Efficacy and Safety of BI 1358894 in Patients With Borderline Personality Disorder:

Results of a Phase 2 Randomized, Placebo-Controlled, Parallel Group Dose-Ranging Trial

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Abstract

Objective: To provide proof-of-concept (PoC), dose-range finding, and safety data for BI 1358894, a TRPC4/5 ion channel inhibitor, in patients with borderline personality disorder (BPD).

Methods: This was a phase 2, multinational, randomized, double-blind, placebo-controlled trial. Patients were randomized to oral placebo or BI 1358894 (5 mg, 25 mg, 75 mg, or 125 mg) once daily in a 2.5:1:1:1:2 ratio for 12 weeks. The primary end point was change from baseline in the Zanarini Rating Scale for BPD (ZAN-BPD) total score at Week 10. Secondary end points included ≥30% ZAN-BPD reduction response from baseline at Week 10, change from baseline at Week 10 in the Difficulties in Emotion Regulation Scale-16 item total, State-Trait Anxiety Inventory–State Anxiety total, Patient Health Questionnaire-9 total, Clinical Global Impressions–Severity, and Patient Global Impression–Severity scores.

Results: Of 655 enrolled patients, 390 were randomized and 323 (82.8%) completed the trial. For primary and secondary end points, no differences were observed between treatment and placebo; therefore, PoC was not established. The proportion of patients with adverse events (AEs, BI 1358894 overall vs placebo: 77.9% vs 75.0%) and serious AEs (SAEs; 10.3% vs 8.6%) was comparable between treatments. The proportion of patients with an SAE of suicidal ideation was 4.2% (BI 1358894 overall) and 6.3% (placebo).

Conclusions: Although the primary end point was not met, BI 1358894 was well tolerated with no increase in self-harm or suicidality. More targeted populations, alternative outcome assessments, and additional measures to minimize placebo effects should be considered for future trials.

Trial Registration: ClinicalTrials.gov identifier: NCT04566601.

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Borderline personality disorder (BPD) is a serious mental illness with a prevalence of 1.8–5.9%.[1,2] BPD is characterized by pervasive instability in affect regulation, self-image, cognition, interpersonal relationships, and impulse control.[3] Additionally, diagnosed patients often have psychiatric comorbidities, such as mood, anxiety, substance use, and trauma-related or eating disorders.[4,5] BPD psychopathology severity and associated impairment in social and occupational functioning can lead to reduced quality of life (QoL).[6–8] It is estimated that 2–10% of patients with BPD die by suicide,[9,10] and those who do not achieve recovery are at higher risk of premature death.[11]

Despite the clear disease burden, there are currently no Food and Drug Administration-approved pharmacotherapies for BPD.[12,13] However, pharmacotherapy is often used off-label to target symptoms.[13,14] Although medications show specific core symptoms improvement in some cases, there is no evidence of overall severity improvement.[15,16] The current clinical guidelines for BPD recommend structured psychotherapy, such as dialectical behavior therapy and mentalization-based therapy[17–19]; however, there is limited availability of trained professionals to care for treatment-seeking individuals.[20] While some evidence exists that psychotherapy is superior to treatment-as-usual conditions, there is limited evidence to differentiate

Clinical Points

- Despite the burden of untreated BPD on patients and health care systems, no pharmacotherapies are approved, and off-label medications are often used to target symptoms.
- This study showed a strong placebo response, which emerged at week 1 and persisted throughout the trial. The robust placebo effect and the absence of a positive control make it difficult to draw firm conclusions about the efficacy of BI 1358894.
- Future trials in BPD should consider targeting specific populations within BPD, assessing a range of outcomes, and including measures to minimize placebo effects.

between psychotherapy types and to determine optimal duration.[17] As such, there is a clear unmet need for novel BPD treatments.[21]

Emotional dysregulation is a core feature of BPD which has been linked to amygdala hyperreactivity in patients with BPD.[22–24] Transient receptor potential canonical ion channels 4 and 5 (TRPC4/5) are expressed in the brains of both animals and humans, predominantly in areas of the corticolimbic system that regulate emotion and mood, such as the amygdala.[25,26] Therefore, the inhibition of TRPC4/5 ion channels may provide a novel mechanism of attenuating amygdala hyperreactivity to improve BPD.[27] BI 1358894, a novel TRPC4/5 inhibitor, has demonstrated attenuation of amygdala hyperreactivity in people with major depressive disorder[27] and reduction in cholecystokinin-induced panic symptoms in healthy controls.[28] Phase 1 studies have demonstrated that BI 1358894 is generally safe and well-tolerated at doses up to 200 mg in healthy male volunteers, with a favorable pharmacokinetic profile.[29,30]

This trial aimed to provide proof-of-concept (PoC) for TRPC4/5 ion channel inhibition and dose-ranging data for BI 1358894 vs placebo in patients with BPD to support dose selection for pivotal studies and establish BI 1358894 safety in this population.

METHODS

Trial Design, Randomization, and Blinding

In this phase 2, multinational, randomized, double-blind, placebo-controlled, parallel-group trial (ClinicalTrials.gov identifier: NCT04566601), patients with BPD across 67 centers in 17 countries (Figure 1) were randomized via interactive response technology to receive placebo or BI 1358894 (5 mg, 25 mg, 75 mg, or 125 mg) orally, once daily in a 2.5:1:1:1:2 ratio for 12 weeks. Randomization was stratified by the baseline Zanarini Rating Scale for BPD (ZAN-BPD) total score (≤18 vs ≥19). The trial encompassed a screening period of 2 visits, a minimum of 5 phone call visits and 8 in-person visits during treatment, and 3 visits during the 4-week follow-up. The chosen BI 1358894 doses were intended to explore potential exposure-response curves over a broad dose range.

Using a multiple comparison procedure with modelling (MCPMod) approach, a total sample size of approximately 355 patients was needed to determine PoC with 81% average power across models, with one-sided 10% α level, assuming 285 evaluable patients across treatment arms and 20% dropout rate.

The trial was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonization of Good Clinical Practice guidelines, applicable regulatory requirements, and Boehringer Ingelheim standard operating procedures. The trial protocol and informed consent form were reviewed by the Independent Ethics Committees and/or Institutional Review Boards of the participating centers. Study protocol is available through the clinicaltrials.gov portal.

Patients

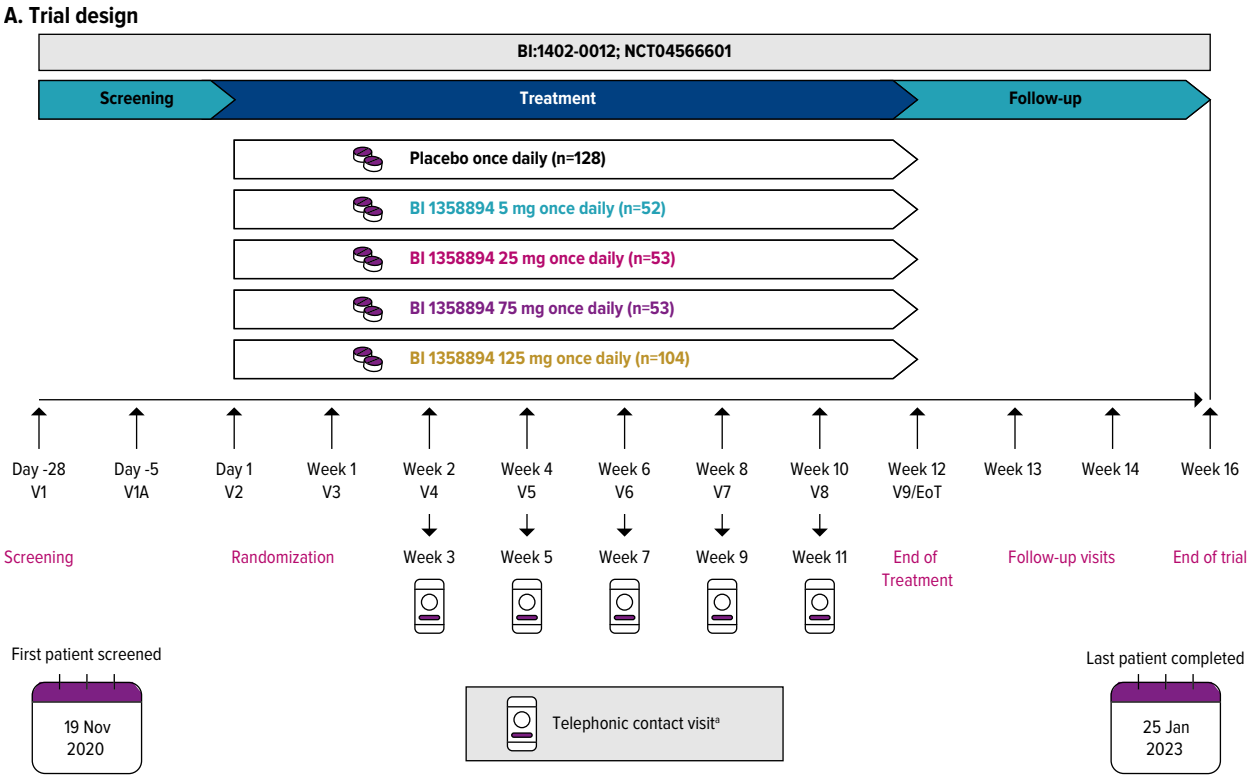
The trial included patients aged 18–65 years, with a confirmed BPD diagnosis (per Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders,* 5th Edition [*DSM-5*]-Personality Disorders) at screening who provided informed consent at Visit 1. Patients were required to have a ZAN-BPD total score ≥9 with an Affective Instability score of ≥2 at screening and randomization. Patients with a current diagnosis of paranoid, schizoid, schizotypal personality disorders or a lifetime diagnosis of schizophrenia, schizoaffective or schizophreniform disorder, bipolar disorder, or delusional disorder were excluded. Patients were also excluded if they had another major psychiatric disorder that was the primary focus of treatment in the previous 6 months, any suicidal behavior in the previous year, suicidal ideation of type 4/5 (Columbia-Suicide Severity Rating Scale [C-SSRS]) in the previous 3 months, or hospitalization due to nonsuicidal self-injury or BPD worsening within the previous 3 months. Patients could not be on any ongoing psychotropic comedication for at least 7 days prior to randomization or, per investigator discretion, a washout of at least 3 half-lives must have been completed at least 7 days prior to randomization. Patients could continue any ongoing psychotherapy, provided there was no initiation or change in type or frequency in the 3 months prior to screening. The full eligibility criteria are included in the Supplementary Methods.

