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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

1. Methods
2. Figure 1 Patient Disposition Flowchart
3. 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
4. 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 – Full Analysis Set
5. 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 – Full Analysis Set
6. 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
7. Table 1 MMRM Estimates for Change From Baseline to Week 10 in ZAN-BPD Total Score – Full Analysis Set
8. Table 2 Total ZAN–BPD Score by Visit – Full Analysis Set
9. Table 3 Primary Endpoint POC Testing: Multiple Contrast Test Results for Non-Flat Dose Response Shape for Absolute Change From Baseline – Full Analysis Set
10. Table 4 Change from Baseline at Week 10 in FAS in EQ-5D-5L, SDS, and PGI-I Scores – Full Analysis Set

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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):

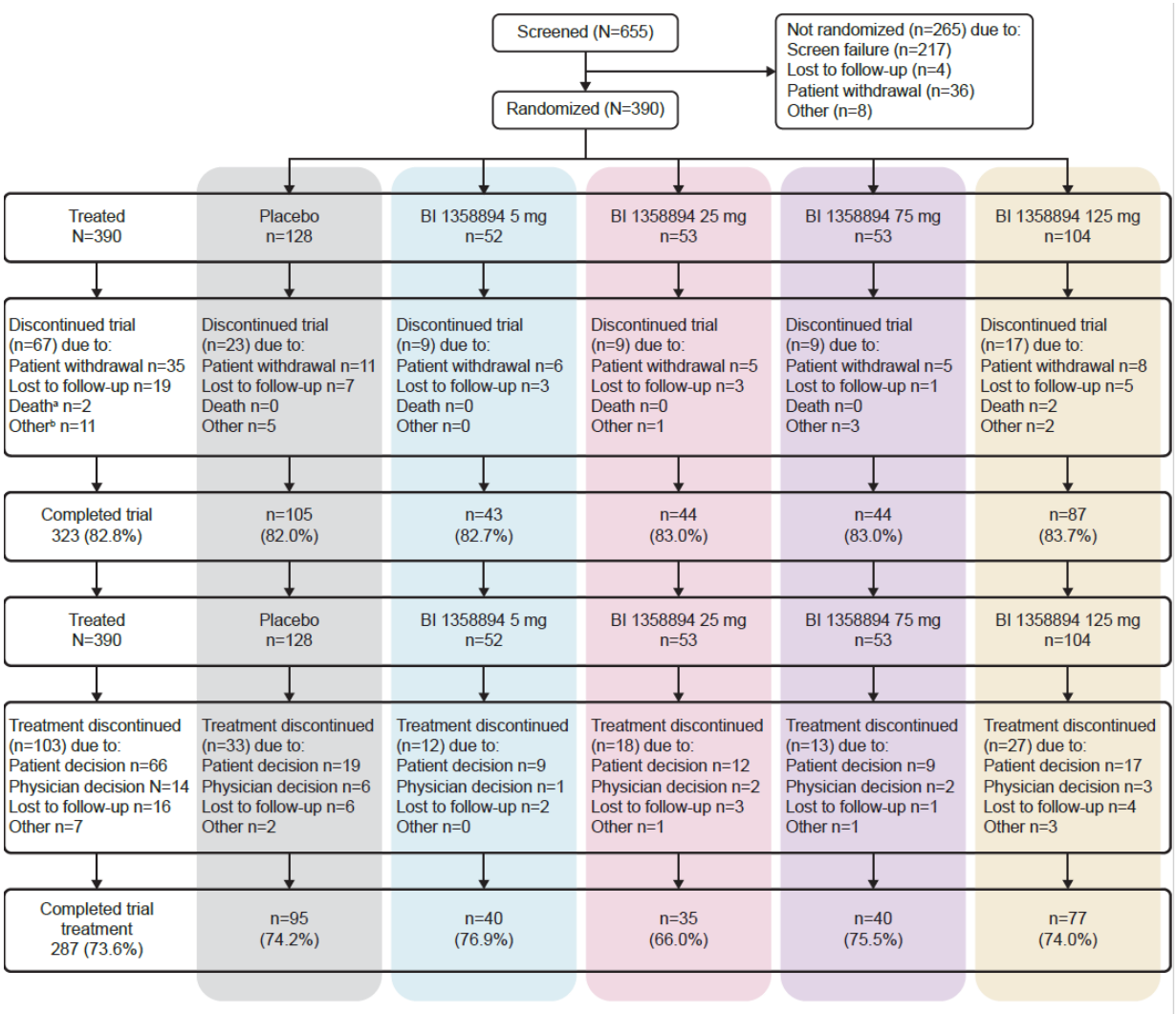
    i. Change from baseline in Affective Instability (as measured by the square of successive differences) at Week 10

