Brexpiprazole in Combination With Sertraline and as Monotherapy in Posttraumatic Stress Disorder:

A Full-Factorial Randomized Clinical Trial

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Abstract

Objective: To investigate the efficacy, safety, and tolerability of brexpiprazole in combination with sertraline and as monotherapy for posttraumatic stress disorder (PTSD).

Methods: The trial comprised a 1-week placebo run-in period followed by an 11-week, randomized, double-blind, active-referenced, placebo-controlled, parallel-arm treatment period (with 14-day follow-up). The trial ran from January 2017–November 2018 at 48 clinical trial sites in the United States. Adult outpatients with PTSD (*DSM-5*) were randomized (1:1:1:1) to oral brexpiprazole + sertraline, brexpiprazole + placebo, sertraline + placebo, or placebo + placebo. Doses were flexible (brexpiprazole 1–3 mg/d; sertraline 100–200 mg/d). The primary endpoint was change in Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5) total score from randomization (Week 1) to Week 10. Safety assessments included adverse events.

Results: Among 321 randomized participants, completion rates were 58/82 (70.7%) for brexpiprazole + sertraline, 50/75 (66.7%) for brexpiprazole + placebo, 59/81 (72.8%) for sertraline + placebo, and 64/83 (77.1%) for placebo + placebo. At Week 10, brexpiprazole + sertraline demonstrated greater improvement in CAPS-5 total score (randomization, 35.7; least-squares [LS] mean change, −16.4; n = 77) vs sertraline + placebo (randomization, 36.5; LS mean change, −11.4; n = 75) with LS mean difference, −5.08 (95% CI, −8.96 to −1.20; $P = .011$), and also vs brexpiprazole + placebo and vs placebo + placebo. Brexpiprazole + placebo and sertraline + placebo did not differ from placebo + placebo. Treatment-emergent adverse events with incidence ≥10% were weight increased (12.5%) and somnolence (10.0%) for brexpiprazole + sertraline, akathisia (13.3%) for brexpiprazole + placebo, and nausea (20.3%) and dry mouth (12.7%) for sertraline + placebo.

Conclusions: Brexpiprazole in combination with sertraline (but not as monotherapy) has potential to be a new efficacious treatment for PTSD, with a safety profile consistent with brexpiprazole in approved indications.

Trial Registration: ClinicalTrials.gov identifier: NCT03033069.

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Posttraumatic stress disorder (PTSD) is a potentially chronic and disabling mental health condition that can develop following exposure to a traumatic event.[1] The lifetime prevalence of PTSD is estimated at 4% globally and 6%–7% in US total/civilian populations, with a higher prevalence in women than in men.[2–4] Despite a public perception that PTSD predominantly affects military populations, most PTSD cases occur in the general population due to reasons such as sexual and physical violence.[5]

Symptoms of PTSD can be categorized into 4 clusters: intrusion (re-experiencing the trauma as recurrent memories or dreams), avoidance (of activities, people, or places associated with the trauma), negative cognitions and mood, and marked alterations in arousal and reactivity.[1] PTSD is associated with impairments in relationships, work/academic performance, and finances[6]; increased suicidality[7,8]; and comorbid psychiatric disorders.[9] The estimated economic burden of PTSD in the US is $232 billion annually.[10]

Many patients with PTSD do not seek treatment due to stigma, shame, and fear of negative social consequences.[2,11] For those who do seek treatment, PTSD is often misdiagnosed or diagnosed after a delay, which can lead to greater symptomatic burden.[12,13] US Food and Drug Administration-approved

Clinical Points

- There is an urgent need for new effective pharmacologic treatments for PTSD.
- The combination of brexpiprazole and sertraline has the potential to be an effective and tolerated new treatment for people with PTSD.

pharmaceutical options for PTSD are limited to the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine.[14] Sertraline and paroxetine have demonstrated efficacy in PTSD, with meta-analyses showing response in 50%–59% of patients[15] and small but clinically significant effect sizes vs placebo (0.3–0.4).[16] Off-label polypharmacy with other antidepressants, benzodiazepines, and atypical antipsychotics is common,[17,18] despite a lack of established efficacy and safety.[19] There is an urgent need for new pharmacologic treatments for PTSD.[19]

Brexpiprazole acts as an antagonist at noradrenaline α_{1B}/α_{2C} and serotonin 5-HT_{2A} receptors, and as a partial agonist at serotonin 5-HT_{1A} and dopamine D_2 receptors,[20] thereby acting on systems implicated across PTSD symptom clusters.[21–23] Brexpiprazole has demonstrated efficacy, and is approved in various regions, for the treatment of schizophrenia,[24,25] the treatment of agitation in Alzheimer's dementia,[26–28] and the adjunctive treatment of major depressive disorder.[29–32] The aim of the present Phase 2 trial was to investigate the efficacy, safety, and tolerability of brexpiprazole as combination treatment with sertraline and as monotherapy in adults with PTSD.

METHODS

This was a Phase 2, multicenter, 12-week, randomized, double-blind, placebo- and active-controlled, parallel-arm trial of brexpiprazole in patients with PTSD. The trial was registered at ClinicalTrials.gov (identifier: NCT03033069), where the protocol and statistical analysis plan are available. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Consolidated Guideline and local regulatory requirements. The trial protocol was approved by the governing institutional review board for each investigational site. All participants provided written electronic informed consent after trial procedures and possible side effects were fully explained, and they were reimbursed for time and travel.

Participants and Study Design

Participants (a volunteer sample) were screened by investigators at 48 sites in the US (sites and principal investigators are listed in Supplementary Table 1). Key inclusion criteria were as follows: outpatient status; age 18–65 years; diagnosis of PTSD as defined by *DSM-5* criteria[33] and confirmed by the Mini-International Neuropsychiatric Interview version 7,[34] with symptoms for ≥6 months prior to screening; and a Clinician-Administered PTSD Scale for *DSM-5* (CAPS-5)[35,36] total score ≥33 at screening and baseline (Day 0). Key exclusion criteria were as follows: receiving disability payments or being engaged in compensation litigation related to PTSD or another psychiatric disorder; an index traumatic event before age 16 or >15 years before screening; a traumatic event within 3 months of screening; considered psychotropic-treatment resistant/refractory by history in the investigator's opinion; currently receiving sertraline with adequate dose and duration; any previous exposure to brexpiprazole; a change in PTSD treatment within 28 days of screening; a current *DSM-5* major depressive episode; a current or recent (within 6 months of screening) anxiety disorder that has been the primary focus of psychiatric treatment; a current or recent (within 120 days of screening) *DSM-5* substance/alcohol use disorder; at significant risk of committing suicide; or any other psychiatric or medical condition as listed in the protocol.

After a 3–14-day screening/washout period, eligible participants entered a 1-week, double-blind, placebo run-in period (Period A), followed by an 11-week, double-blind, active-treatment period (Period B) in which participants were randomized 1:1:1:1 to brexpiprazole + sertraline, brexpiprazole + placebo, sertraline + placebo, or placebo + placebo. To reduce potential bias in efficacy outcomes, aspects of the trial design (illustrated in Supplementary Figure 1) were blinded to participants and trial site personnel. In the blinded protocol, the existence of the placebo run-in period, the timing and nature of randomization (ie, parallel treatment arms and randomization ratio), and the timing of the primary efficacy endpoint (Week 10) were not revealed, such that the trial appeared to comprise a single, 12-week, double-blind treatment period (with 14-day follow-up). Visits occurred weekly from baseline to Week 4, then every 2 weeks.