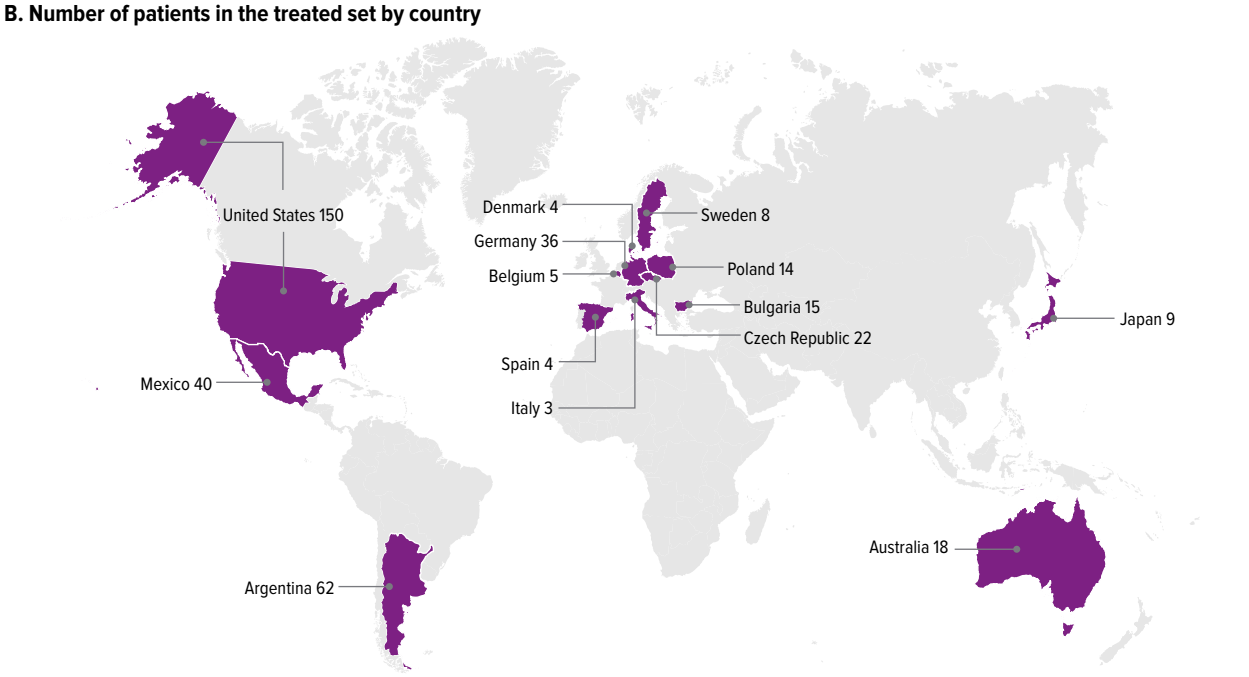
End Points and Assessments

Primary end point. The primary end point of change from baseline in ZAN-BPD total score was evaluated at

Figure 1.

Trial Design (A) and Total Number of Patients in the Treated Set (N = 390) by Participating Country (B)





[a]Protocol was amended to allow certain assessments to be conducted via telemedicine during the COVID-19 pandemic.
Abbreviations: EoT = end of treatment, n = number of patients randomized in each treatment arm, V = visit.

Week 10 of 12 to avoid any potential issues related to perceived abandonment at the end-of-treatment period. The ZAN-BPD is a clinician-administered scale for the assessment of change in *DSM-5* borderline psychopathology over time.[31] The subgroup analyses of the primary end point were carried out for baseline

disorder severity (ie, ZAN-BPD total score strata indicator [≤18 vs ≥19]), video-confirmed adherent subgroups, US vs non-US patients, region, ethnicity and race, and Asian vs non-Asian patients.

Secondary end points. The secondary end points were response, defined as ≥30% ZAN-BPD reduction from baseline at Week 10, change from baseline at Week 10 in the Difficulties in Emotion Regulation Scale-16 item version total score, the State-Trait Anxiety Inventory–State Anxiety total score, the Patient Health Questionnaire-9 total score, the Clinical Global Impressions–Severity score, and the Patient Global Impression–Severity scores.

Selected exploratory end points. The selected exploratory end points include the change from baseline in ZAN-BPD total score over time, response defined as ≥30% ZAN-BPD reduction from baseline over time, and patient-reported outcomes related to QoL at Week 10 (change from baseline in EuroQol 5-Dimensions 5-Levels [EQ-5D-5L], Sheehan Disability Scale [SDS], and Patient Global Impression–Impact [PGI-I] scales).

Safety. Safety was assessed through percentage of patients with adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI; protocol-specified AESI was hepatic injury, ie, an elevation of 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 trial discontinuations due to AEs. Occurrences of any clinically significant abnormalities in vital signs, electrocardiogram, laboratory tests, and suicidality (frequency of suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent as assessed by C-SSRS) were also reported.

Statistical Analysis

The primary end point was analyzed via hypothetical estimand, focusing on the treatment effect assuming that trial medication was taken as directed and excluding intercurrent events. The primary end point analysis included all on-treatment data collected from first to last trial medication dose plus 7 days. Any data collected after a patient discontinued treatment was censored and not included in the primary analysis. The primary analysis utilized the MCPMod for dose finding, which enabled simultaneous evaluation of various potential dose-response patterns, while minimizing false positives (probability of type I error) using a one-sided α level of 10%. For the MCPMod analysis, a mixed model repeated measures model (MMRM) analysis was used to generate covariate-adjusted estimates of mean change from baseline to Week 10 in ZAN-BPD total score and associated covariance matrices. The secondary end point of ZAN-BPD response was analyzed through a logistic regression model; other secondary end points were analyzed using the MMRM model to obtain adjusted change from baseline at Week 10 for each treatment arm vs placebo. Efficacy was evaluated in the full analysis set (ie, all randomized patients who had a baseline and ≥1 evaluable postbaseline measurement for the primary end point), and safety was evaluated descriptively in the treated set (ie, all randomized patients who received ≥1 dose of trial medication).

RESULTS

Patient Disposition and Demographics

Of 655 enrolled patients, 390 patients were randomized and 323 (82.8%) completed the trial, while 287 (73.6%) completed trial medication administration (Supplementary Figure 1). The mean (standard deviation [SD]) patient age was 30.2 (10.3) years, and the majority (86.2%) were female. The mean (SD) [range] time since BPD diagnosis was 4.2 (6.2) [0.0–36.4] years and included some patients diagnosed at study entry or after consent date. The use of previous psychiatric medications, washed out before baseline, was low (n = 64; 16.4%); the frequency of previous psychiatric medication use was higher in the BI 1358894 5 mg, 75 mg, and 125 mg arms vs placebo, but less frequent in the BI 1358894 25 mg arm vs placebo. Overall, 76 (19.5%) patients were attending psychotherapy sessions at baseline (Table 1). Of the randomized patients, 383 had pill count data available (as per case report forms), and median overall compliance was 99% over the 12-week treatment period.

Efficacy

Primary end point. BPD symptoms improved in all treatment arms, including placebo, as indicated by decreases in ZAN-BPD total score from baseline to Week 10 (Figure 2) with no significant group difference. Thus, the trial did not meet its primary end point criterion. The adjusted mean (SE) change from baseline to Week 10 in ZAN-BPD total score was between −8.0 and −9.2 across BI 1358894 dose groups and −8.7 in placebo group (Supplementary Table 1). A substantial placebo response was observed, with a rapid reduction of 5.3 points in the mean ZAN-BPD total score at Week 1 and a further slower reduction of 9.8 points continuous over time from baseline at Week 12 (Supplementary Table 2). For PoC testing, the adjusted *P* value of the multiple contrast test was not significant for any of the candidate models in MCPMod analysis (Supplementary Table 3). Further, no subgroup analyses revealed any differences between treatment arms and placebo, except for the subgroup by baseline disorder severity wherein higher severity (ZAN-BPD total score ≥19) subgroup had a higher placebo response vs lower severity subgroup (ZAN-BPD total score ≤18; Supplementary Figure 2). However, patients receiving

Table 1.

