 2.3%), and somnolence (7.4% vs 3.1%). Extrapyramidal motor AEs were reported in 8 (4.2%) patients in the BI 1358894-total group, 4 (5.6%) patients in the quetiapine group, and 1 (0.8%) patient in the placebo group. The most common SAE, suicidal ideation, was reported in 6 (4.7%) patients in the placebo group, 2 (5.1%) patients in the BI 1358894 75 mg group, and 1 (1.4%) patient in the quetiapine group. No pattern of events was observed in the BI 1358894-treated groups, and no dose-dependent trend was seen in SAEs in BI 1358894-treated groups. There were no AESI and no deaths in any group. There were no clinically relevant changes from baseline for vital signs, 12-lead ECG, or any safety laboratory parameters during the trial. Overall, there was no worsening of C-SSRS scores over time for most patients, and suicidal ideation and behavior reported at any time

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on-treatment were infrequent. There were no completed suicides during the trial (Supplementary Table 5).

DISCUSSION

This phase 2 trial evaluated the efficacy and safety of 6 weeks of adjunctive BI 1358894 treatment vs placebo in patients with moderate-to-severe MDD receiving an ongoing antidepressant treatment. The trial failed to meet the primary and secondary end points as there were no significant differences between treatment groups and placebo, including the subgroup analyses. As PoC was not established, the dose-response modeling was not conducted. While this trial was not powered for statistical comparisons between the quetiapine and placebo or BI 1358894 treatment groups, the exploratory post hoc analysis of the primary end point, including the quetiapine arm, suggested a potential trend of antidepressant efficacy for quetiapine.

BI 1358894 was well tolerated, with the majority of events being nonserious and no pattern of serious events and drug discontinuations; therefore, the safety profile was consistent with the previous phase 1 trials in healthy volunteers.[20–22] AEs leading to treatment discontinuation were less frequent in the BI 1358894-total treatment group (2.6%) than in the placebo (5.5%) or quetiapine treatment groups (9.9%). There were no completed suicides or increases in suicidal ideation or behavior while on treatment with BI 1358894, reflecting prior findings from a phase 2 decentralized clinical trial (DCT) in patients with MDD[28] and a phase 2 trial in patients with borderline personality disorder.[29]

While BI 1358894 demonstrated reduced activation in corticolimbic regions including the amygdala in a previous functional magnetic resonance imaging phase 1b trial in patients with MDD,[19] it did not demonstrate efficacy in the current phase 2 trial. This discrepancy between these trial results may be attributed to various factors. First, the neuroimaging biomarkers, such as reduced corticolimbic activation observed in the phase 1b trial, may not necessarily correlate with clinical outcomes or reliably predict clinical response. Second, the phase 1b trial included people with mild MDD (mean baseline MADRS total score of 17.7 in the BI 1358894 group) who were not receiving antidepressant treatment. In contrast, this PoC trial comprised patients with moderate-to-severe MDD (mean baseline MADRS total score ranged from 32.1 to 34.1 across BI 1358894 treatment groups). Third, the phase 1b trial had a small sample size of 73 participants (only 25 received BI 1358894), whereas in the present trial, 389 patients were randomized to receive treatment. The greater sample size and the large number of trial sites in 14 countries may have introduced heterogeneity. Lastly, the participants in the phase 1b trial received BI 1358894 monotherapy whereas in the present trial, patients were receiving BI 1358894 as an adjunctive treatment. These factors highlight the challenges of applying early-phase trial results to broader and more varied clinical populations.

The lack of positive efficacy results in the present trial is in alignment with a parallel phase 2 DCT with BI 1358894 in patients with MDD (terminated due to insufficient recruitment).[28] However, there were notable differences between the patient population of the DCT and the present trial, ie, in terms of geographic recruitment (present trial, 14 countries; DCT, exclusively in US), sex (present trial, 67.8% females; DCT, 83.7% females), depression severity (mean baseline MADRS total score in present trial, 32.9; DCT, 26.6), and history of MDD (mean time since diagnosis of MDD in the present trial, 10.3 years; DCT, 15.5 years). Despite these differences, neither trial showed efficacy for BI 1358894 (5–125 mg) as an adjunctive treatment when administered daily over a 6-week period in the patient populations studied.