    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



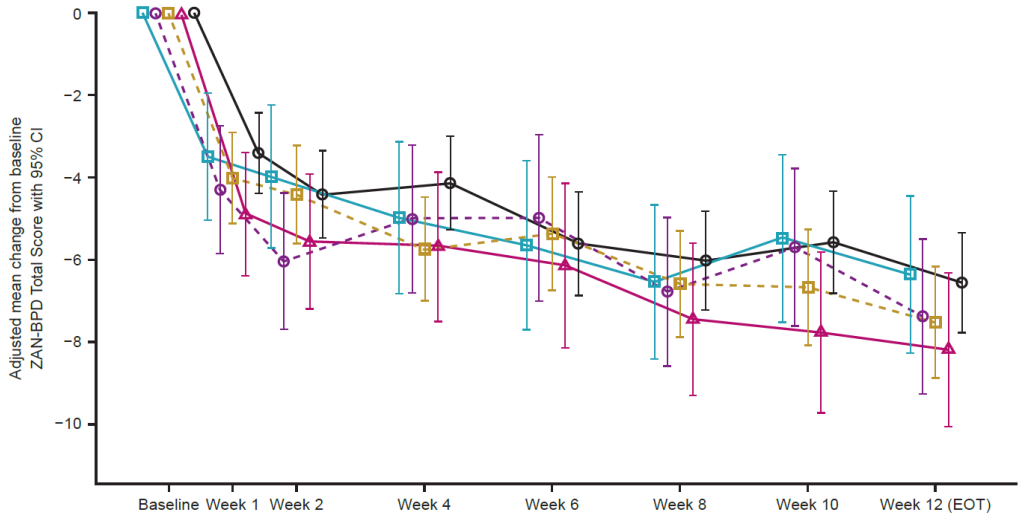
[a]Other reasons for premature discontinuation of the trial included: SAE of suicidal ideation, AE of headache, AE of weight increase, and pregnancy.

[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.

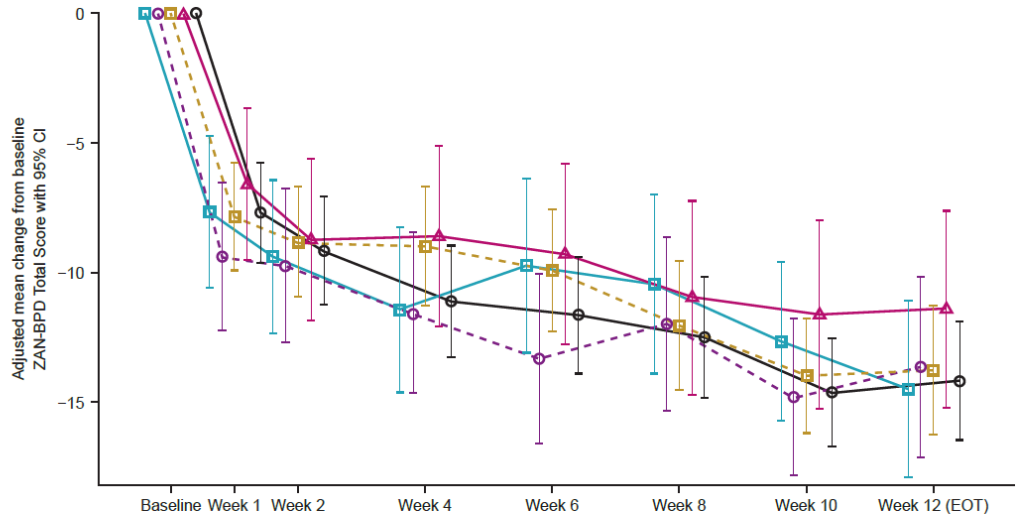
Supplementary Figure 2. Subgroup-analysis by severity: Adjusted mean change (95% CI) of MMRM estimates for absolute change from baseline in ZAN-BPD total score; ≤18 (A) vs ≥19 (B) – Full analysis set