Baseline Demographics and Assessments—Treated Set

Baseline demographic characteristic	BI 1358894 5 mg (n = 52)	BI 1358894 25 mg (n = 53)	BI 1358894 75 mg (n = 53)	BI 1358894 125 mg (n = 104)	Placebo (n = 128)	Total (N = 390)
Female, n (%)	50 (96.2)	48 (90.6)	48 (90.6)	83 (79.8)	107 (83.6)	336 (86.2)
Age, mean (SD), y	29.2 (9.6)	31.0 (11.1)	30.6 (9.7)	29.9 (11.2)	30.4 (9.9)	30.2 (10.3)
Race, n (%)						
Black or African American	3 (5.8)	3 (5.7)	1 (1.9)	4 (3.8)	8 (6.3)	19 (4.9)
American Indian or Alaska native	2 (3.8)	1 (1.9)	1 (1.9)	6 (5.8)	5 (3.9)	15 (3.8)
Asian	3 (5.8)	2 (3.8)	4 (7.5)	7 (6.7)	2 (1.6)	18 (4.6)
Native Hawaiian or other Pacific Islander	0	0	0	0	1 (0.8)	1 (0.3)
White	44 (84.6)	46 (86.8)	46 (86.8)	85 (81.7)	112 (87.5)	333 (85.4)
More than one	0 (0.0)	1 (1.9)	1 (1.9)	2 (1.9)	0 (0.0)	4 (1.0)
Hispanic/Latino ethnicity (yes), n (%)	17 (32.7)	25 (47.2)	20 (37.7)	34 (32.7)	50 (39.1)	146 (37.4)
Baseline characteristics						
Headache or migraine,[a] n (%)	19 (36.5)	23 (43.4)	13 (24.5)	40 (38.5)	38 (29.7)	133 (34.1)
Substance use,[b] mean (SD)	1.5 (1.1)	1.2 (1.1)	1.5 (1.0)	1.5 (1.2)	1.4 (1.1)	1.4 (1.1)
Self-injurious behavior,[c] n (%)	27 (51.9)	26 (49.1)	21 (39.6)	57 (54.8)	69 (53.9)	200 (51.3)
Time since diagnosis[d] (years), mean (SD), range	4.2 (6.2), 0.0–36.4	5.8 (7.6), 0.0–32.6	3.0 (4.0), 0.0–15.3	4.7 (7.1), 0.0–35.3	3.7 (5.4), 0.0–25.7	4.2 (6.2), −0.0 to 36.4
Psychotherapy,[e] n (%)	6 (11.5)	12 (22.6)	18 (34.0)	19 (18.3)	21 (16.4)	76 (19.5)
≥1 psychiatric medication washed out prior to baseline,[f] n (%)	10 (19.2)	6 (11.3)	13 (24.5)	17 (16.3)	18 (14.1)	64 (16.4)
Baseline assessments						
ZAN-BPD total score, mean (SD)	15.7 (5.4)	15.8 (4.8)	16.1 (4.6)	16.4 (5.2)	16.6 (5.0)	16.3 (5.0)
Lifetime C-SSRS suicidal ideation, n (%)	36 (69.2)	41 (77.4)	36 (67.9)	79 (76.0)	98 (76.6)	290 (74.4)
Lifetime C-SSRS suicidal behavior, n (%)	24 (46.2)	27 (50.9)	18 (34.0)	50 (48.1)	58 (45.3)	177 (45.4)

[a]Headache (pattern of headaches) or migraine data for the past 3 months was collected at screening visit (Visit 1) only.
[b]Substance use displayed at baseline. Data were collected at Visit 2 (Baseline). Calculated as a sum of counts to 'Yes' responses to the following: alcohol use, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, stimulants, tobacco, and other or unknown substances.
[c]Self-injurious behavior: The standard AE on-treatment definition of plus 28 days was applied.
[d]Time since diagnosis was defined as the time of first primary diagnosis in medical history to the consent date of the patient, ie, duration of the diagnosis prior to consent date.
[e]Psychotherapy was defined as whether psychotherapy was started greater than or equal to 3 months prior to screening.
[f]Psychiatric medications end date within 28 days–7 days before randomization. Patients could have taken multiple psychiatric medications.
Abbreviations: AE = adverse event, C-SSRS = Columbia-Suicide Severity Rating Scale, MDD = major depressive disorder, N = number of patients in the treated set, n = number of patients in respective treatment arm, SD = standard deviation, ZAN-BPD = Zanarini Rating Scale for BPD.

concomitant psychotherapy showed lower placebo responses vs those who did not (Supplementary Figure 3). There were no discernible differences between the subgroup of patients who completed prior washout of psychotropic medications and those who did not (Supplementary Figure 4).

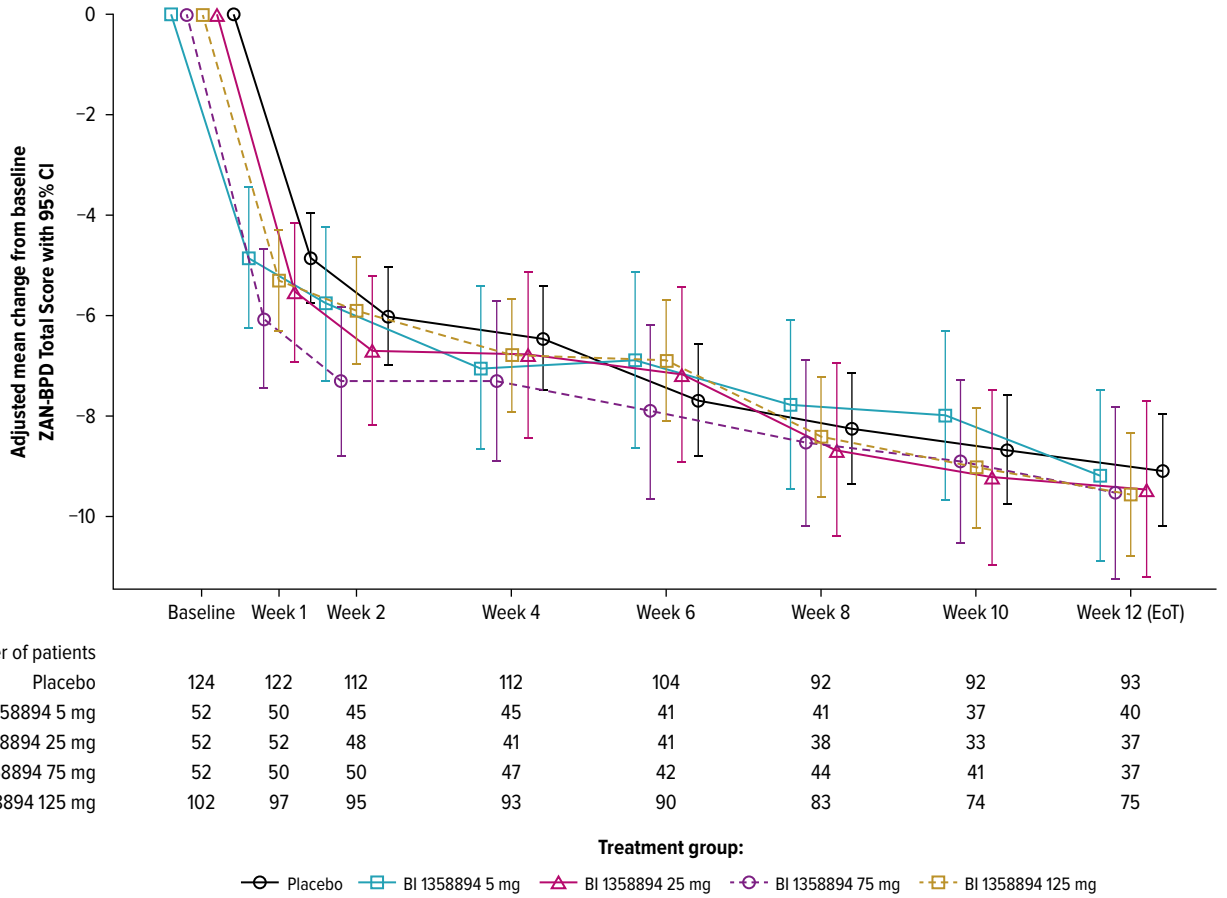
Secondary end points. Treatment with BI 1358894 (all doses) had a similar effect to placebo with no significant differences observed between treatment groups for any of the secondary end points (Table 2).

Exploratory end points. Across treatment arms, the mean ZAN-BPD total score improved from moderate at baseline (mean [SD] total score of 16.26 [5.07]) to mild at Week 10 (7.24 [5.45]; Supplementary Table 2). Overall, the frequency of responders increased from baseline up to Week 12 (Supplementary Figure 5). Regarding overall well-being, there were no improvements observed in the mean change from baseline in EQ-5D-5L index and EQ-5D-5L VAS scores over the 10 weeks; however, the SDS and PGI-I scale scores decreased (improved) from baseline to Week 10 (Supplementary Table 4).

Safety. AEs were reported by 77.9% of patients receiving BI 1358894 across all doses and 75.0% receiving placebo. Proportion of patients with severe AEs (BI 1358894 vs placebo: 13.4% vs 13.3%), SAEs (10.3% vs 8.6%), AEs leading to discontinuation (9.9% vs 5.5%), and other significant AEs (7.3% vs 3.9%) was generally comparable between treatment arms (Table 3). The most common AEs leading to discontinuation were suicidal ideation (BI 1358894 vs placebo: 1.1% vs 1.6%), headache (1.1% vs 0.8%), and somnolence (1.1% vs 0.0%). AEs related to trial drug occurred more frequently with BI 1358894 vs placebo; however, they were not dose-dependent. Headache was the most frequently reported AE for BI 1358894 compared with placebo (34.0% vs 25.0%). There were no clinically relevant changes from baseline for vital signs or any safety laboratory parameters, except for the AESI observed in 3 patients (hepatitis A and hepatic enzyme increase in 2 patients with BI 1358894 75 mg and cholestatic jaundice in 1 patient with BI 1358894 125 mg). The most common SAE was suicidal ideation (BI 1358894: 4.2%; placebo: 6.3%).