Despite the negative outcome, the trial had several strengths. This was a large, high-quality randomized controlled trial evaluating a novel treatment target and assessing 4 doses of BI 1358894 vs placebo plus an active control group for trial sensitivity. Notably, 93% of participants completed the trial, including those who discontinued treatment but remained in the study. A limitation of this study was its timing, as it commenced during the COVID-19 pandemic and may have impacted patient functionality and consequently their overall scores or participation in the trial.

In conclusion, this PoC trial evaluated the efficacy and safety of a 6-week treatment with BI 1358894 compared with placebo in patients with MDD with inadequate response to ongoing antidepressant pharmacotherapy. Although efficacy was not demonstrated in this trial, BI 1358894 was well tolerated and did not lead to an increase in self-harm or suicidality.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Efficacy, Tolerability, and Safety of TRPC4/5 Inhibitor BI 1358894 in Patients With Major Depressive Disorder and Inadequate Response to Antidepressants: A Phase 2 Randomized, Placebo-Controlled, Parallel Group, Dose-Ranging Trial

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The Journal of Clinical Psychiatry

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODS

Inclusion criteria

1. Established diagnosis of Major Depressive Disorder (MDD), single episode or recurrent, as confirmed at the time of screening by the Structured Clinical Interview for DSM-5 (SCID-5), with a duration of current depressive episode ≥8 weeks and ≤24 months[a] at the time of screening visit

   [a]*Initially, the maximum duration of the current depressive episode was 12 months, however, this was increased to 18 months and then to 24 months, following 2 protocol amendments*

2. Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥24[b] at screening, as confirmed by a trained site-based rater AND interactive, computer administered MADRS. The difference between the rater and computer administered MADRS must not exceed more than 7 points. In addition, trial participants must have a score of ≥3 on the Reported Sadness Item on both MADRS scales (computer administered and rater-administered MADRS)

   [b]*Initially, the minimum required total score was 26, however, this was later changed to 24 by a protocol amendment*

3. A documented ongoing monotherapy treatment of ≥4 weeks[c] at the screening visit, with bupropion[d] or a protocol specified[e] selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) at adequate dose (at least minimum effective dose as per prescribing information and as confirmed per detectable drug levels in the screening blood[f] or urine[g] sampling)

   [c]*Initially, the minimum required duration of ongoing monotherapy was 8 weeks, this was changed to 6 weeks, then to 4 weeks, following 2 protocol amendments*

   [d]*Following a protocol amendment, as a result of the removal of restrictions on sensitive CYP2B6 concomitant medications, participants with background bupropion monotherapy could be recruited*

[e]Duloxetine, Citalopram / Escitalopram, Paroxetine, Sertraline, Desmethylsertraline, Fluoxetine, Norfluoxetine, Venlafaxine, Desmethylvenlafaxine, Desvenlafaxine

[f]Duloxetine was assessed in serum only

[g]Documentation in urine was first allowed with a protocol amendment

4. Male and female participants, 18–65 years of age, both inclusively at the time of consent
5. Women who are of child-bearing potential (WOCBP) must be able and willing, as confirmed by the investigator, to use 2 methods of contraception which include 1 highly effective method of birth control that result in a low failure rate of less than 1%, plus 1 additional barrier
6. Signed and dated written informed consent in accordance with the International Council for Harmonisation of technical requirements for pharmaceuticals for human use guideline for good clinical practice and local legislation prior to admission to the trial
7. Able to communicate well, and to understand and comply with trial requirements

Exclusion criteria

1. Per Structured Clinical Interview for Diagnostic and Statistical manual of mental disorders-5 [DSM-5], had ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, delusional disorder or MDD with psychotic features at the time of screening

2. Diagnosis of any other mental disorder (in addition to those as described in Exclusion Criterion #1) that was the primary focus of treatment within 6 months prior to screening or at baseline (as per clinical discretion of the investigator)

3. Diagnosis with antisocial, paranoid, schizoid, or schizotypal personality disorder as per DSM-5 criteria, at the time of screening visit. Any other personality disorder at screening visit that

significantly affects current psychiatric status and likely to impact trial participation, as per the judgment of investigator