Brexpiprazole and sertraline were flexibly dosed at 1–3 mg/d and 100–200 mg/d, respectively (titration was over 2–3 weeks, with details in Supplementary Figure 1). Study drugs were taken orally, together, at the same time each day (once daily), without regard to meals. Brexpiprazole tablets (or matching placebo) and sertraline capsules (or matching placebo) were provided by the sponsor or designated agent in blister cards. Treatments were assigned to participants via a fixed-block (block size 4) computer-generated randomization code provided by the sponsor and stratified by site and type of trauma (combat-related: yes/no). Treatment assignments were blinded to participants, investigators, and sponsor personnel, including those involved in data

analysis. Prohibited medications, including psychotropic agents (antipsychotics, antidepressants, etc.), were washed out during the screening period. Benzodiazepines and nonbenzodiazepine sleep aids were prohibited except when used in the short term to manage emergent agitation/anxiety and insomnia, respectively. Psychotherapy was permitted provided it was ongoing for ≥28 days prior to screening, and the participant committed to continue the therapy during the trial.

Assessments

Participant demographics and medical history were recorded at the screening visit. Sex, race, and ethnicity were self-reported using US Census Bureau classifications. The Life Events Checklist for *DSM-5*[37] was used to identify index traumatic events. The Emory Treatment Resistance Interview for PTSD[38] was used to collect information on prior PTSD treatments.

The CAPS-5,[35,36] an extensively validated structured interview,[39] was used to assess PTSD diagnostic status and symptom severity. The CAPS-5 includes 20 *DSM-5* PTSD-symptom items that are each scored from 0 (absent) to 4 (extreme/incapacitating); total score is calculated by summing the 20 items, and symptom cluster scores by summing specific items: Intrusion (items 1–5); Avoidance (items 6–7); Negative cognitions and mood (items 8–14); and Arousal and reactivity (items 15–20).[35,36] The CAPS-5 Past Month version was completed at screening, and the Past Week version at baseline (Day 0) and Weeks 1, 3, 6, 10, and 12, by trained raters. PTSD symptom severity was also assessed using the clinician-reported Clinical Global Impression–Severity of illness (CGI-S) scale,[40] the clinician-reported Symptoms of Trauma Scale (SOTS),[41] and the patient-reported PTSD Checklist for *DSM-5* (PCL-5).[42] Patient-reported anxiety and depression symptom severity were assessed using the Hospital Anxiety and Depression Scale (HADS).[43]

Safety was assessed via standard variables including treatment-emergent adverse events (TEAEs), body weight, laboratory tests, vital signs, electrocardiograms, the Columbia-Suicide Severity Rating Scale (C-SSRS),[44] and 3 extrapyramidal symptom rating scales: Simpson–Angus Scale (SAS),[45] Abnormal Involuntary Movement Scale (AIMS),[40] and Barnes Akathisia Rating Scale (BARS).[46]

Statistical Analysis

The primary efficacy endpoint was change from randomization (Week 1) to Week 10 (ie, 9 weeks of active treatment) in CAPS-5 total score in the efficacy sample. Comparisons (mean difference between treatment arms) were made for brexpiprazole + sertraline vs brexpiprazole + placebo, vs sertraline + placebo, and vs placebo + placebo; brexpiprazole + placebo vs placebo + placebo; and sertraline + placebo vs placebo + placebo (for assay sensitivity). No testing hierarchy or adjustment for multiplicity was prespecified, and thus *P* values were tested at a nominal .05 level (2-sided). Using the hypothetical strategy that all participants tolerated and adhered to treatment,[47] missing data were considered missing at random and handled using a mixed model for repeated measures (MMRM) approach based on observed data. Details of the sample size calculation and MMRM are provided in the Supplementary Methods. Prespecified subgroup analyses of the primary efficacy endpoint were performed by sex, race, age, Period A response, trauma type, psychosocial support, previous PTSD pharmacotherapy, and time since index traumatic event. Missing-not-at-random sensitivity analyses were performed.

"Other" efficacy endpoints (CAPS-5 symptom clusters, CGI-S, SOTS total, HADS Anxiety, HADS Depression, and PCL-5 total scores; and CAPS-5 response rate [≥30% or >11-point improvement from Week 1]) were tested at a nominal .05 level (2-sided).

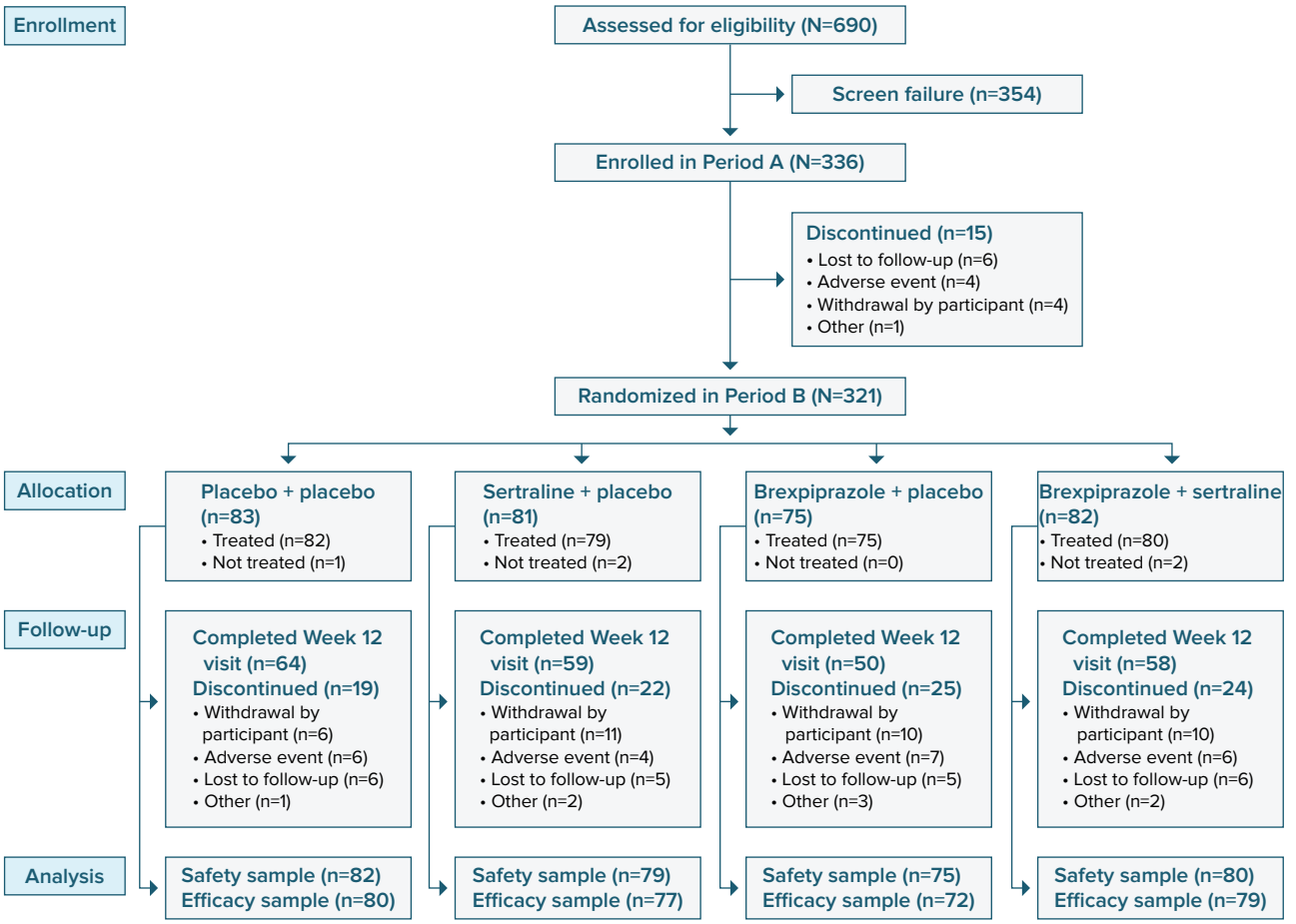
RESULTS

Participants

The trial was conducted between January 26, 2017, and November 12, 2018. Of 336 participants who entered Period A, 321 entered Period B and were randomized to brexpiprazole + sertraline (N = 82), brexpiprazole + placebo (N = 75), sertraline + placebo (N = 81), or placebo + placebo (N = 83) (Figure 1). Period B completion rates were 58/82 (70.7%) for brexpiprazole + sertraline, 50/75 (66.7%) for brexpiprazole + placebo, 59/81 (72.8%) for sertraline + placebo, and 64/83 (77.1%) for placebo + placebo. The most common reasons for discontinuation postrandomization were withdrawal by the participant, lost to follow-up, and adverse event (Figure 1). The safety sample comprised 316 treated participants. The efficacy sample comprised 308 participants; however, 299 patients were included in the primary efficacy analysis since 9 patients who discontinued did not have a CAPS-5 value within the permitted window.