Figure 2.

Adjusted Mean (95% CI) of MMRM Estimates for Absolute Change From Baseline in ZAN-BPD Total Score up to Week 12—Full Analysis Set



Number of patients	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12 (EoT)
Placebo	124	122	112	112	104	92	92	93
BI 1358894 5 mg	52	50	45	45	41	41	37	40
BI 1358894 25 mg	52	52	48	41	41	38	33	37
BI 1358894 75 mg	52	50	50	47	42	44	41	37
BI 1358894 125 mg	102	97	95	93	90	83	74	75

Abbreviations: CI = confidence interval, EoT = end of treatment, MMRM = mixed model repeated measures model, ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

Based on C-SSRS, the frequency of suicidal ideation was numerically lower for BI 1358894 across all doses compared with placebo (38.5% vs 44.5%). The frequency of suicidal behavior was low throughout the trial (BI 1358894: 1.9%; placebo: 0.8%), and both treated and placebo-controlled patients had similar frequencies of self-injurious behavior without suicidal intent (BI 1358894: 17.2%; placebo: 16.4%). Two patients treated with BI 1358894 125 mg died due to 3 fatal SAEs (1 patient with fatal opioid overdose, and another with severe esophageal varices hemorrhage and a myocardial infarction). However, these deaths were assessed as unrelated to the trial medication by the investigator. There were no completed suicides during this trial.

DISCUSSION

This phase 2 trial evaluated the efficacy and safety of 12-week BI 1358894 treatment vs placebo in patients with BPD. The trial did not meet the primary end point as there were no significant differences between treatment groups and placebo. This was observed in most scales used and in all subgroup analyses. The PoC was not established, and so the dose-response modeling was not carried out.

BI 1358894 was well tolerated, with a safety profile consistent with previous clinical studies.[28,29] A relatively high rate of AEs (BI 1358894: 204 [77.9%]; placebo: 96 [75.0%]) was observed in all treatment arms including placebo, suggesting a nocebo effect. However, there was no worsening of symptoms hypothesized as an "abandonment effect" at the last timepoint of efficacy assessment (Week 12) unlike a prior BPD trial.[32]

Given the high placebo response and the absence of a suitable positive control, it is difficult to interpret whether lack of separation between treatment and placebo reflects the absence of treatment efficacy or methodological issues leading to trial failure. Placebo response was substantial, with a 5.0 point reduction in

Table 2.

Secondary End Points[a]—Full Analysis Set

	BI 1358894 5 mg (n = 52)	BI 1358894 25 mg (n = 52)	BI 1358894 75 mg (n = 52)	BI 1358894 125 mg (n = 102)	Placebo (n = 124)
ZAN-BPD response (≥30% reduction) from baseline at Week 10					
Patients, n	37	33	41	74	92
Patients with outcome (%)	22 (59.5)	28 (84.9)	34 (82.9)	59 (79.7)	68 (73.9)
Comparison vs placebo					
OR	0.49	2.29	1.75	1.35	—
95% CI	(0.21, 1.14)	(0.83, 7.48)	(0.70, 4.86)	(0.64, 2.91)	—
Change from baseline in DERS-16 total score at Week 10					
Patients, n	52	52	52	102	124
Adjusted mean change (SE)	−9.9 (2.1)	−9.8 (2.2)	−10.6 (2.1)	−8.6 (1.5)	−9.8 (1.4)
Comparison vs placebo					
Adjusted mean difference (SE)	−0.1 (2.5)	0.0 (2.6)	−0.8 (2.5)	1.2 (2.0)	—
95% CI	(−5.11, 4.90)	(−5.08, 5.10)	(−5.73, 4.15)	(−2.86, 5.19)	—
P value	.9675	.9969	.7542	.5683	—
Change from baseline in STAI-S total score at Week 10					
Patients, n	52	52	52	102	124
Adjusted mean change (SE)	−8.7 (1.9)	−5.4 (2.0)	−7.0 (1.8)	−5.5 (1.3)	−6.6 (1.2)
Comparison vs placebo					
Adjusted mean difference (SE)	−2.0 (2.2)	1.2 (2.3)	−0.4 (2.2)	1.2 (1.8)	—
95% CI	(−6.49, 2.35)	(−3.33, 5.75)	(−4.70, 3.98)	(−2.41, 4.71)	—
P value	.3568	.6009	.8705	.5262	—
Change from baseline in PHQ-9 total score at Week 10					
Patients, n	52	52	52	102	124
Adjusted mean change (SE)	−3.1 (0.9)	−1.1 (0.9)	−1.6 (0.9)	−1.4 (0.6)	−1.3 (0.6)
Comparison vs placebo					
Adjusted mean difference (SE)	−1.8 (1.0)	0.2 (1.1)	−0.3 (1.0)	−0.1 (0.8)	—
95% CI	(−3.87, 0.21)	(−1.86, 2.32)	(−2.28, 1.74)	(−1.77, 1.51)	—
P value	.0782	.8266	.7910	.8743	—
Change from baseline in CGI-S total score at Week 10					
Patients, n	52	51	51	102	124
Adjusted mean change (SE)	−1.3 (0.2)	−1.5 (0.2)	−1.2 (0.2)	−1.4 (0.1)	−1.2 (0.1)
Comparison vs placebo					
Adjusted mean difference (SE)	−0.1 (0.2)	−0.2 (0.2)	−0.0 (0.2)	−0.2 (0.2)	—
95% CI	(−0.47, 0.37)	(−0.67, 0.20)	(−0.42, 0.40)	(−0.52, 0.15)	—
P value	.8016	.2929	.9666	.2833	—
Change from baseline in PGI-S total score at Week 10					
Patients, n	52	50	52	102	124
Adjusted mean change (SE)	−0.7 (0.1)	−0.7 (0.2)	−0.6 (0.1)	−0.7 (0.1)	−0.6 (0.1)
Comparison vs placebo					
Adjusted mean difference (SE)	−0.1 (0.2)	−0.1 (0.2)	−0.0 (0.2)	−0.1 (0.1)	—
95% CI	(−0.45, 0.20)	(−0.47, 0.22)	(−0.36, 0.29)	(−0.35, 0.19)	—
P value	.4552	.4734	.8388	.5540	—

[a]Logistic regression included treatment, baseline ZAN-BPD score, and baseline ZAN-BPD strata indicator (≤18 vs ≥19) as covariates. Least square means, differences, and CIs were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit, and the continuous fixed covariate of baseline CGI-S total score or DERS-16 total score or PHQ-9 total score or PGI-S total score or STAI-S total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used. Data from Week 1 through Week 10 were used in the MMRM model.

Abbreviations: CGI-S = Clinical Global Impression Severity Scale, CI = confidence interval, DERS-16 = difficulties in Emotion Regulation Scale 16 items, MMRM = mixed model repeated measures model, n = number of patients in respective treatment arm, OR = odds ratio, PGI-S = Patient Global Impression of Severity, PHQ-9 = Patient Health Questionnaire 9 items, REML = residual maximum likelihood method, SE = standard error, STAI-S = State-Trait Anxiety Inventory for measuring state anxiety, ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder.

Table 3.
Overall Summary of AEs—Treated Set[a]

	Total BI 1358894 (n = 262)	BI 1358894 5 mg (n = 52)	BI 1358894 25 mg (n = 53)	BI 1358894 75 mg (n = 53)	BI 1358894 125 mg (n = 104)	Placebo (n = 128)
Patients with any AE, n (%)	204 (77.9)	36 (69.2)	44 (83.0)	42 (79.2)	82 (78.8)	96 (75.0)
Patients with severe AEs, n (%)	35 (13.4)	6 (11.5)	6 (11.3)	8 (15.1)	15 (14.4)	17 (13.3)
Patients with investigator defined trial medication-related AEs, n (%)	118 (45.0)	18 (34.6)	28 (52.8)	29 (54.7)	43 (41.3)	42 (32.8)
Patients with AEs leading to discontinuation of trial medication, n (%)	26 (9.9)	3 (5.8)	6 (11.3)	5 (9.4)	12 (11.5)	7 (5.5)
Patients with AESI, n (%)	3 (1.1)	0 (0.0)	0 (0.0)	2 (3.8)	1 (1.0)	0 (0.0)
Patients with SAEs, n (%)	27 (10.3)	4 (7.7)	3 (5.7)	4 (7.5)	16 (15.4)	11 (8.6)
Results in death, n (%)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)
Is life threatening, n (%)	2 (0.8)	1 (1.9)	0 (0.0)	0 (0.0)	1 (1.0)	2 (1.6)
Requires or prolongs hospitalization, n (%)	13 (5.0)	2 (3.8)	2 (3.8)	3 (5.7)	6 (5.8)	3 (2.3)
Other medically important serious event, n (%)	12 (4.6)	2 (3.8)	1 (1.9)	1 (1.9)	8 (7.7)	6 (4.7)
Patients with other significant AEs, n (%)	19 (7.3)	3 (5.8)	6 (11.3)	3 (5.7)	7 (6.7)	5 (3.9)

[a]A patient may have had serious AE(s) with multiple seriousness criteria. MedDRA version used for reporting: 25.1.
Abbreviations: AEs = adverse events, AESI = adverse event of special interest, MedDRA = Medical Dictionary for Drug Regulatory Activities, n = number of patients in respective treatment arm, SAEs = serious AEs.

mean ZAN-BPD total score from baseline to Week 1. The average ZAN-BPD score at Week 10 fell in the mild range for all groups; therefore, a ceiling effect for improvement may obscure full interpretation of any treatment effects or lack thereof. While significant placebo responses have been observed in some studies (decrease from baseline in ZAN-BPD total score at Week 10 of −6.8 and −6.25 in olanzapine studies[33,34] and −6.25 in brexpiprazole studies),[32] the present trial had a higher placebo response than previously published studies.

