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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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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

The Journal of Clinical Psychiatry

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)

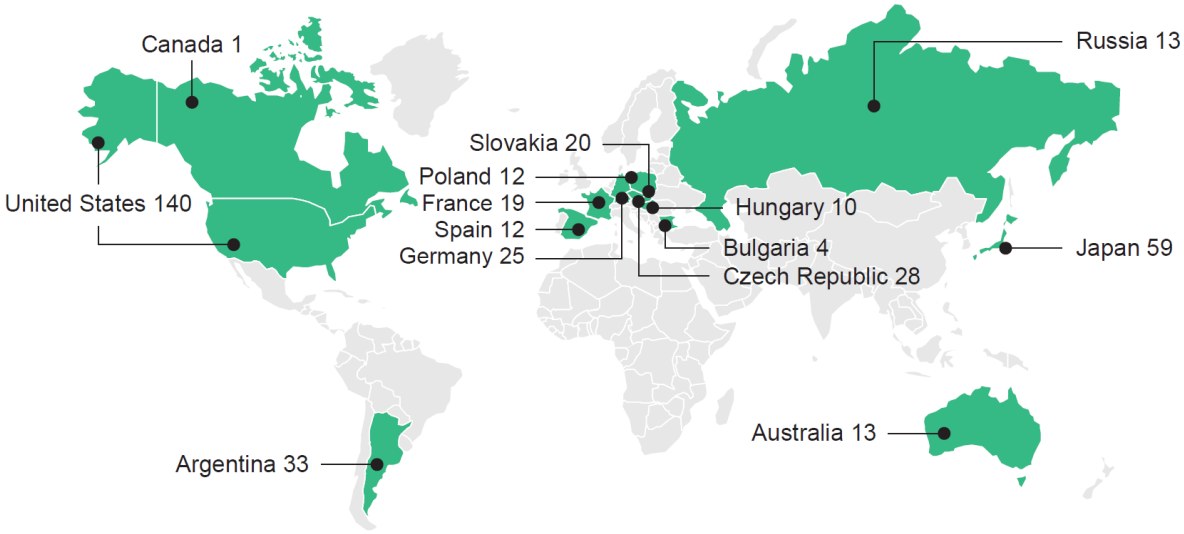
C-SSRS category	Placebo n=128	BI 1358894				Quetiapine 300/150mg n=71
		5 mg n=36	25 mg n=39	75 mg n=39	125 mg n=75	
			n* (%)			
Any event	30 (23.4)	12 (33.3)	6 (15.4)	10 (25.6)	14 (18.7)	6 (8.5)
Suicidal ideation (1-5)	29 (22.7)	11 (30.6)	6 (15.4)	10 (25.6)	14 (18.7)	6 (8.5)
1	28 (21.9)	11 (30.6)	6 (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.