Baseline demographics, clinical characteristics, and treatment history were similar between treatment groups (Table 1). Overall, the randomized sample had a mean (SD) age of 39.2 (11.1) years, 199/321 (62.0%) participants were female, and 197 (61.4%) were White, with a mean (SD) of 6.4 (4.3) years since the index trauma. Psychiatric disorders with incidence >5% by history (MedDRA preferred terms) were major depression (n = 74, 23.1%), insomnia (n = 28, 8.7%), anxiety (n = 17, 5.3%), and depression (n = 17, 5.3%). Overall, 142/321 (44.2%) participants had previously received any

Figure 1.
Participant Disposition



prescription medication for PTSD (Table 1), of whom 78 (24.3%) had previously received an SSRI.

During the placebo run-in period, mean (SD) CAPS-5 total score change from baseline (Day 0) to randomization (Week 1) was −7.7 (9.3) points (n = 308).

By group, the mean dose at each participant's last visit was brexpiprazole 2.2 mg + sertraline 161 mg (n = 80), brexpiprazole 2.1 mg + placebo (n = 75), and sertraline 158 mg + placebo (n = 79).

Efficacy

Primary endpoint. Brexpiprazole + sertraline demonstrated greater improvement vs sertraline + placebo, vs brexpiprazole + placebo, and vs placebo + placebo on the LS mean change in CAPS-5 total score from randomization (Week 1) to Week 10, with treatment differences of −5.08 (95% CI, −8.96 to −1.20; $P = .011$), −4.24 (95% CI, −8.26 to −0.23; $P = .038$), and −5.99 (95% CI, −9.79 to −2.19; $P = .0021$), respectively. Greater improvement ($P < .05$) for brexpiprazole + sertraline vs brexpiprazole + placebo and vs placebo + placebo was observed from Week 6 onwards (Figure 2A). Neither brexpiprazole + placebo nor sertraline + placebo differed from placebo + placebo at Week 10, with treatment differences of −1.74 (95% CI, −5.70 to 2.22; $P = .39$) and −0.91 (95% CI, −4.74 to 2.92; $P = .64$), respectively. Subgroup analyses are presented in Supplementary Figure 2; notably, nonresponse in the placebo run-in period led to greater treatment difference at Week 10. Missing-not-at-random sensitivity analyses indicated that primary endpoint results were robust (Supplementary Table 2).

Other efficacy endpoints. Brexpiprazole + sertraline showed greater improvement ($P < .05$) vs sertraline + placebo on the following efficacy endpoints at Week 10: CAPS-5 Intrusion, Avoidance, and Negative cognitions and mood symptom cluster scores; CGI-S score; PCL-5 total score; HADS Anxiety score; and HADS Depression score (Table 2). Brexpiprazole + sertraline showed greater improvement ($P < .05$) vs brexpiprazole + placebo and vs placebo + placebo on various efficacy endpoints, as presented in Table 2, Figure 2B, and Supplementary Figures 3 and 4.

Table 1.

Baseline Demographics, Clinical Characteristics, and Treatment History

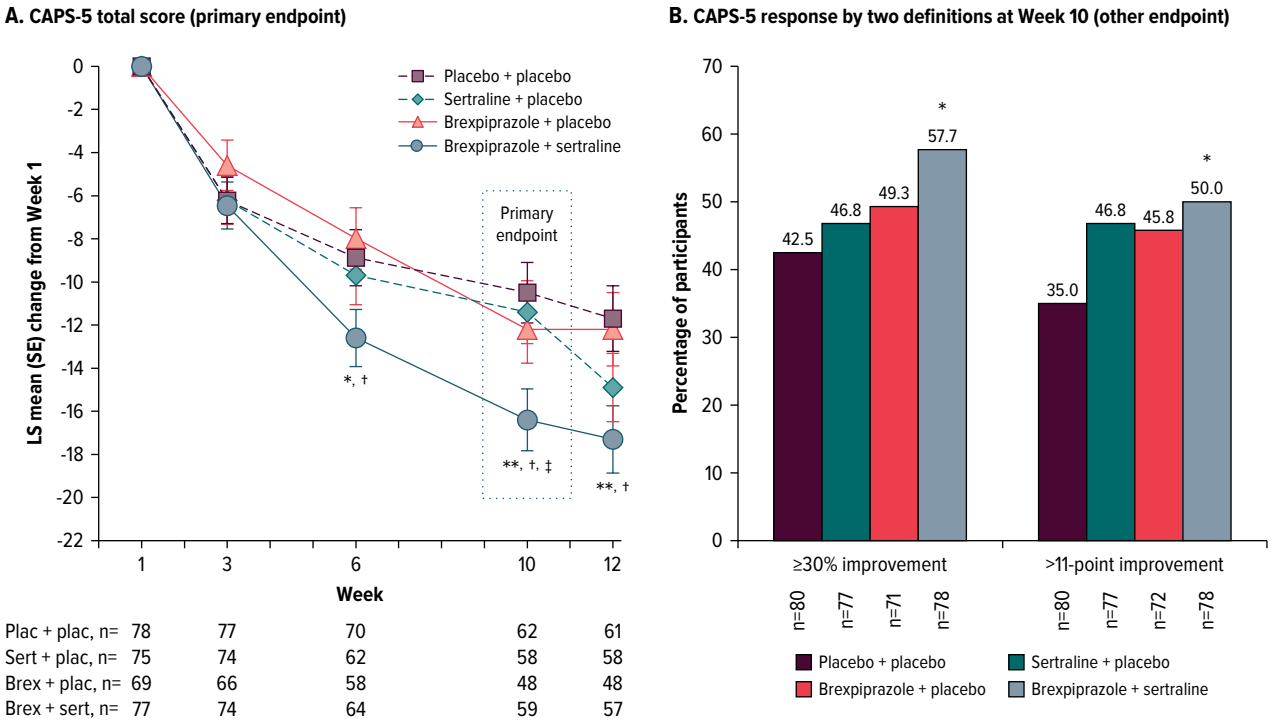
Characteristic[a]	Placebo + placebo	Sertraline + placebo	Brexpiprazole + placebo	Brexpiprazole + sertraline
Demographics (randomized sample)	**(N = 83)**	**(N = 81)**	**(N = 75)**	**(N = 82)**
Age, mean (SD), y	40.3 (11.0)	38.6 (10.9)	39.3 (10.6)	38.4 (11.9)
Age group				
<55 y	71 (85.5)	72 (88.9)	66 (88.0)	71 (86.6)
≥55 y	12 (14.5)	9 (11.1)	9 (12.0)	11 (13.4)
Weight, mean (SD), kg	86.6 (17.6)	87.2 (23.3)	82.9 (22.6)	85.2 (23.8)
BMI, mean (SD), kg/m^2	30.3 (6.1)	30.0 (7.5)	29.8 (7.1)	29.9 (7.0)
Sex				
Female	48 (57.8)	51 (63.0)	49 (65.3)	51 (62.2)
Male	35 (42.2)	30 (37.0)	26 (34.7)	31 (37.8)
Race				
American Indian or Alaska Native	2 (2.4)	0	1 (1.3)	1 (1.2)
Asian	1 (1.2)	0	2 (2.7)	1 (1.2)
Black or African American	26 (31.3)	22 (27.2)	23 (30.7)	21 (25.6)
Native Hawaiian or Other Pacific Islander	0	0	1 (1.3)	1 (1.2)
White	46 (55.4)	53 (65.4)	43 (57.3)	55 (67.1)
Other	8 (9.6)	6 (7.4)	5 (6.7)	3 (3.7)
Ethnicity				
Hispanic or Latino	14 (16.9)	11 (13.6)	11 (14.7)	13 (15.9)
Not Hispanic or Latino	69 (83.1)	70 (86.4)	64 (85.3)	68 (82.9)
Unknown/Other	0	0	0	1 (1.2)
Clinical (randomized sample)	**(N = 83)**	**(N = 81)**	**(N = 75)**	**(N = 82)**
Time since index traumatic event, mean (SD), y	6.9 (4.5)	5.5 (4.1)	6.3 (4.4)[b]	6.8 (4.3)[c]
Time since onset of symptoms, mean (SD), y	6.7 (4.4)	5.5 (4.2)	6.0 (4.3)[b]	6.7 (4.2)
Index traumatic event				
Combat-related	19 (22.9)	16 (19.8)	12 (16.0)	22 (26.8)
Other	64 (77.1)	65 (80.2)	63 (84.0)	60 (73.2)
PTSD treatment history (randomized sample)	**(N = 83)**	**(N = 81)**	**(N = 75)**	**(N = 82)**
Prescription medication for PTSD				
Yes	41 (49.4)	39 (48.1)	26 (34.7)	36 (43.9)
No	42 (50.6)	42 (51.9)	49 (65.3)	46 (56.1)
Psychotherapy for PTSD				
Yes	30 (36.1)	31 (38.3)	27 (36.0)	29 (35.4)
No	53 (63.9)	50 (61.7)	48 (64.0)	53 (64.6)
Any PTSD treatment (prescription medication or psychotherapy)				
Yes	51 (61.4)	46 (56.8)	39 (52.0)	49 (59.8)
No	32 (38.6)	35 (43.2)	36 (48.0)	33 (40.2)
Psychiatric scales at Week 1 (efficacy sample)	**(n = 78)**	**(n = 75)**	**(n = 69)**	**(n = 77)**
CAPS-5 total, mean (SD)	35.1 (10.7)	36.5 (10.2)	33.9 (13.3)	35.7 (11.5)
Intrusion	8.4 (3.9)	8.8 (3.8)	7.9 (4.7)	8.4 (3.4)
Avoidance	4.6 (1.8)	4.7 (1.9)	4.1 (2.0)	4.5 (1.7)
Negative cognitions and mood	12.3 (4.4)	13.1 (5.2)	12.1 (6.1)	13.1 (5.3)
Arousal and reactivity	9.9 (3.4)	10.0 (2.7)	9.7 (3.9)	9.8 (3.7)
CGI-S, mean (SD)	4.4 (0.8)[d]	4.4 (1.0)[e]	4.3 (1.0)[f]	4.4 (0.9)[g]
SOTS total at baseline, mean (SD)	39.6 (9.3)[h]	40.6 (9.6)[i]	40.2 (8.8)[j]	40.8 (9.5)[b]
PCL-5 total, mean (SD)	42.5 (13.2)	44.6 (16.5)	44.2 (16.9)	44.2 (14.7)
HADS Anxiety, mean (SD)	12.5 (3.9)	12.6 (4.4)	12.0 (4.5)[k]	12.6 (4.0)
HADS Depression, mean (SD)	9.0 (3.8)	9.6 (4.4)	9.4 (4.5)[k]	10.3 (4.5)