Several factors may explain a high placebo response in this trial. The lack of approved BPD therapies may have led patients and clinicians to have optimistic expectations for this new treatment.[35] The large number of treatment arms may have increased the perceived likelihood of receiving treatment vs placebo, further increasing expectations.[36] The trial also had high intensity visit schedules, which patients with BPD may have found supportive. Moreover, the trial period's coincidence with the COVID-19 pandemic may have intensified this effect, considering social contact and structure can be more therapeutically impactful after isolation. Since many patients were not receiving any other medication at the time of randomization, the clinician-patient bonds formed through regular, high-quality interaction during the trial may have enhanced the nonspecific therapeutic effects of trial participation.[37]

Despite psychotherapy being the most effective current treatment for BPD,[38] only 19% of trial participants were attending psychotherapy sessions at baseline. Interestingly, these patients had a lower placebo response vs those who did not receive psychotherapy. One hypothesis that these data generate is that patients with background psychotherapy were already receiving professional attention via their therapist and, therefore, were less likely to experience therapeutic gains related to the nonspecific effects of trial participation. Psychiatric medication use in this patient sample was also low (16.4% conducted a medication washout before the trial), which is a departure from real-world assessments of BPD treatment, in which off-label psychiatric medication prescribing is frequent.[39] This departure from real-world patients who have higher medication use generates several hypotheses. Given considerable burdens in access to mental health care for BPD,[20] it is possible that lack of medication reflects treatment-seeking patients unable to access timely psychiatric care, ie, if these patients had access to care, they may have been prescribed off-label medication. Furthermore, for patients with high severity of BPD at trial entry, those actively seeking treatment may be more likely to have a significant therapeutic benefit from the connection to care within the trial, as supported by the higher placebo response observed in patients with an entry ZAN-BPD score >19. However, when patients who conducted a washout were compared with those who did not, no significant differences were found. Finally, gaining psychoeducation about BPD following diagnosis has been shown to lead to symptomatic improvements,[40] which could have affected overall symptomatic improvement for patients diagnosed upon enrollment or previously unable to access care.

This trial is one of the largest conducted in patients with BPD with retention numbers (82.8%) closer to those seen in psychotherapy trials (78% overall)[41] than in medication trials (65%).[33] Moreover, there were no documented suicides during this trial. However, this trial has significant limitations. Foremost, patient and investigator expectations were not measured, so no

data address the hypothesis that observed placebo responses may be due to high expectations in newly diagnosed patients or those not receiving any medication outside of the trial. Second, it may be difficult to show further improvement in the drug-treated groups given the substantial improvement in ZAN-BPD scores of the placebo-treated patients and the low levels of BPD symptoms at Week 10, ie, a ceiling effect.

Since individuals with BPD may present very heterogenous symptoms, future trials in BPD may consider enriching the patient population for the symptom domain of interest, aligned with the expected mechanism of action of the drug. Additionally, implementing strategies to mitigate the placebo effect may be beneficial. The mitigation of the placebo effect is an important and complex issue in clinical trials for all mental health conditions,[42] but perhaps particularly so for BPD, a condition in which the quality of therapeutic relationships is an important factor in predicting treatment outcomes.[43] Traditional clinical trial design approaches aimed at mitigating the placebo effect in psychiatry, such as placebo lead-ins, have not been successful in improving treatment effect sizes, as they tend to reduce both the placebo response and the therapeutic response to the investigational compound.[44] Therefore, a multipronged approach to placebo mitigation should be considered for future BPD trials to reduce the risk of ceiling effects observed in the current trial. Potential strategies may include design features (eg, lead-ins or habituation to study procedures and study staff prior to baseline), ensuring the use of clinical outcome assessments with adequate room for change, and providing tailored placebo response training for study sites, informed by the lived experiences of individuals with BPD.

In conclusion, this phase 2 trial aimed to evaluate the efficacy and safety of a 12-week treatment with BI 1358894 compared with placebo in patients with BPD. Although efficacy was not demonstrated, BI 1358894 was well tolerated with no increase in self-harm or suicidality.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Efficacy and Safety of BI 1358894 in Patients With Borderline Personality Disorder: Results of a Phase 2 Randomized, Placebo-Controlled, Parallel Group Dose-Ranging Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

The Journal of Clinical Psychiatry

SUPPLEMENTARY MATERIALS

METHODS

Inclusion criteria

Patients who met the following criteria were eligible for the trial:

1. Patients meeting diagnostic criteria of borderline personality disorder (BPD) per Diagnostic and Statistical manual of mental disorders-5 (DSM-5) at screening visit, confirmed by Structured Clinical Interview for Diagnostic and Statistical manual of mental disorders-5 [DSM-5]-Personality Disorders (SCID-5-PD)
2. Zanarini rating scale for BPD (ZAN-BPD) of ≥9 at screening (Visit 1) and randomization (Visit 2), with question #2 Affective Instability score of ≥2
3. Male or female patients, 18 to 65 years of age at the time of consent
4. Women of childbearing potential (WOCBP) able and willing to use 2 methods of contraception, as confirmed by the investigator, which include 1 highly effective method of birth control that results in a low failure rate of <1%, plus 1 barrier method. A woman was considered WOCBP i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods included hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal occlusion or ligation was NOT a method of permanent sterilization.
5. Signed and dated written informed consent prior to admission to the trial

Exclusion criteria

Patients who met any of the following criteria were not eligible for the trial:

1. Current diagnosis of paranoid, schizoid, schizotypal, and antisocial personality disorders, as confirmed by SCID-5-PD at screening visit
2. Lifetime diagnosis for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar I disorder, or delusional disorder as confirmed by the SCID-5 at the screening visit
3. Any other mental disorder (in addition to those described in Exclusion #1 and #2) that was the primary focus of treatment in the last 6 months prior to randomization, as per the clinical judgement of the investigator
4. Inpatient stay or hospitalization due to worsening of BPD within 3 months prior to randomization
5. Initiation or change in any type or frequency of psychotherapy (e.g., Dialectical Behavior Therapy (DBT), cognitive behavior therapy, interpersonal therapy) for BPD within 3 months prior to screening. Patients with ongoing, stable psychotherapy >3 months prior to screening (and intend to maintain the same frequency during the trial) could qualify as per clinical judgement of the investigator
6. Any ongoing use of psychotropic medications within 7 days prior to randomization or during the course of trial (unless allowed per protocol). Investigators could have used their clinical discretion to wash out (at least 3 half-lives of referenced medication) psychotropic medications during the screening period. Such washout of ongoing psychotropic medication had to be complete at least 7 days prior to randomization
7. Any suicidal behavior in the past 1 year (i.e., actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior) prior to screening and during the screening period

8. Any suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity Rating Scale (C-SSRS) in the past 3 months (i.e., active suicidal thought with intent but without specific plan or active suicidal thought with plan and intent) prior to screening and during the screening period
9. Any non-suicidal self-injury that leads to hospitalization within 3 months prior to randomization
10. Diagnosis of moderate or severe substance use disorder within the last 3 months of screening visit (as defined in DSM-5-substance use disorder) or at randomization visit. In case of a positive drug screen, a patient could have been considered for inclusion in the trial, at the discretion of the investigator, if the patient did not have moderate or severe substance use disorder as per DSM-5
11. Use of alternative or traditional medicine (e.g., Chinese traditional medicine, herbal medication, St. John's Wort, etc.) at the time of randomization and/or planned use during the course of the trial
12. Patients who had to or wished to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
13. Known history of HIV infection or positive result for active, ongoing Hepatitis B or C infection
14. History of seizure disorders, stroke, brain tumor, or any other major neurological or developmental illness
15. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to randomization or planned elective surgery requiring general anesthesia or hospitalization for more than 1 day during the trial period, e.g., hip replacement

16. 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
17. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (that, in the investigator's opinion, made the patient an unreliable trial participant)
18. Women who were pregnant, nursing, or who planned to become pregnant while in the trial
19. Clinically significant finding of the physical examination, vital signs (including BP and PR), ECG, or laboratory value that would jeopardize the patient´s safety while participating in the trial or their capability to participate in the trial.
20. Symptomatic, unstable, uncontrolled, or clinically relevant concomitant disease (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.) or any other clinical condition that would jeopardize the patient´s safety while participating in the trial or capability to participate in the trial
21. Use of any investigational procedure within 30 days prior to randomization. In case of exposure to an investigational medicinal product, the investigator had to ensure that it was adequately washed out prior to randomization (at least 30 days or 5 half-lives of the investigational medicinal product, whatever was longer)
22. Patients with an allergy to BI 1358894 and/or any of the excipients. A list of BI 1358894 and placebo ingredients was provided in the investigator site file

Models for the MCPMod analysis

Model	Estimate	Rationale
Emax1	50% of the maximum effect was achieved at 25 mg	Emax curve corresponds the assumed true estimate of ED50=25 mg*
Emax2	70% of the maximum effect was achieved at 5 mg	To cover the possibility for which 70% of the maximum effect was achieved at 5 mg. This was a scenario in which much of the effect was achieved early on with relatively low doses. The rationale behind the 2 Emax models was to construct one (emax1) where the dose-response was achieved as expected, while the other (emax2) accounts for the setting of which the assumed dose-response was not as expected
Sigmax	50% of the maximum effect was achieved at 25 mg, and 90% of the maximum effect was achieved at 75 mg	Another more flexible model to cover the new estimate ED50 = 25 mg

Exponential	5% of the maximum effect was achieved at 25 mg	To cover the case where the effect of drug was mainly achieved at the higher doses
Linear	No parameter assumptions required	In the event, dose-response was linear

EC50, Half maximal effective concentration; ED, Effective dose; MCPMod, Multiple comparison procedure with modelling.