4. Diagnosis of a substance-related disorder within 3 months prior to screening visit (with exception of caffeine and tobacco)
5. History of seizure disorders, stroke, brain tumor or any other major neurological illness that can impact participation in the trial
6. History of more than 2 unsuccessful monotherapy treatments (at adequate dosage and duration, per local prescribing information of the product) with an approved antidepressant medication for the current ongoing major depressive episode. These include ongoing monotherapy treatment with bupropion, or a protocol-specified SSRI or SNRI as described in Inclusion Criterion #3
7. Any suicidal behavior in the past 12 months prior to screening (per investigator judgment including an actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
8. Any suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity Rating Scale (CSSRS) in the past 3 months prior to screening or at screening or baseline visit (i.e., active suicidal thought with method and intent but without specific plan, or active suicidal thought with method, intent, and plan)
9. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix
10. Known history of HIV infection and/or a positive result for ongoing Hepatitis B or C infection
11. Have initiated psychotherapy or other non-drug therapies (e.g., acupuncture or hypnosis) within 3 months prior to screening or planning to start any time during the trial. The participant should not

have a change in type, intensity and/or frequency of psychotherapy within the last 8 weeks prior to screening and it is not anticipated to change during the entire course of trial

12. Any use of restricted medications within 7 days prior to randomization and during the entire course of the trial

Please note:

- Investigators may use their clinical discretion to wash out (at least 3 half-lives of referenced medication) the restricted medications during the screening period. The participant must adhere to the screening visit dose of the background SSRI/SNRI/bupropion until the end of the trial or end of treatment, respectively
- Participants who, in addition to their monotherapy with an SSRI/SNRI/bupropion, are taking additional low dose antidepressant medications for purposes other than treating depressive symptoms, are not excluded. The dose must be less than the lowest dose indicated for MDD
- Participants who are on stable treatment with ongoing benzodiazepines and/or nonbenzodiazepine hypnotics for insomnia or anxiety for at least 28 days prior to screening should continue without change for the entire trial duration. For participants who are not on current treatment of insomnia and anxiety symptoms at the time of screening, the protocol will allow short term treatment of these symptoms during the course of trial

13. Participants who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial

14. Use of alternative medicine (e.g., Chinese traditional medicine, herbal medication, St. John's wort, etc.) during the entire course of the trial

15. Have initiated or discontinued hormone treatment (including hormone replacement therapy) within the 3 months prior to screening (however use of hormonal contraceptives is allowed)
16. Known hypersensitivity to any of the excipients of BI 1358894 or quetiapine or the matching placebos, respectively
17. Use of any investigational procedure within 30 days prior to randomization. In case of exposure to an investigational medicinal product, investigator must ensure that it is adequately washed out prior to randomization (at least 5 half-lives of the investigational medicinal product)
18. Positive drug screen at the screening visit (in case of positive drug screen for benzodiazepines or cannabis, investigator to confirm that there is no active substance-related disorder)
19. Have received electroconvulsive therapy and/or administration of Ketamine/S-Ketamine for the current ongoing depressive episode and/or transcranial magnetic stimulation (TMS)[a] for the current ongoing depressive episode or within 12 months prior to screening

    [a]Prior to a protocol amendment, patients with any lifetime use of TMS were excluded
20. Have a lifetime history of vagal nerve stimulation or psychosurgery
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
22. Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening
23. Participants not expected to comply with the protocol requirements or not expected to complete the trial as scheduled
24. Considered by the investigator, for any other reason, to be an unsuitable candidate for the trial
25. Participants who were confined to an institution by court or administrative order
26. Participants who are dependent on the Sponsor, the investigator, or the trial site

Further exploratory endpoints

- Response defined as ≥50% MADRS reduction from baseline over time
- Time to response defined as ≥50% MADRS total score reduction from baseline
- Time to remission, defined as MADRS total score ≤10
- Change from baseline in Euro Quality of Life -5 Dimensions -5 Levels total score at Week 6
- Change from baseline in Sheehan Disability Scale at Week 6
- Change from baseline in Facial Expression Recognition Task over time
- Time to treatment onset (measured with Ecological momentary assessment [EcMA])
- Time to treatment response (measured with EcMA)

Models for the MCPMod analysis

The following candidate models were selected based on healthy volunteer data to cover a plausible and diverse range of dose-response patterns for trial medication:

- Emax1: 50% of the maximum effect is achieved at 25 mg; corresponding to the assumed true ED50=25 mg
- Emax2: 70% of the maximum effect is achieved at 5 mg; corresponding to a drug effect achieved mainly with low doses, ED50=2.14 mg
- Sigmoid Emax: 50% of the maximum effect is achieved at 25 mg, and 90% of the maximum effect is achieved at 75 mg; corresponding to a more flexible model of the assumed true ED50=25 mg.
- Exponential: 5% of the maximum effect is achieved at 25 mg; corresponding to a drug effect achieved mainly at higher doses
- Linear: No parameter assumptions required. Corresponding dose response is linear

SUPPLEMENTARY RESULTS

Medication adherence

The overall medication adherence (≥80%–≤100%) as determined by pill counting was recorded in 89.8% of patients, while video-recorded adherence (≥80%-≤100%) determined using the smartphone application, based on the highest confidence level, was recorded in 45.2% of patients.