[a]Values are n (%) unless otherwise described as mean (SD).
[b]n = 74.
[c]n = 81.
[d]n = 80.
[e]n = 77.
[f]n = 72.
[g]n = 78.
[h]n = 75.
[i]n = 70.
[j]n = 67.
[k]n = 68.

Abbreviations: BMI = body mass index, CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, CGI-S = Clinical Global Impression–Severity of illness, HADS = Hospital Anxiety and Depression Scale, PCL-5 = PTSD Checklist for *DSM-5*, PTSD = posttraumatic stress disorder, SOTS = Symptoms of Trauma Scale.

Figure 2.

(A) Change in CAPS-5 Total Score (Primary Endpoint) and (B) CAPS-5 Response Rates[a]



[a]CAPS-5 total score at randomization (Week 1): brexpiprazole + sertraline, 35.7; brexpiprazole + placebo, 33.9; sertraline + placebo, 36.5; placebo + placebo, 35.1. CAPS-5 total score was analyzed with a mixed model for repeated measures. CAPS-5 response was analyzed using last observation carried forward data and the Cochran–Mantel–Haenszel general association test. *P* values are nominal with no adjustment for multiplicity. All analyses were performed in the efficacy sample.
*$P < .05$ vs placebo + placebo. **$P < .01$ vs placebo + placebo. †$P < .05$ vs brexpiprazole + placebo. ‡$P < .05$ vs sertraline + placebo.
Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, PTSD = posttraumatic stress disorder.

Safety

Postrandomization, TEAEs were reported by 230/316 (72.8%) participants overall, with similar incidence between treatment groups (Table 3). TEAEs with incidence ≥10% were weight increased and somnolence for brexpiprazole + sertraline, akathisia for brexpiprazole + placebo, and nausea and dry mouth for sertraline + placebo (details in Table 3). Most TEAEs were mild or moderate in severity. Extrapyramidal-symptom-related TEAEs were reported by 13 (16.3%) participants on brexpiprazole + sertraline, 12 (16.0%) on brexpiprazole + placebo, 11 (13.9%) on sertraline + placebo, and 4 (4.9%) on placebo + placebo. No specific TEAE led to discontinuation in >2 participants in any treatment group. One participant died during the trial, on placebo + placebo, from a bile duct stone.

Mean change in body weight from randomization (Week 1) to each participant's last visit was +1.4 kg for brexpiprazole + sertraline, +0.7 kg for brexpiprazole + placebo, −0.2 kg for sertraline + placebo, and +0.3 kg for placebo + placebo (details in Supplementary Table 3). At last visit, weight gain ≥7% from Week 1 was experienced by 4/80 (5.0%) participants on brexpiprazole + sertraline, 4/75 (5.3%) on brexpiprazole + placebo, 1/79 (1.3%) on sertraline + placebo, and 2/82 (2.4%) on placebo + placebo. The corresponding values for weight loss ≥7% were 1/80 (1.3%), 1/75 (1.3%), 2/79 (2.5%), and 3/82 (3.7%), respectively.

No clinically meaningful differences between treatment groups were observed for changes from baseline to last visit in laboratory test parameters, vital signs, or electrocardiograms, except that triglycerides increased by a greater amount in the 2 sertraline groups (Supplementary Table 3). One participant (1.3%) on sertraline + placebo and 2 participants (2.4%) on placebo + placebo reported TEAEs of suicidal ideation; 1 participant (1.3%) on brexpiprazole + sertraline survived a suicide attempt and withdrew from the trial. C-SSRS findings suggested treatment-emergent suicidal ideation at any visit for 4/80 (5.0%) participants on brexpiprazole + sertraline, 6/75 (8.0%) on brexpiprazole + placebo, 9/79 (11.4%) on sertraline + placebo, and 8/82 (9.8%) on placebo + placebo, and treatment-emergent suicidal behavior at any visit for 1/79 (1.3%) participant on sertraline + placebo (0 in the other treatment groups). Changes in SAS, AIMS, and BARS scores were

Table 2.