A)

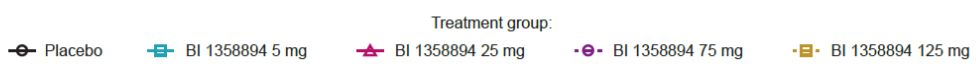


Number of patients								
Placebo	85	83	76	78	70	59	60	60
BI 1358894 5 mg	34	34	27	29	26	26	22	25
BI 1358894 25 mg	35	35	32	29	27	26	24	26
BI 1358894 75 mg	34	32	32	30	26	28	26	25
BI 1358894 125 mg	67	64	60	63	59	54	46	49

B)

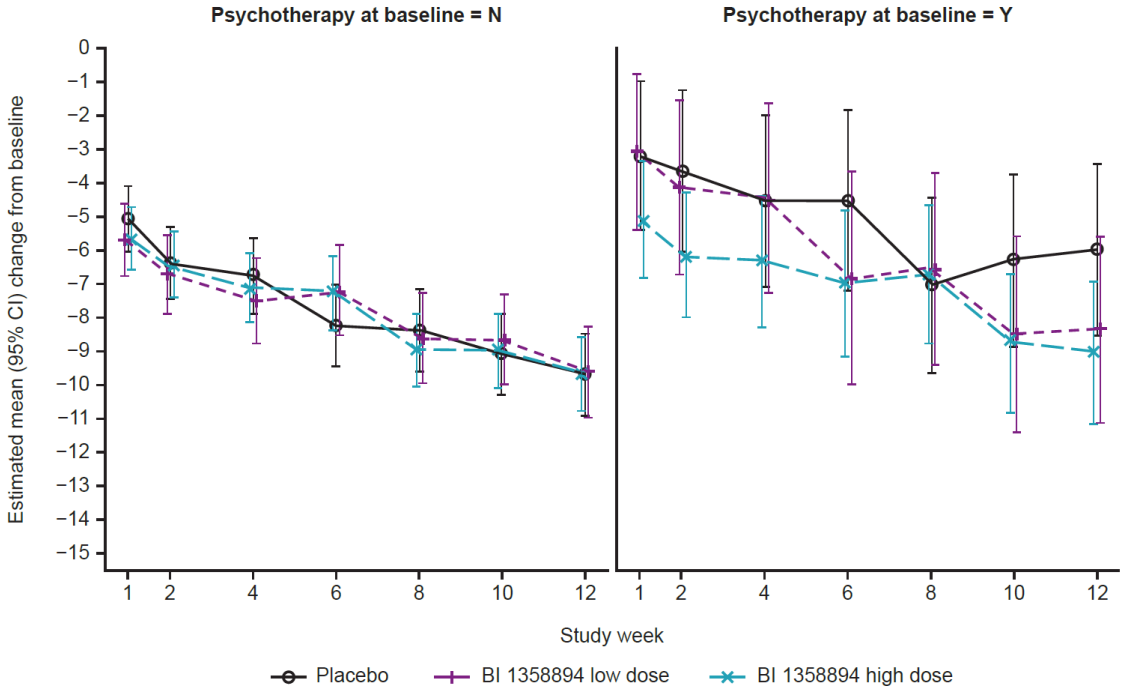


Number of patients								
Placebo	39	39	36	34	34	33	32	33
BI 1358894 5 mg	18	16	18	16	15	15	15	15
BI 1358894 25 mg	17	17	16	12	14	12	9	11
BI 1358894 75 mg	18	18	18	17	16	16	15	12
BI 1358894 125 mg	35	33	35	30	31	29	28	26