SUPPLEMENTARY TABLES

Supplementary Table 1. Change from baseline in MADRS total score (Full analysis set)

	Placebo	**BI 1358894**			
	n=126	**5 mg**	**25 mg**	**75 mg**	**125 mg**
		n=36	**n=39**	**n=39**	**n=72**
Baseline					
n*	124	36	39	39	72
MADRS total score, mean (SE)	31.9 (6.3)	34.0 (4.8)	34.1 (5.6)	32.1 (6.4)	33.0 (6.1)
Week 6					
n*	112	30	32	33	64
Adjusted mean change from baseline (SE) [90% CI]	−13.0 (1.0) [−14.7, −11.3]	−12.4 (2.0) [−15.6, −9.1]	−10.8 (1.9) [−14.0, −7.6]	−10.8 (1.9) [−14.0, −7.7]	−11.5 (1.4) [−13.8, −9.2]
Comparison to placebo, adjusted mean (SE) [90% CI]	-	0.7 (2.2) [−3.0, 4.3]	2.3 (2.2) [−1.4, 5.9]	2.2 (2.2) [−1.4, 5.7]	1.5 (1.7) [−1.3, 4.4]
P value	-	0.7636	0.3040	0.3090	0.3694

Adjusted (least squares) means, differences and confidence intervals are 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 MADRS total score. Visit will be treated as a repeated measure with an unstructured covariance matrix.

Abbreviations: CI, confidence interval; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measure; n, number of patients in the full analysis set; n*, number of patients with available data at a particular timepoint; REML, restricted maximum likelihood; SE, standard error.

Supplementary Table 2. Primary endpoint PoC testing: Multiple contrast test results of non-flat dose response shape for MADRS change from baseline at Week 6 (Full analysis set)

	Estimates	Exponential	Linear	Sigmoid Emax	Emax1	Emax2
MMRM estimates						
Placebo	−13.04					
BI 1358894 5 mg	−12.37					
BI 1358894 25 mg	−10.78					
BI 1358894 75 mg	−10.85					
BI 1358894 125 mg	−11.49					
Contrast						
Placebo		0.5433	0.6444	0.7330	0.7734	0.8672
BI 1358894 5 mg		0.1501	0.1612	0.1880	0.1209	−0.0690
BI 1358894 25 mg		0.1298	0.0762	−0.0529	−0.0814	−0.1765
BI 1358894 75 mg		−0.0075	−0.1544	−0.2794	−0.2479	−0.2139
BI 1358894 125 mg		−0.8157	−0.7274	−0.5887	−0.5649	−0.4079
Multiple contrast test						
t-statistic		−0.6757	−0.9228	−1.1806	−1.2244	−1.2946
Adjusted *P* value		0.8676	0.9158	0.9507	0.9552	0.9619
Critical value: 1.605 (alpha = 0.100, one-sided)						

Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; PoC, proof of concept.

Supplementary Table 3. Descriptive results for quetiapine group for efficacy endpoints (Full analysis set)

Endpoints	n	Placebo	n	Quetiapine 300/150 mg
MADRS total score at baseline, mean (SD)	126	31. 9 (6.3)	71	33.6 (5.6)
Change in MADRS total score at Week 1, mean (SD)	124	−5.1 (8.6)	67	−6.9 (7.7)
Change in MADRS total score at Week 2, mean (SD)	120	−7.2 (8.7)	63	−9.4 (8.1)
Change in MADRS total score at Week 4, mean (SD)	118	−11.2 (11.2)	58	−14.7 (10.2)
Change in MADRS total score at Week 6 (EoT), mean (SD)	112	−12.9 (12.0)	59	−14.4 (10.5)
STAI State Anxiety total score at baseline, mean (SD)	126	55.1 (10.4)	71	55.9 (11.7)
Change from baseline in STAI State Anxiety total score at Week 6	112	−11.3 (14.4)	59	−11.8 (15.1)
STAI Trait Anxiety total score at baseline, mean (SD)	126	59.4 (9.6)	71	58.4 (11.3)
Change from baseline in STAI Trait Anxiety total score at Week 6	112	−11.2 (13.2)	59	−10.3 (13.8)
CGI−S score at baseline, mean (SD)	126	4.8 (0.6)	71	4.8 (0.7)
Change from baseline in CGI-S score at Week 6	112	−1.4 (1.4)	59	−1.4 (1.2)
SMDDS total score at baseline, mean (SD)	126	36.2 (8.5)	71	36.8 (8.7)
Change from baseline in SMDDS score at Week 6	112	−13.3 (13.9)	59	−13.7 (12.2)