Summary of Primary and Other Efficacy Results (Efficacy Sample)

Endpoint	Treatment group	N	Mean (SD) score at Week 1	LS mean (SE) change from Week 1 to Week 10	Treatment difference at Week 10								
					Vs placebo + placebo			Vs brexpiprazole + placebo			Vs sertraline + placebo		
					LS mean (95% CI)	*P* value	ES	LS mean (95% CI)	*P* value	ES	LS mean (95% CI)	*P* value	ES
Clinician-reported[a]													
CAPS-5 total (primary)[b]	Brexpiprazole + sertraline	77	35.7 (11.5)	−16.4 (1.4)	−5.99 (−9.79 to −2.19)	.0021	0.50	−4.24 (−8.26 to −0.23)	.038	0.35	−5.08 (−8.96 to −1.20)	.011	0.42
	Brexpiprazole + placebo	69	33.9 (13.3)	−12.2 (1.6)	−1.74 (−5.70 to 2.22)	.39	0.14	–	–	–	–	–	–
	Sertraline + placebo	75	36.5 (10.2)	−11.4 (1.5)	−0.91 (−4.74 to 2.92)	.64	0.08	–	–	–	–	–	–
	Placebo + placebo	78	35.1 (10.7)	−10.5 (1.4)	–	–	–	–	–	–	–	–	–
Intrusion	Brexpiprazole + sertraline	77	8.4 (3.4)	−4.9 (0.5)	−1.38 (−2.80 to 0.04)	.056	0.31	−0.76 (−2.26 to 0.75)	.32	0.16	−2.06 (−3.51 to −0.60)	.0058	0.45
	Brexpiprazole + placebo	69	7.9 (4.7)	−4.2 (0.6)	−0.63 (−2.11 to 0.86)	.41	0.14	–	–	–	–	–	–
	Sertraline + placebo	75	8.8 (3.8)	−2.9 (0.5)	0.67 (−0.76–2.10)	.36	−0.15	–	–	–	–	–	–
	Placebo + placebo	78	8.4 (3.9)	−3.6 (0.5)	–	–	–	–	–	–	–	–	–
Avoidance	Brexpiprazole + sertraline	77	4.5 (1.7)	−2.1 (0.3)	−0.52 (−1.21 to 0.17)	.14	0.24	−0.76 (−1.49 to −0.02)	.044	0.34	−0.79 (−1.50 to −0.09)	.027	0.36
	Brexpiprazole + placebo	69	4.1 (2.0)	−1.4 (0.3)	0.23 (−0.50–0.96)	.53	−0.10	–	–	–	–	–	–
	Sertraline + placebo	75	4.7 (1.9)	−1.3 (0.3)	0.27 (−0.42–0.97)	.44	−0.12	–	–	–	–	–	–
	Placebo + placebo	78	4.6 (1.8)	−1.6 (0.3)	–	–	–	–	–	–	–	–	–
Negative cognitions and mood	Brexpiprazole + sertraline	77	13.1 (5.3)	−6.1 (0.6)	−2.79 (−4.39 to −1.20)	.0007	0.55	−2.13 (−3.81 to −0.44)	.014	0.41	−1.82 (−3.44 to −0.19)	.029	0.36
	Brexpiprazole + placebo	69	12.1 (6.1)	−4.0 (0.7)	−0.67 (−2.33 to 0.99)	.43	0.13	–	–	–	–	–	–
	Sertraline + placebo	75	13.1 (5.2)	−4.3 (0.6)	−0.98 (−2.58 to 0.63)	.23	0.19	–	–	–	–	–	–
	Placebo + placebo	78	12.3 (4.4)	−3.3 (0.6)	–	–	–	–	–	–	–	–	–
Arousal and reactivity	Brexpiprazole + sertraline	77	9.8 (3.7)	−3.3 (0.4)	−1.19 (−2.30 to −0.07)	.037	0.34	−0.40 (−1.58 to 0.78)	.50	0.11	−0.56 (−1.69 to 0.58)	.33	0.16
	Brexpiprazole + placebo	69	9.7 (3.9)	−2.9 (0.5)	−0.79 (−1.95 to 0.38)	.19	0.22	–	–	–	–	–	–
	Sertraline + placebo	75	10.0 (2.7)	−2.8 (0.4)	−0.63 (−1.75 to 0.49)	.27	0.18	–	–	–	–	–	–
	Placebo + placebo	78	9.9 (3.4)	−2.1 (0.4)	–	–	–	–	–	–	–	–	–
CGI-S[c]	Brexpiprazole + sertraline	78	4.4 (0.9)	−1.4 (0.1)	−0.47 (−0.81 to −0.14)	.0056	0.44	−0.26 (−0.61 to 0.09)	.15	0.24	−0.42 (−0.76 to −0.08)	.017	0.39
	Brexpiprazole + placebo	72	4.3 (1.0)	−1.1 (0.1)	−0.21 (−0.56 to 0.13)	.23	0.20	–	–	–	–	–	–
	Sertraline + placebo	77	4.4 (1.0)	−0.9 (0.1)	−0.06 (−0.39 to 0.28)	.74	0.05	–	–	–	–	–	–
	Placebo + placebo	80	4.4 (0.8)	−0.9 (0.1)	–	–	–	–	–	–	–	–	–
SOTS total[d]	Brexpiprazole + sertraline	74	40.8 (9.5)	−15.2 (1.2)	−2.36 (−5.56 to 0.84)	.15	0.24	−2.46 (−5.86 to 0.94)	.16	0.24	−1.15 (−4.42 to 2.11)	.49	0.12
	Brexpiprazole + placebo	67	40.2 (8.8)	−12.7 (1.4)	0.10 (−3.26–3.46)	.96	−0.01	–	–	–	–	–	–
	Sertraline + placebo	70	40.6 (9.6)	−14.0 (1.3)	−1.21 (−4.44 to 2.02)	.46	0.12	–	–	–	–	–	–
	Placebo + placebo	75	39.6 (9.3)	−12.8 (1.2)	–	–	–	–	–	–	–	–	–
Patient-reported[a]													
PCL-5 total[e]	Brexpiprazole + sertraline	77	44.2 (14.7)	−18.6 (1.8)	−6.01 (−10.8 to −1.21)	.014	0.40	−4.84 (−9.90 to 0.22)	.061	0.31	−4.93 (−9.83 to −0.03)	.049	0.32
	Brexpiprazole + placebo	69	44.2 (16.9)	−13.8 (2.0)	−1.18 (−6.17 to 3.82)	.64	0.08	–	–	–	–	–	–
	Sertraline + placebo	75	44.6 (16.5)	−13.7 (1.8)	−1.08 (−5.91 to 3.74)	.66	0.07	–	–	–	–	–	–
	Placebo + placebo	78	42.5 (13.2)	−12.6 (1.8)	–	–	–	–	–	–	–	–	–
HADS anxiety[f]	Brexpiprazole + sertraline	77	12.6 (4.0)	−4.0 (0.5)	−1.20 (−2.54 to 0.14)	.079	0.28	−2.41 (−3.83 to −0.98)	.0010	0.55	−1.55 (−2.92 to −0.17)	.027	0.36
	Brexpiprazole + placebo	68	12.0 (4.5)	−1.6 (0.6)	1.20 (−0.20–2.61)	.093	−0.28	–	–	–	–	–	–
	Sertraline + placebo	75	12.6 (4.4)	−2.5 (0.5)	0.34 (−1.01–1.70)	.62	−0.08	–	–	–	–	–	–
	Placebo + placebo	78	12.5 (3.9)	−2.8 (0.5)	–	–	–	–	–	–	–	–	–

(continued)

Table 2 (continued).