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

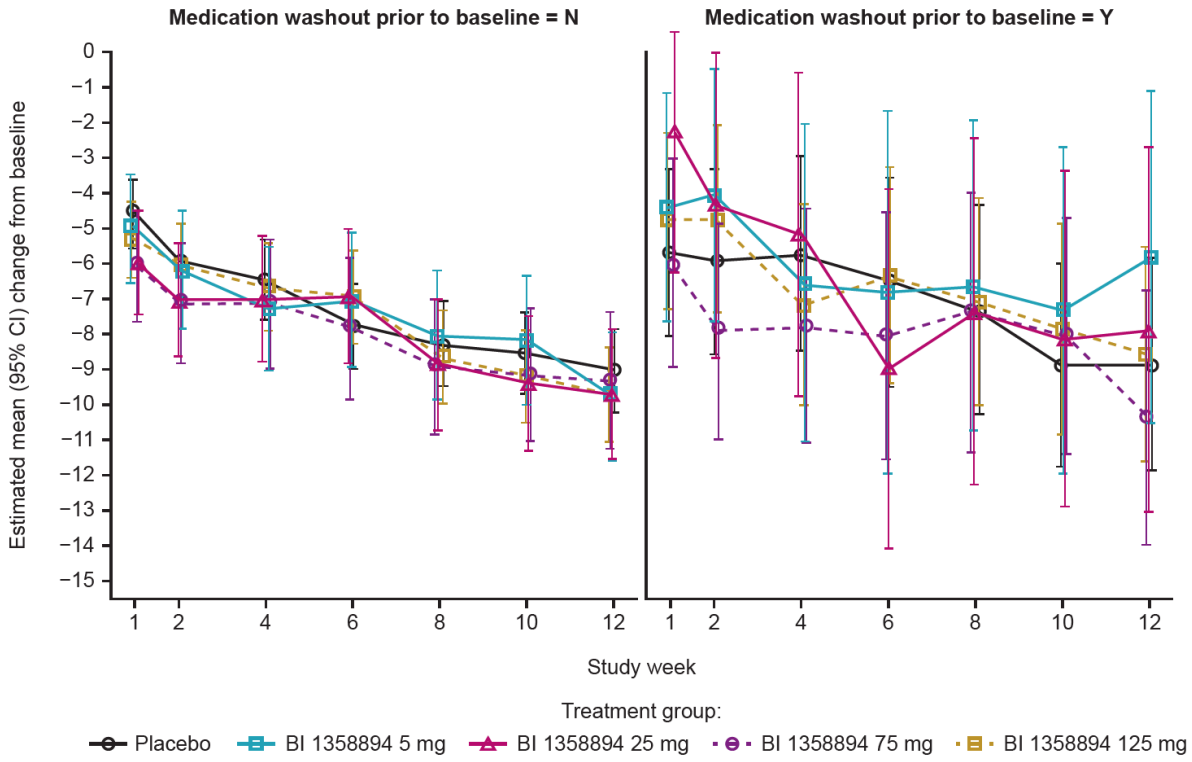
Supplementary Figure 3: Mean (95% CI) of MMRM estimates for absolute change from baseline in ZAN-BPD total score up to Week 12 stratified by baseline psychotherapy versus non-psychotherapy with pooled dose groups[a] – Full analysis set



[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.