Abbreviations: CGI-S, Clinical Global Impression Severity Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; n, number of patients with data available for the respective timepoint; SMDDS, Symptoms of Major Depressive Disorder Scale; SD, standard deviation; STAI, State-Trait Anxiety Inventory.

Supplementary Table 4. AEs leading to treatment discontinuation in ≥0.5% of patients overall (Treated Set)

Preferred term	Placebo n=128	BI 1358894					Quetiapine 300/150mg n=71
		5 mg n=36	25 mg n=39	75 mg n=39	125 mg n=75	Total n=189	
				n* (%)			
Any AE leading to discontinuation	7 (5.5)	-	2 (5.1)	1 (2.6)	2 (2.7)	5 (2.6)	7 (9.9)
Fatigue	1 (0.8)	-	1 (2.6)	-	-	1 (0.5)	1 (1.4)
Disturbance in attention	-	-	1 (2.6)	1 (2.6)	-	2 (1.1)	-
Arthralgia	-	-	1 (2.6)	1 (2.6)	-	2 (1.1)	-
Somnolence	1 (0.8)	-	-	-	-	-	1 (1.4)
Confusional state	1 (0.8)	-	-	-	1 (1.3)	1 (0.5)	-
Insomnia	1 (0.8)	-	-	-	-	-	1 (1.4)
Suicidal ideation	2 (1.6)	-	-	-	-	-	-

AEs were coded using MedDRA version 26.1.

Abbreviations: AEs, adverse events; MedDRA, Medical dictionary for drug regulatory activities; n, number of patients in respective treatment group; n*, number of patients who discontinued.

Supplementary Table 5. Summary of suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent at any time on treatment (Treated Set)

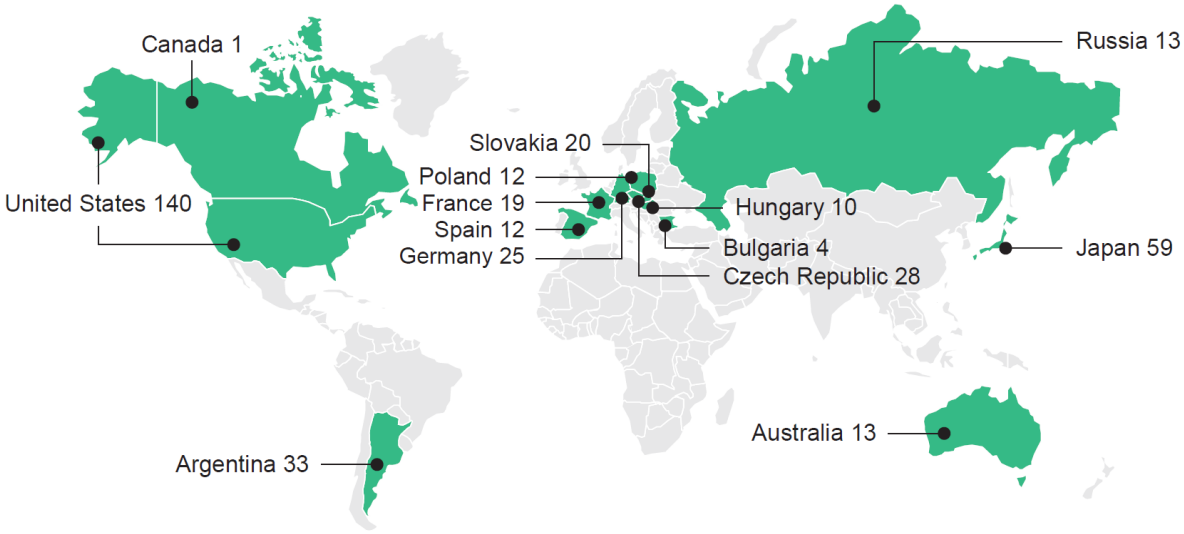
C-SSRS category	Placebo n=128	BI 1358894				Quetiapine 300/150mg n=71
		5 mg n=36	25 mg n=39	75 mg n=39	125 mg n=75	
			n* (%)			
Any event	30 (23.4)	12 (33.3)	6 (15.4)	10 (25.6)	14 (18.7)	6 (8.5)
Suicidal ideation (1-5)	29 (22.7)	11 (30.6)	6 (15.4)	10 (25.6)	14 (18.7)	6 (8.5)
1	28 (21.9)	11 (30.6)	6 (15.4)	9 (23.1)	14 (18.7)	6 (8.5)
2	9 (7.0)	3 (8.3)	2 (5.1)	2 (5.1)	-	1 (1.4)
3	2 (1.6)	1 (2.8)	2 (5.1)	2 (5.1)	1 (1.3)	1 (1.4)
4	1 (0.8)	-	-	1 (2.6)	-	1 (1.4)
5	-	-	-	2 (5.1)	-	-
Suicidal behavior (6-10)	-	-	-	1 (2.6)	-	-
6	-	-	-	1 (2.6)	-	-
7	-	-	-	-	-	-
8	-	-	-	1 (2.6)	-	-
9	-	-	-	1 (2.6)	-	-
10	-	-	-	-	-	-
Self-injurious behavior without suicidal intent	1 (0.8)	2 (5.6)	-	-	-	-