Endpoint	Treatment group	N	Mean (SD) score at Week 1	LS mean (SE) change from Week 1 to Week 10	Treatment difference at Week 10								
					Vs placebo + placebo			Vs brexpiprazole + placebo			Vs sertraline + placebo		
					LS mean (95% CI)	*P* value	ES	LS mean (95% CI)	*P* value	ES	LS mean (95% CI)	*P* value	ES
HADS depression[f]	Brexpiprazole + sertraline	77	10.3 (4.5)	−3.7 (0.5)	−1.45 (−2.72 to −0.18)	.025	0.36	−1.91 (−3.25 to −0.57)	.0053	0.47	−1.94 (−3.23 to −0.65)	.0033	0.48
	Brexpiprazole + placebo	68	9.4 (4.5)	−1.8 (0.5)	0.46 (−0.86–1.78)	.49	−0.11	–	–	–	–	–	–
	Sertraline + placebo	75	9.6 (4.4)	−1.7 (0.5)	0.49 (−0.78–1.76)	.45	−0.12	–	–	–	–	–	–
	Placebo + placebo	78	9.0 (3.8)	−2.2 (0.5)	–	–	–	–	–	–	–	–	–

Response	Treatment group	N	n (%)	Vs placebo + placebo		Vs brexpiprazole + placebo		Vs sertraline + placebo	
				Response ratio (95% CI)	*P* value	Response ratio (95% CI)	*P* value	Response ratio (95% CI)	*P* value
CAPS-5 ≥30% improvement[g]	Brexpiprazole + sertraline	78	45 (57.7)	1.50 (1.07–2.09)	.015	1.19 (0.87–1.63)	.28	1.31 (0.96–1.80)	.086
	Brexpiprazole + placebo	71	35 (49.3)	1.20 (0.84–1.72)	.32	–	–	–	–
	Sertraline + placebo	77	36 (46.8)	1.14 (0.81–1.59)	.46	–	–	–	–
	Placebo + placebo	80	34 (42.5)	–	–	–	–	–	–
CAPS-5 >11-point improvement[g]	Brexpiprazole + sertraline	78	39 (50.0)	1.56 (1.08–2.26)	.016	1.11 (0.78–1.58)	.55	1.12 (0.80–1.57)	.50
	Brexpiprazole + placebo	72	33 (45.8)	1.33 (0.89–1.99)	.16	–	–	–	–
	Sertraline + placebo	77	36 (46.8)	1.42 (0.97–2.07)	.074	–	–	–	–
	Placebo + placebo	80	28 (35.0)	–	–	–	–	–	–

[a]Mixed model for repeated measures; n-values are for participants with measurements at randomization (Week 1), unless stated otherwise; participants in the efficacy sample were excluded from these analyses if they only had unscheduled postbaseline visits.
[b]CAPS-5 total score ranges from 0 (absent) to 80 (extreme/incapacitating); symptom cluster score ranges are as follows: Intrusion (0–20), Avoidance (0–8); Negative cognitions and mood (0–28); Arousal and reactivity (0–24).[36]
[c]CGI-S score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).[40]
[d]SOTS total score ranges from 12 (absent) to 84 (extreme).[41] SOTS data are presented for baseline (Day 0) and Week 12 (assessments were not made at Week 1 or Week 10); n-values are for participants with measurements at baseline (Day 0).
[e]PCL-5 total score ranges from 0 (not at all) to 80 (extremely).[42]
[f]HADS Anxiety and Depression scores range from 0 (absent) to 21 (maximum severity).[43]
[g]From randomization (Week 1) to Week 10. Last observation carried forward, Cochran–Mantel–Haenszel general association test.
Abbreviations: CAPS-5 = Clinician-Administered PTSD Scale for *DSM-5*, CGI-S = Clinical Global Impression–Severity of illness, ES = Cohen *d* effect size, HADS = Hospital Anxiety and Depression Scale, PCL-5 = PTSD Checklist for *DSM-5*, SOTS = Symptoms of Trauma Scale.

Table 3.

Postrandomization Treatment-Emergent Adverse Events (Week 1 to Week 12) (Safety Sample)

Event, n (%)	Placebo + placebo (N = 82)	Sertraline + placebo (N = 79)	Brexpiprazole + placebo (N = 75)	Brexpiprazole + sertraline (N = 80)
At least 1 TEAE	64 (78.0)	55 (69.6)	53 (70.7)	58 (72.5)
At least 1 potentially drug-related TEAE	47 (57.3)	43 (54.4)	39 (52.0)	44 (55.0)
At least 1 serious TEAE	4 (4.9)[a]	0	1 (1.3)[b]	2 (2.5)[c]
At least 1 severe TEAE	6 (7.3)	3 (3.8)	4 (5.3)	6 (7.5)
Discontinuation due to adverse event	6 (7.3)	4 (5.1)	6 (8.0)	5 (6.3)
Death	1 (1.2)[d]	0	0	0
TEAEs with an incidence ≥5% in any active treatment group and greater than placebo + placebo				
Weight increase	7 (8.5)	1 (1.3)	6 (8.0)	10 (12.5)
Somnolence	7 (8.5)	3 (3.8)	5 (6.7)	8 (10.0)
Appetite decrease	1 (1.2)	1 (1.3)	5 (6.7)	6 (7.5)
Headache	7 (8.5)	7 (8.9)	4 (5.3)	6 (7.5)
Akathisia	2 (2.4)	3 (3.8)	10 (13.3)	5 (6.3)
Diarrhea	5 (6.1)	7 (8.9)	3 (4.0)	5 (6.3)
Dry mouth	7 (8.5)	10 (12.7)	6 (8.0)	5 (6.3)
Anorgasmia	0	1 (1.3)	1 (1.3)	4 (5.0)
Ejaculation delayed	0	1 (1.3)	0	4 (5.0)
Contact dermatitis	1 (1.2)	1 (1.3)	0	4 (5.0)
Constipation	4 (4.9)	4 (5.1)	2 (2.7)	4 (5.0)
Nausea	4 (4.9)	16 (20.3)	1 (1.3)	4 (5.0)
URTI	7 (8.5)	7 (8.9)	7 (9.3)	3 (3.8)
Sedation	0	0	5 (6.7)	3 (3.8)
Anxiety	4 (4.9)	0	4 (5.3)	3 (3.8)
Irritability	3 (3.7)	4 (5.1)	1 (1.3)	3 (3.8)
Insomnia	3 (3.7)	4 (5.1)	5 (6.7)	2 (2.5)
Dizziness	5 (6.1)	5 (6.3)	2 (2.7)	2 (2.5)
Fatigue	0	4 (5.1)	6 (8.0)	2 (2.5)
Vomiting	0	4 (5.1)	0	1 (1.3)
Other TEAEs of interest				
Agitation	0	2 (2.5)	3 (4.0)	2 (2.5)
Restlessness	0	1 (1.3)	2 (2.7)	2 (2.5)
Hypersomnia	0	1 (1.3)	1 (1.3)	1 (1.3)
Orthostatic hypotension	0	0	0	0

[a]Back pain, bile duct stone, chest pain, and osteonecrosis.
[b]Animal bite.
[c]Back pain and suicide attempt.
[d]Bile duct stone.
Abbreviations: TEAE = treatment-emergent adverse event, URTI = upper respiratory tract infection.

minimal in all treatment groups (Supplementary Table 3).

DISCUSSION

In this randomized clinical trial, brexpiprazole and sertraline combination treatment improved the symptoms of PTSD vs sertraline + placebo, vs brexpiprazole + placebo, and vs placebo + placebo on the primary efficacy endpoint of change in CAPS-5 total score at Week 10. Although this trial had no prespecified adjustment for multiplicity, the statistical significance of brexpiprazole + sertraline vs sertraline + placebo ($P = .011$ for primary endpoint) was indicated by 3 retrospective procedures to adjust for multiplicity: Bonferroni (tested at 0.0167 level), Holm step-down (0.025 level), and Hochberg step-up (0.025 level). Other efficacy endpoints were generally supportive of the primary efficacy endpoint, with brexpiprazole + sertraline showing improvement vs sertraline + placebo on overall symptoms (clinician-reported CGI-S and patient-reported PCL-5), 3 of 4 PTSD symptom clusters, and anxious and depressive symptoms (HADS). In contrast, there was no efficacy signal in the brexpiprazole + placebo or sertraline + placebo arms. Sertraline has been extensively studied in PTSD, and, while a number of randomized clinical trials support its efficacy on overall PTSD symptoms,[48–51] several did not demonstrate significant efficacy vs placebo,[52–55] meaning that the lack of efficacy for sertraline + placebo in the present trial is not unanticipated.