*ED50, 25 mg assumes dose corresponding to EC50=77 nM (observed in a forced swim test in mice) plasma concentration in trough at 16 h.

Exploratory endpoints

The exploratory endpoints to assess efficacy included:

1. Zanarini rating scale for BPD ZAN-BPD:
    i. Change from baseline in ZAN-BPD total score over time
    ii. Response defined as ≥30% ZAN-BPD reduction from baseline over time
    iii. Response defined as ≥50% ZAN-BPD reduction from baseline over time
    iv. Change from baseline in ZAN-BPD total affective instability score over time
    v. Relative percent change in total ZAN-BPD score from baseline over time
2. Change from baseline in Difficulties in Emotion Regulation Scale-16 item version (DERS-16) total score over time
3. Change from baseline in Patient Health Questionnaire-9 (PHQ-9) total score over time
4. Change from baseline in State-Trait Anxiety Inventory – State Anxiety (STAI-S) total score over time

5. Change from baseline in shortened version of the original Urgency, Perseverance, Premeditation, and Sensation Seeking - Positive Urgency (S-UPPS-P) impulsive behaviour scale score over time

6. Patient-reported outcomes:

    i. Change from baseline in EuroQol 5-dimensions 5-levels (EQ-5D-5L) at Week 10

    ii. Change from baseline in Sheehan disability scale (SDS) at Week 10

    iii. Change from baseline in Patient Global Impression – severity (PGI-I) at Week 10

7. Ecological momentary assessment (EcMA):

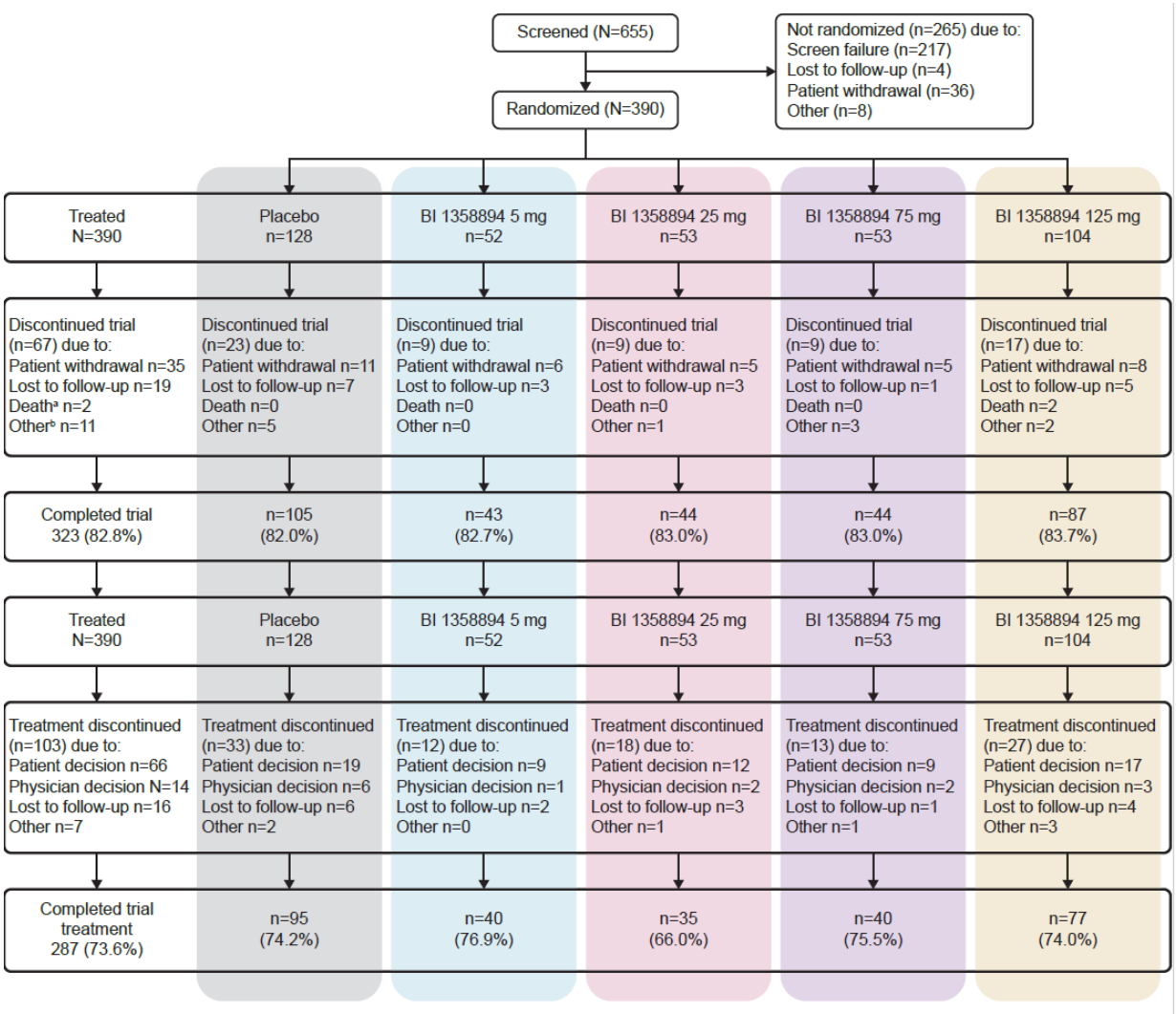
    i. Change from baseline in Affective Instability (as measured by the square of successive differences) at Week 10

    ii. Change from baseline in Negative Valence at Week 10

    iii. Change from baseline in Anxiety at Week 10

SUPPLEMENTARY FIGURES

Supplementary Figure 1: Patient disposition flowchart



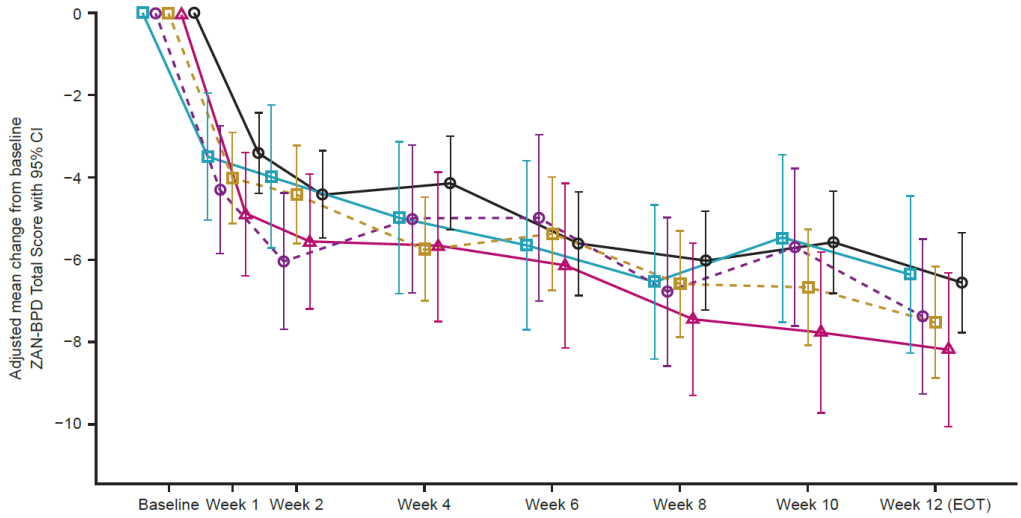
[a]Other reasons for premature discontinuation of the trial included: SAE of suicidal ideation, AE of headache, AE of weight increase, and pregnancy.

[b]Death was caused by a fatal SAE, (opioid overdose in one patient and esophageal varices hemorrhage and myocardial infarction in another patient).

Abbreviations: AE, adverse event; N, number of patients in the treated set; n, number of patients in each treatment group; SAE, serious adverse event.