The categories (1−5) are not mutually exclusive. The categories (6−10) are not mutually exclusive. On-treatment values are those assessed after first trial drug intake until the end of the Residual Effect Period. C-SSRS categories: 1 wish to be dead, 2 non-specific active suicidal thoughts, 3 active suicidal ideation with any methods (not plan) without intent to act, 4 active suicidal ideation with some intent to act, without specific plan, 5 active suicidal ideation with specific plan and intent, 6 preparatory acts or behavior, 7 aborted or self-interrupted attempt, 8 interrupted attempt, 9 actual attempt non-fatal, 10 completed suicide.

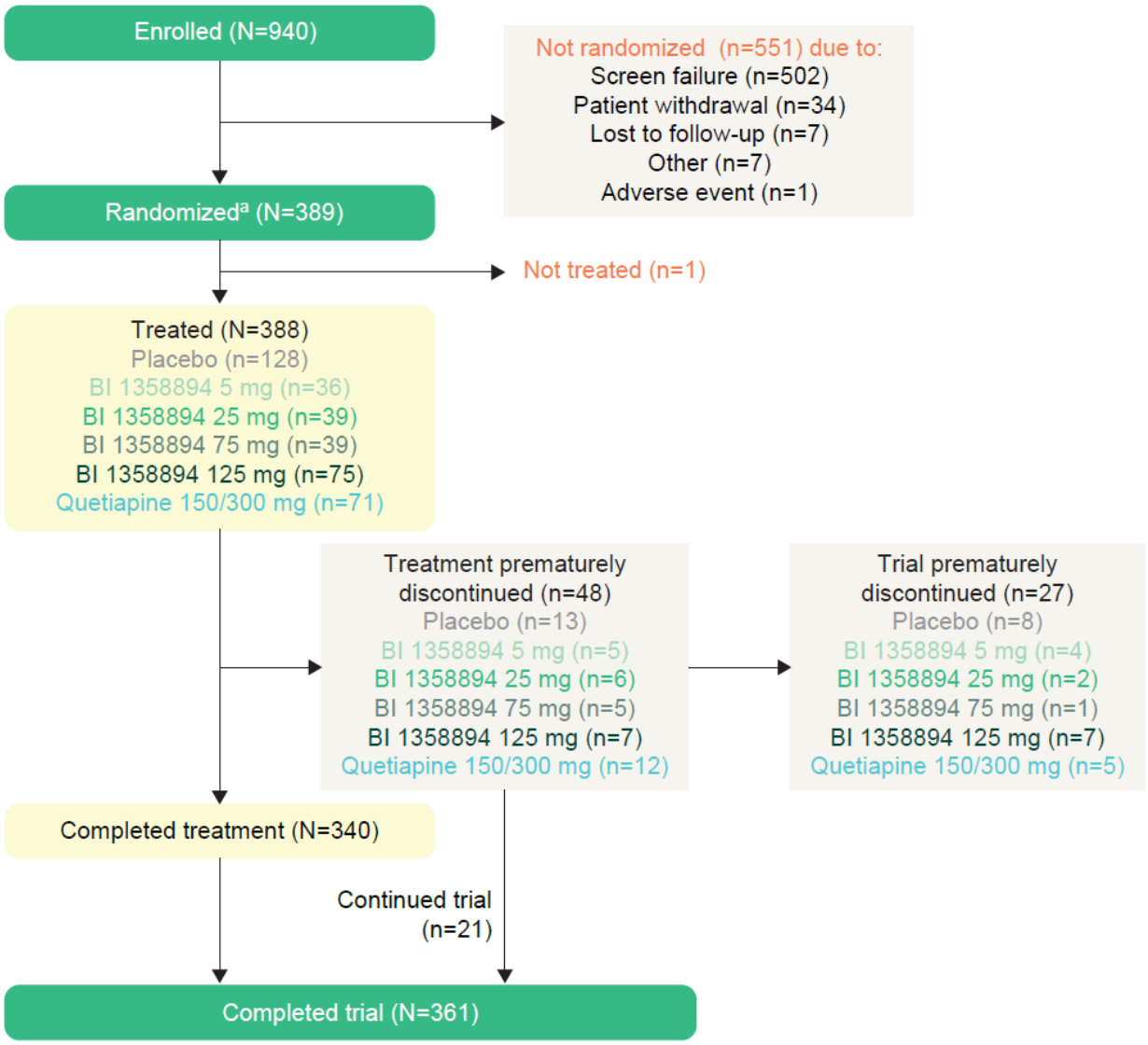
Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; n, number of randomized patients; n*, number of patients within a particular treatment group at a specific C-SSRS category.