There were no unexpected safety events with brexpiprazole and sertraline combination treatment in the present trial, and the safety profile of brexpiprazole was comparable to that in approved indications.[56–62] Weight increase was highest in the brexpiprazole + sertraline group (+1.4 kg; reported as a TEAE by 12.5%); moderate weight gain has been noted with brexpiprazole in other indications.[56,57] Akathisia, a concern with some antipsychotics,[63] was reported as a TEAE by 6.3% on brexpiprazole + sertraline and 13.3% on brexpiprazole + placebo but was not identified by objective rating scales. The incidence of somnolence was comparable for brexpiprazole + sertraline (10.0%) and placebo + placebo (8.5%). Sertraline + placebo was associated with nausea (20.3%) and dry mouth (12.7%); these are known side effects of sertraline treatment.[64] There were no clinically meaningful changes in metabolic parameters or prolactin across groups, in line with brexpiprazole in other indications.[56–60,65] Rates of discontinuation due to adverse events were similar between active treatment groups (5.1–8.0%) and placebo (7.3%) (indicating that most participants tolerated treatment) and were slightly lower than in prior 10–12-week randomized clinical trials of sertraline in PTSD (9.8% in a meta-analysis).[15]

Brexpiprazole and sertraline combination treatment may improve PTSD symptoms via synergistic activity in the amygdala. In PTSD, high noradrenaline levels can increase fear response via overactivation of α_1 receptors in the amygdala, while low serotonin levels can prevent regulation of amygdala activity.[21,66–68] With combination treatment, sertraline may increase serotonin levels to help regulate amygdala activity,[69–71] while brexpiprazole acts via blockade of α_1 and 5-HT_{2A} receptors and partial agonism of serotonin 5-HT_{1A} and D_2 receptors to help to normalize fear processing.[20,72]

A strength of this trial is the use of a blinded placebo run-in period to reduce the bias (placebo response) that can occur when participants enter a clinical trial (reflected by a mean 7.7-point CAPS-5 total score improvement during Period A), thereby allowing for a more accurate assessment of the efficacy in the randomized period.[73] Other strengths are the full-factorial design with an active reference, the exclusion of patients with a current major depressive episode, and the concurrent use of clinician- and patient-reported outcomes. This trial also demonstrated the value of blinding the timing of the primary efficacy endpoint, since brexpiprazole + sertraline had $P < .05$ vs sertraline + placebo at Week 10 but not at Week 12 (attributed to an end-of-trial improvement in the sertraline + placebo group, rather than a loss of improvement in the brexpiprazole + sertraline group).

Limitations include the lack of prespecified adjustment for multiplicity (addressed retrospectively) and the lack of efficacy in the sertraline + placebo assay sensitivity arm. Both brexpiprazole and sertraline were flexibly dosed, which reflects clinical practice but may limit conclusions in the combination treatment arm. Participant selection criteria and restrictions surrounding concomitant medications and comorbidities mean that results may not be generalizable to a broader patient population. An established CAPS-5 meaningful within-patient change threshold is needed to help interpret clinical relevance.

In conclusion, this clinical trial suggests that brexpiprazole in combination with sertraline (but not as monotherapy) has the potential to be a new efficacious treatment for PTSD. Improvement was shown on overall PTSD symptoms, as well as anxious and depressive symptoms. No new safety signals were identified for brexpiprazole, and rates of discontinuation due to adverse events suggested that brexpiprazole and sertraline combination treatment was tolerated by most participants. Results of this trial need to be replicated, and a larger trial has recently provided further evidence for the efficacy and tolerability of brexpiprazole in combination with sertraline in PTSD.[74]

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Brexpiprazole in Combination with Sertraline and as Monotherapy in Posttraumatic Stress Disorder: A Full-Factorial Randomized Clinical Trial

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eMethods. Statistical Analysis

Efficacy was analyzed in a modified intention-to-treat sample, comprising all randomized participants who took at least one dose of trial drug, and had a randomization (Week 1) and at least one post-randomization CAPS-5 total score measurement. All continuous efficacy endpoints, including the primary endpoint, were analyzed using separate MMRMs, with an unstructured variance–covariance structure and with score change from randomization (Week 1) as the dependent variable. The model for the fixed effects included terms of treatment, site, type of trauma (combat-related: yes/no), visit, an interaction term of treatment by visit, and the interaction term of Week 1 score by visit as a covariate. Small sites that did not have ≥1 evaluable participant in each treatment arm and each type of trauma (combat-related: yes/no) in Period B were pooled to form collected sites for the purpose of analysis. The model included all scheduled visits from Week 1 to Week 12. The contrast (i.e., least squares mean difference between specified pairs of treatment groups) at the Week 10 visit was estimated from the interaction term and served as the primary treatment comparison. The point estimate and 95% confidence interval estimate of the contrast at Week 10 are reported. CAPS-5 response was analyzed in a last observation carried forward dataset using the Cochran–Mantel–Haenszel general association test controlling for trial center and type of trauma (combat-related: yes/no).

A planned sample size of 68 participants per arm was estimated to achieve 80% power at a two-sided alpha level of 0.05 to detect a treatment difference of -6.5 points (standard deviation, 13) in CAPS-5 total score change from randomization (Week 1) to Week 10. Adjusting for 10% non-evaluable participants, the total number of participants to be randomized was 75 per arm. Further adjusting for 10% dropout between baseline and randomization, approximately 332 participants were planned to be enrolled in the trial.

A hierarchical testing procedure that was planned in the protocol was removed from the final statistical analysis plan and not performed.

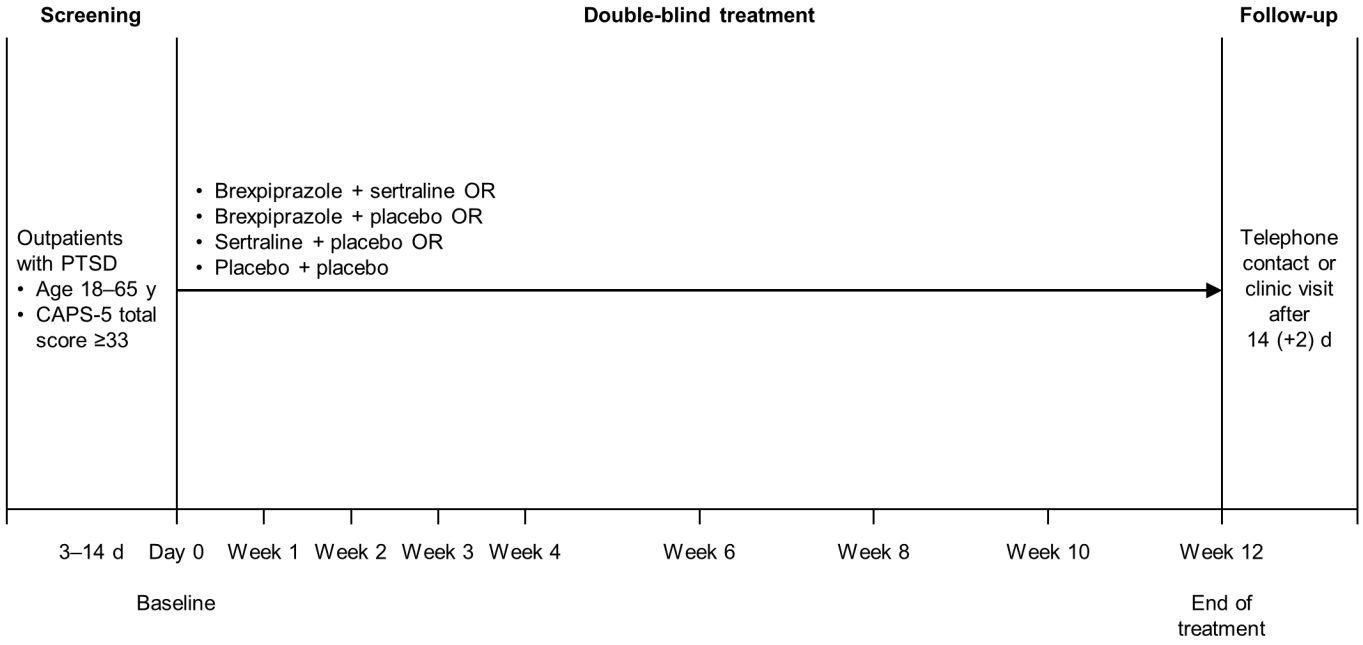
In Period A, CAPS-5 total score change is presented using descriptive statistics.