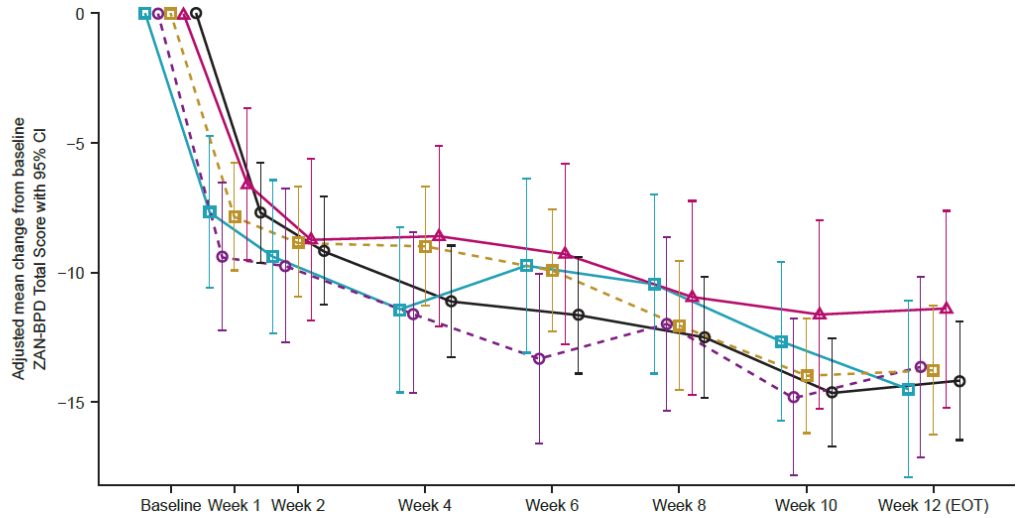
Supplementary Figure 2. Subgroup-analysis by severity: Adjusted mean change (95% CI) of MMRM estimates for absolute change from baseline in ZAN-BPD total score; ≤18 (A) vs ≥19 (B) – Full analysis set

A)

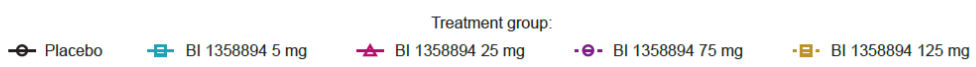


Number of patients								
Placebo	85	83	76	78	70	59	60	60
BI 1358894 5 mg	34	34	27	29	26	26	22	25
BI 1358894 25 mg	35	35	32	29	27	26	24	26
BI 1358894 75 mg	34	32	32	30	26	28	26	25
BI 1358894 125 mg	67	64	60	63	59	54	46	49

B)

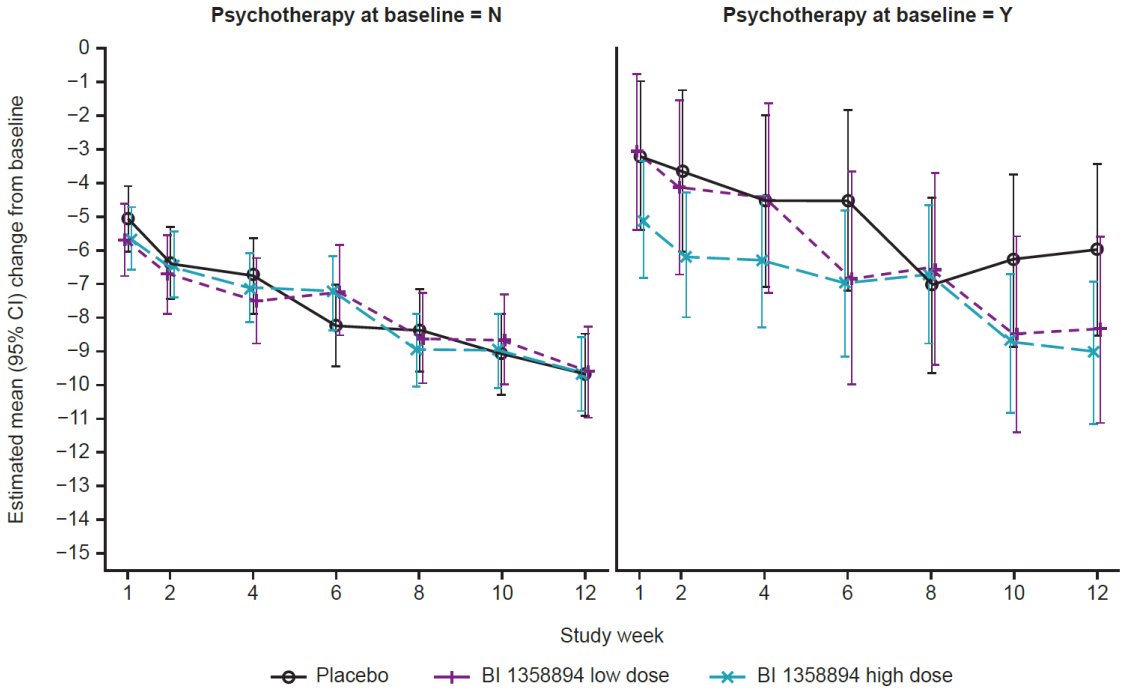


Number of patients								
Placebo	39	39	36	34	34	33	32	33
BI 1358894 5 mg	18	16	18	16	15	15	15	15
BI 1358894 25 mg	17	17	16	12	14	12	9	11
BI 1358894 75 mg	18	18	18	17	16	16	15	12
BI 1358894 125 mg	35	33	35	30	31	29	28	26



Abbreviations: CI, confidence interval; MMRM, Mixed model repeated measures model; ZAN-BPD, Zanarini rating scale for borderline personality disorder.

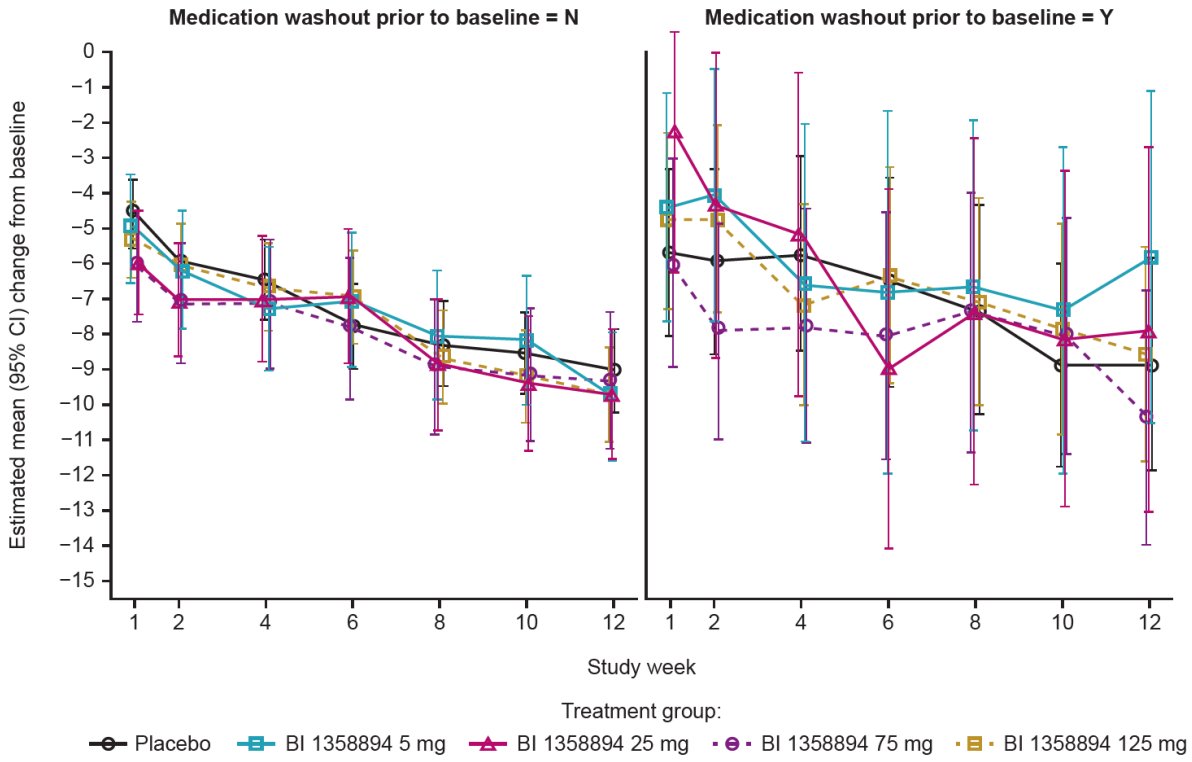
Supplementary Figure 3: Mean (95% CI) of MMRM estimates for absolute change from baseline in ZAN-BPD total score up to Week 12 stratified by baseline psychotherapy versus non-psychotherapy with pooled dose groups[a] – Full analysis set



[a]Patients in the "Yes" concomitant therapy subgroup (n=76) had a lower placebo response and a higher magnitude of treatment effects compared with the patients in the "No" concomitant therapy subgroup (n=314).

Abbreviations: CI, confidence interval; FAS, MMRM, Mixed model repeated measures model; N, no; Y, yes.