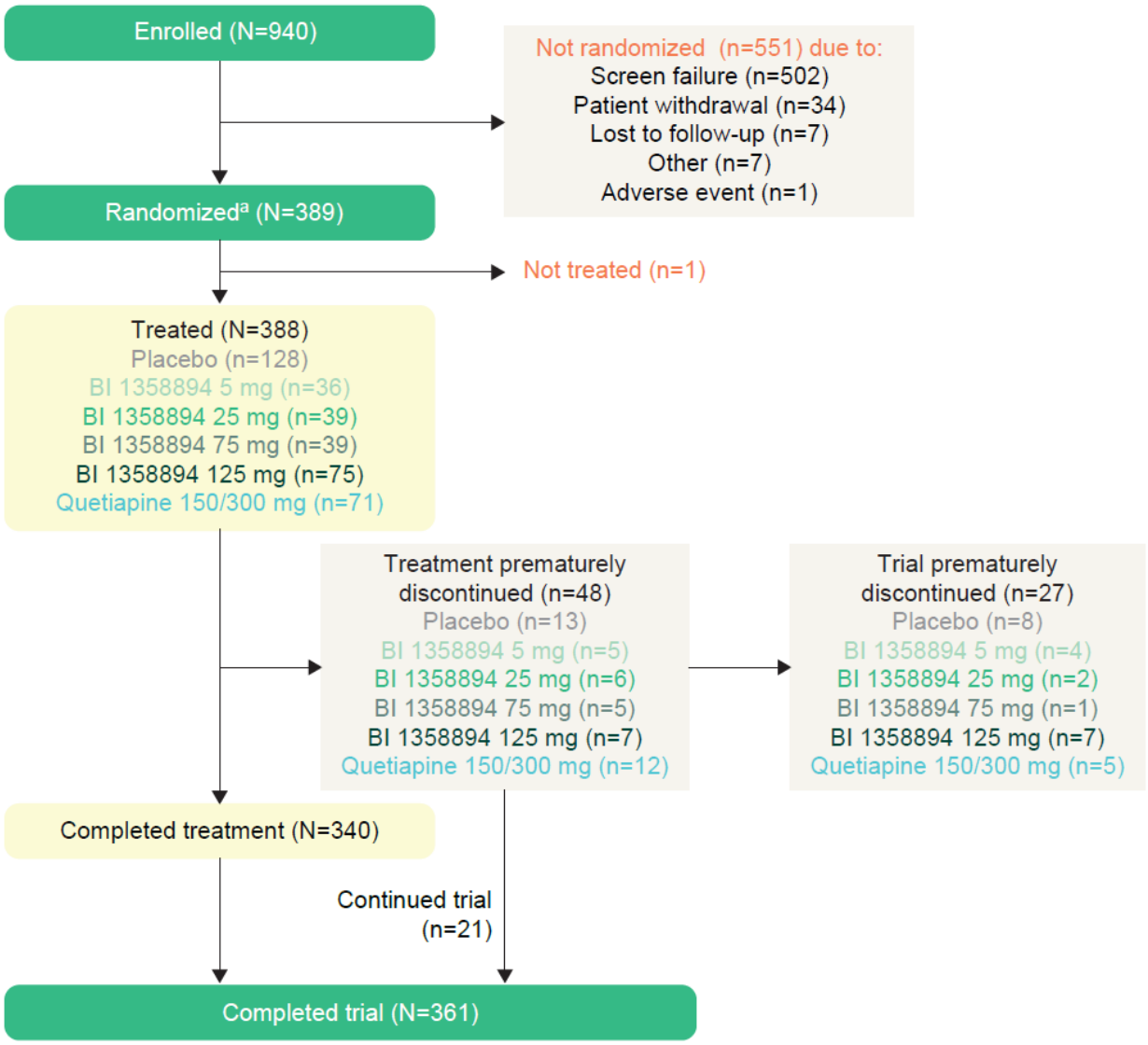
Abbreviations: C-SSRS, Columbia-Suicide Severity Rating Scale; n, number of randomized patients; n*, number of patients within a particular treatment group at a specific C-SSRS category.