SUPPLEMENTARY FIGURES

Supplementary Figure 1: Total number of randomized patients (N=389) by participating country

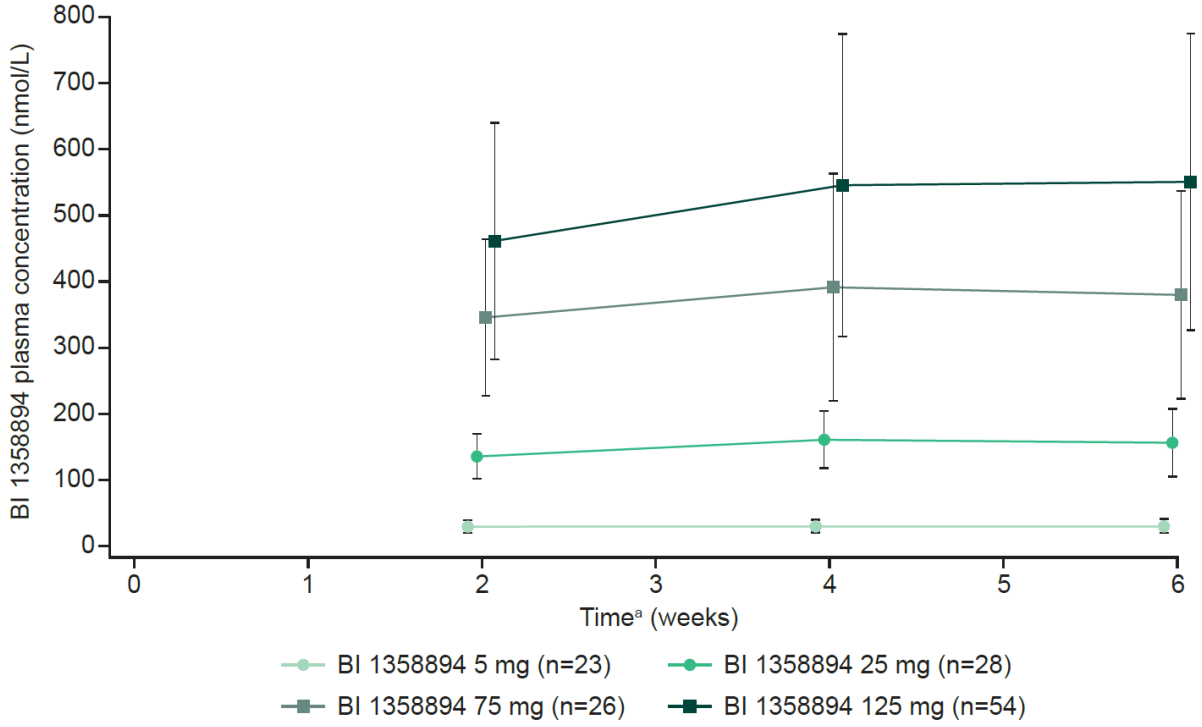


Supplementary Figure 2: Patient disposition flowchart



[a]One participant was randomized to the placebo arm but received a 125 mg treatment kit at Visit 2. The error was detected at Visit 4, and the participant received placebo treatment from that date onwards. This participant was analyzed as treated (125 mg) for the purpose of safety analysis (Treated Set) and as randomized for all other analyses (Full Analysis Set).