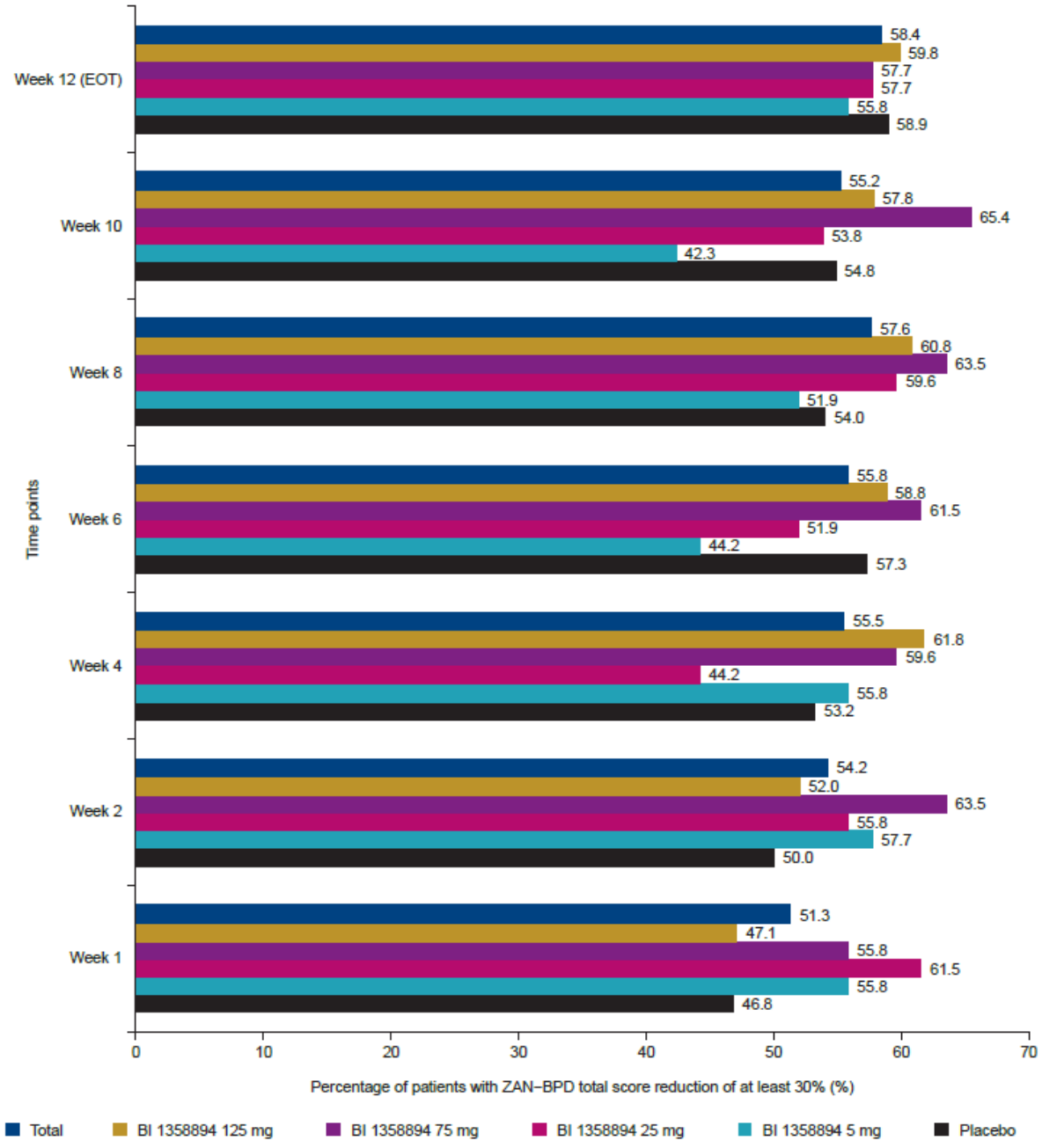
Supplementary Figure 4. Mean (95% CI) of MMRM estimates for absolute change from baseline in ZAN-BPD total score up to Week 12 stratified by those patients who had concomitant medication(s) washed out prior to baseline versus those who did not[a] – Full analysis set



[a]Patients in the "Yes" medication washout subgroup (n=64) had no discernable differences from the patients in "No" medication washout subgroup (n=326).

Abbreviations: CI, confidence interval; MMRM, Mixed model repeated measures model; N, no; Y, yes.

Supplementary Figure 5: Percentage of patients with ZAN-BPD total score reduction of at least 30% from baseline over time up to Week 12 (exploratory endpoint) – Full analysis set



Abbreviations: ZAN-BPD, Zanarini rating scale for borderline personality disorder.

SUPPLEMENTARY TABLES

Supplementary Table 1. MMRM estimates for change from baseline to Week 10 in ZAN-BPD total score – Full analysis set

	BI 1358894 5 mg (n=52)	BI 1358894 25 mg (n=52)	BI 1358894 75 mg (n=52)	BI 1358894 125 mg (n=102)	Placebo (n=124)
Adjusted mean (SE)	−8.0 (0.9)	−9.2 (0.9)	−8.9 (0.8)	−9.0 (0.6)	−8.7 (0.5)
95% CI	(−9.68, −6.30)	(−10.97, −7.48)	(−10.53, −7.29)	(−10.22, −7.85)	(−9.75, −7.60)
Comparison vs placebo					
Adjusted mean difference (SE)	0.7 (1.0)	−0.6 (1.0)	−0.2 (1.0)	−0.4 (0.8)	–
95% CI	(−1.31, 2.69)	(−2.60, 1.51)	(−2.17, 1.72)	(−1.96, 1.24)	–
p-value	0.4994	0.6014	0.8166	0.6588	–

The least square means, differences, and confidence intervals were estimated by REML-based MMRM including the fixed categorical covariates of treatment, visit, and the baseline ZAN-BPD total score strata indicator (≤18 vs ≥19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient was considered as random. Unstructured covariance matrix was used. Abbreviations: CI, confidence interval; MMRM, mixed model repeated measures model; n, number of patients in each treatment group; REML, residual maximum likelihood method; SE, standard error; ZAN-BPD, Zanarini rating scale for borderline personality disorder.

Supplementary Table 2. Total ZAN−BPD score by visit – Full analysis set

	Placebo (n=124)	BI 1358894 5 mg (n=52)	BI 1358894 25 mg (n=52)	BI 1358894 75 mg (n=52)	BI 1358894 125 mg (n=102)	Total (N=382)
Baseline Mean (SD)	16.71 (5.02)	15.40 (5.43)	15.64 (4.78)	16.24 (4.63)	16.45 (5.32)	16.26 (5.07)
Week 1 Mean (SD)	11.70 (5.85)	10.64 (6.00)	10.46 (6.18)	10.10 (5.35)	11.10 (5.96)	11.01 (5.88)
Week 2 Mean (SD)	10.58 (6.13)	10.13 (6.10)	9.13 (5.31)	8.78 (6.31)	10.77 (6.00)	10.12 (6.03)
Week 4 Mean (SD)	9.87 (5.80)	8.64 (5.68)	8.56 (5.37)	9.04 (6.03)	9.29 (6.17)	9.27 (5.86)
Week 6 Mean (SD)	8.62 (6.40)	9.07 (5.93)	9.05 (7.01)	8.14 (5.99)	9.26 (6.00)	8.85 (6.23)
Week 8 Mean (SD)	7.91 (6.17)	8.29 (5.88)	7.05 (4.96)	7.95 (6.61)	7.58 (5.85)	7.77 (5.94)
Week 10 Mean (SD)	7.42 (5.69)	8.49 (6.00)	5.94 (4.51)	7.44 (5.40)	6.86 (5.25)	7.24 (5.45)
Week 12 Mean (SD)	6.92 (5.33)	6.95 (6.60)	6.03 (5.08)	6.14 (6.32)	6.33 (5.34)	6.55 (5.61)

Abbreviations: FAS, full analysis set; N, number of patients in the treated set; number of patients in the treated set; SD, standard deviation; ZAN-BPD, Zanarini rating scale for borderline personality disorder.

Supplementary Table 3. Primary endpoint PoC testing: Multiple contrast test results for non-flat dose response shape for absolute change from baseline – Full analysis set

	estimates	sigmax	emax1	linear	exponential	emax2
MMRM estimates						
Placebo	−8.70					
BI 1358894 5 mg	−8.01					
BI 1358894 25 mg	−9.41					
BI 1358894 75 mg	−8.84					
BI 1358894 125 mg	−8.97					
Contrast						
Placebo		0.6823	0.7330	0.5868	0.4829	0.8591
BI 1358894 5 mg		0.2541	0.1798	0.2126	0.1891	−0.0471
BI 1358894 25 mg		−0.0252	−0.0548	0.1040	0.1492	−0.1608
BI 1358894 75 mg		−0.2912	−0.2568	−0.1421	0.0205	−0.2213
BI 1358894 125 mg		−0.6200	−0.6012	−0.7612	−0.8417	−0.4299
Multiple contrast test						
t-statistic		0.6539	0.6070	0.4973	0.4143	0.3987
Adjusted p-value		0.3914	0.4104	0.4560	0.4908	0.4974
Critical value: 1.615 (alpha = 0.100, one-sided)						

Abbreviations: MMRM, Mixed model repeated measures model, PoC, proof of concept.

Supplementary Table 4. Change from baseline at Week 10 in FAS in EQ-5D-5L, SDS, and PGI-I scores – Full analysis set

	Placebo (n=124)	BI 1358894 5 mg (n=52)	BI 1358894 25 mg (n=52)	BI 1358894 75 mg (n=52)	BI 1358894 125 mg (n=102)	Total (N=382)
Change from baseline at Week 10 in EQ−5D−5L Index Score						
Mean (SD)	0.02 (0.24)	0.04 (0.25)	−0.00 (0.21)	−0.02 (0.24)	−0.01 (0.19)	0.01 (0.22)
Change from baseline at Week 10 in EQ−5D−5L VAS Index Score						
Mean (SD)	1.86 (19.94)	4.33 (19.14)	−0.73 (20.00)	0.29 (19.29)	1.41 (19.91)	1.53 (19.65)
Change from baseline at Week 10 in SDS Score						
Mean (SD)	−4.39 (7.01)	−5.92 (8.40)	−4.24 (8.87)	−6.87 (7.09)	−4.91 (7.79)	−5.07 (7.67)
Change from baseline at Week 10 in PGI-Impact Scale Score						
Mean (SD)	−0.82 (1.19)	−0.73 (1.15)	−1.14 (0.99)	−0.96 (1.16)	−0.74 (1.22)	−0.85 (1.16)

Abbreviations: EQ−5D−5L, The EuroQol five-dimensional questionnaire; N, number of patients in the treated set; number of patients in the treated set;

PGI-I, Patient Global Impressions – Impact scale; SD, standard deviation; SDS, Sheehan disability scale.