SUPPLEMENTARY FIGURES

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

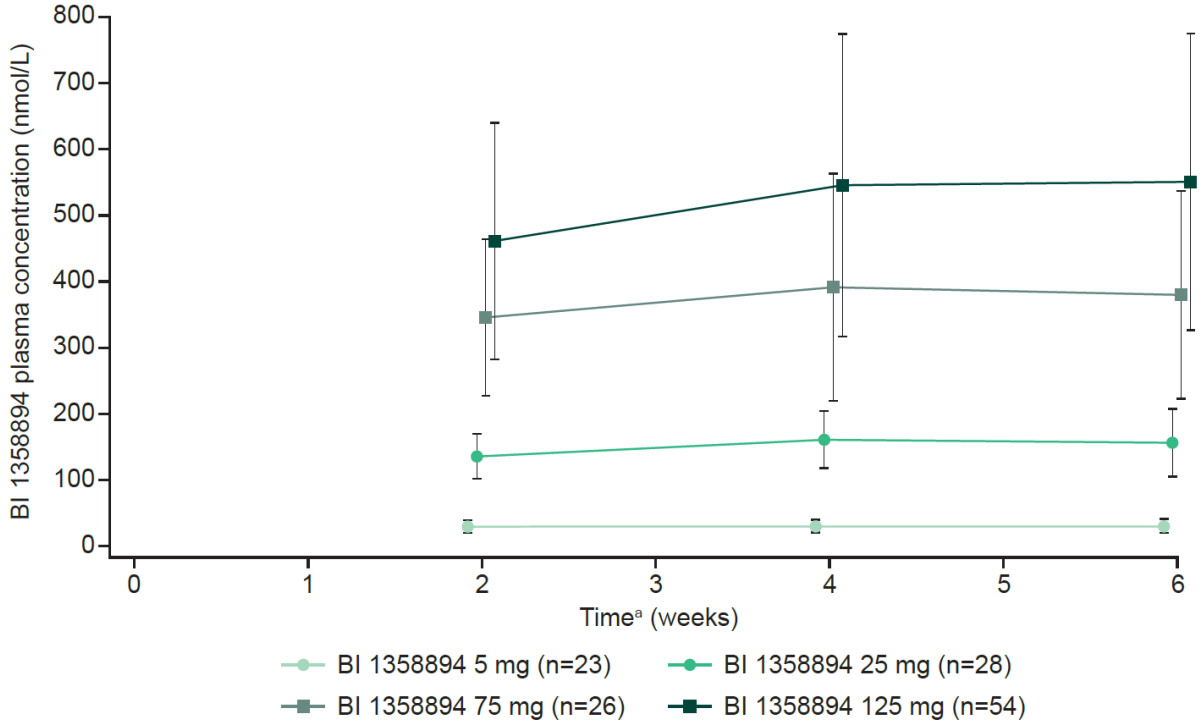


Supplementary Figure 2: Patient disposition flowchart



[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).

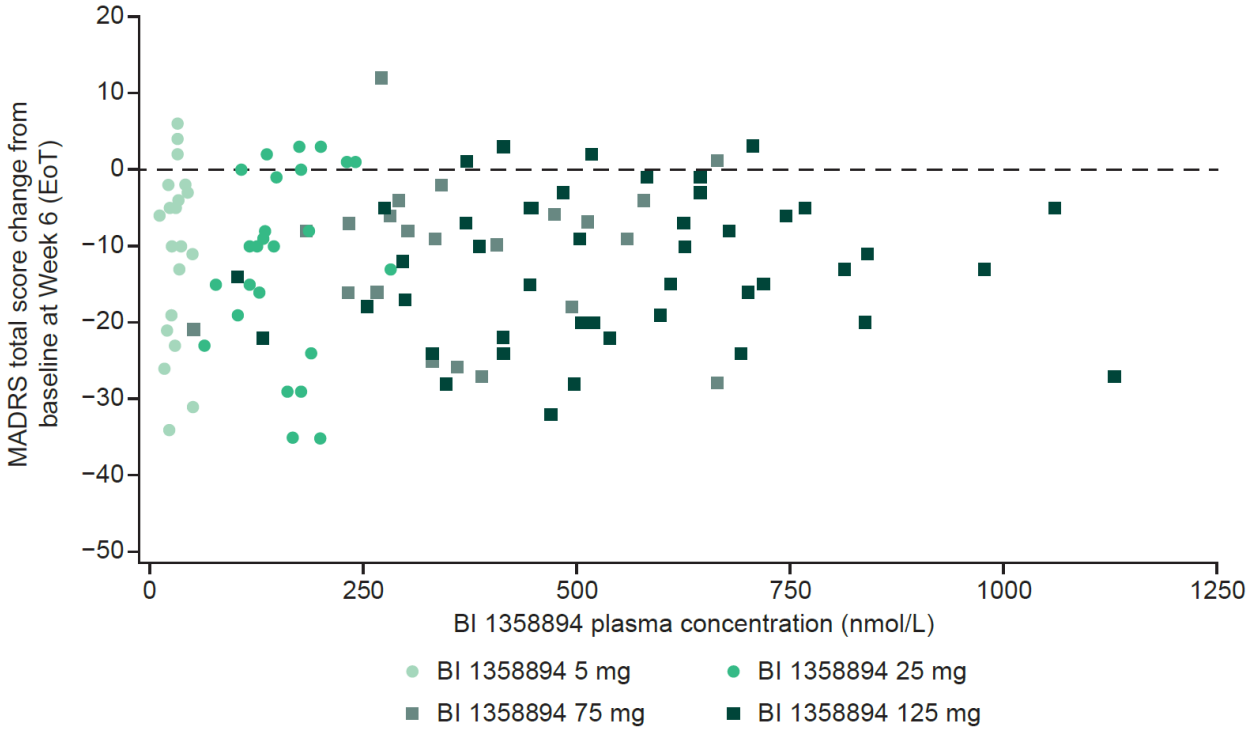
Supplementary Figure 3. Mean (SD) plasma trough concentration-time profiles of BI 1358894 after multiple oral administration



[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.