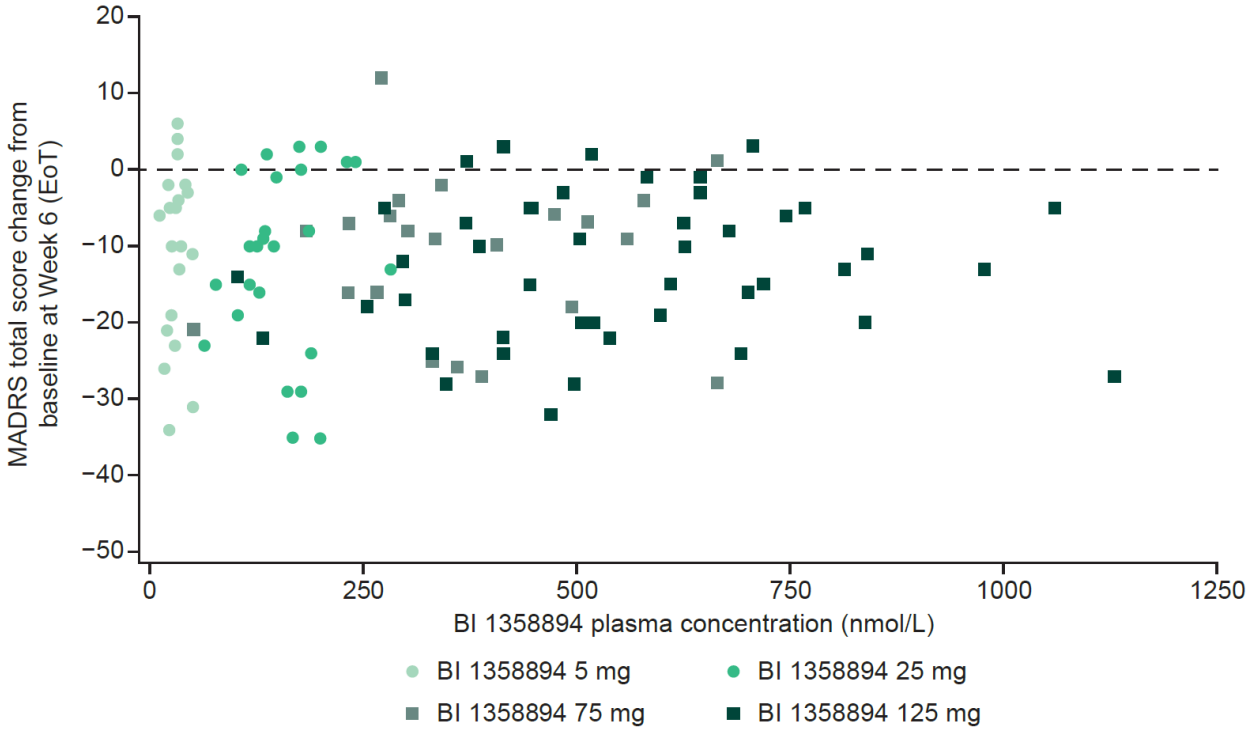
Supplementary Figure 3. Mean (SD) plasma trough concentration-time profiles of BI 1358894 after multiple oral administration



[a]Time scales have been slightly shifted for clarity

Abbreviations: SD, standard deviation.

Supplementary Figure 4. Correlation of MADRS total score change from baseline versus plasma trough concentration of BI 1358894 at Week 6



Abbreviations: EoT, end of treatment; MADRS, Montgomery-Åsberg Depression Rating Scale.