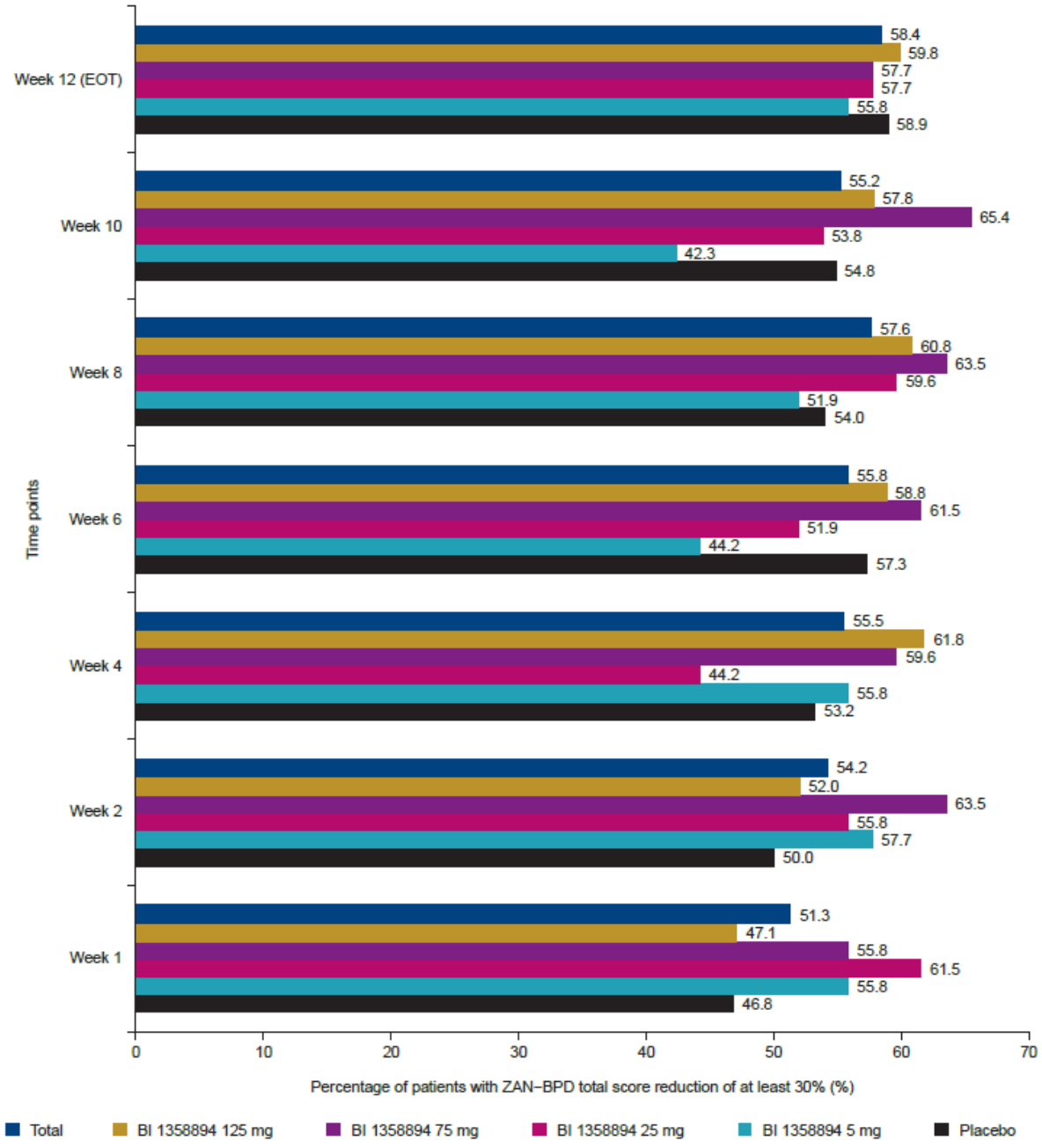
Supplementary Figure 4. Mean (95% CI) of MMRM estimates for absolute change from baseline in ZAN-BPD total score up to Week 12 stratified by those patients who had concomitant medication(s) washed out prior to baseline versus those who did not[a] – Full analysis set



[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.