Safety was analyzed in a sample comprising all randomized participants who took at least one dose of trial drug. Safety results are presented using descriptive statistics.

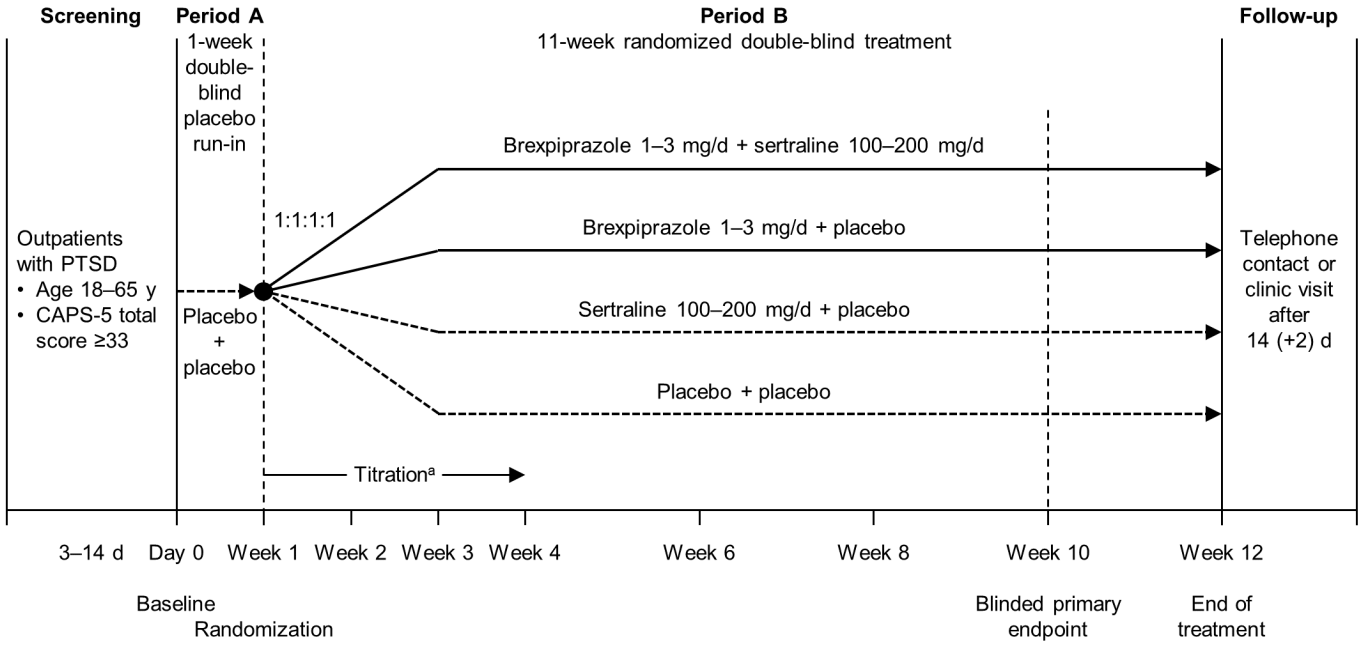
All analyses were performed using SAS version 9.4 (SAS Institute Inc; Cary, NC).

Supplementary Figure 1. Trial Design

A. Blinded design



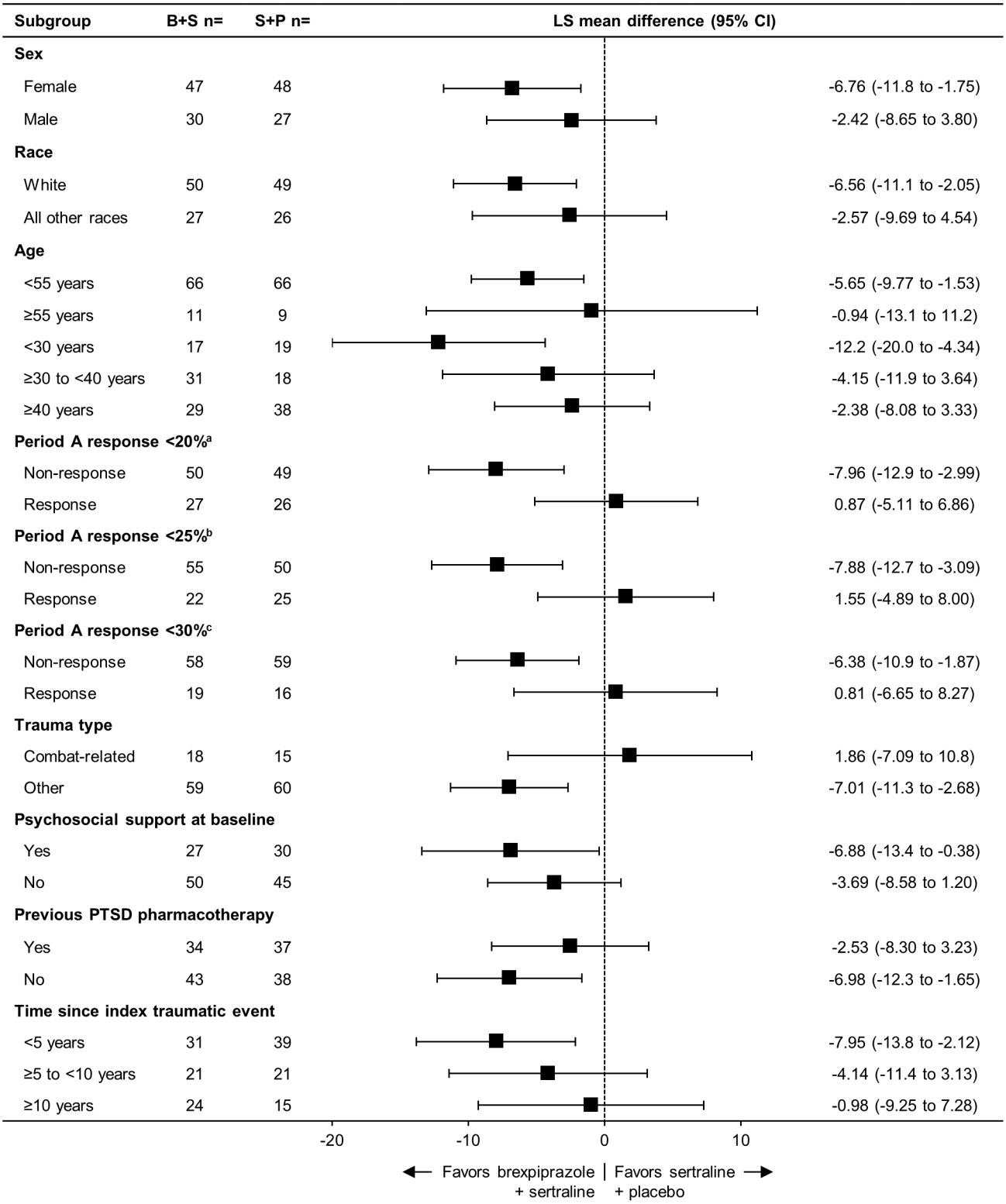
B. Unblinded design



[a]Brexpiprazole: Week 1, 0.5 mg/d; Week 2, 1 mg/d; Week 3, 2 mg/d. At Week 4, based on efficacy and tolerability, options were to stay at 2 mg/d, increase to 3 mg/d, or decrease to 1 mg/d. Dose decreases (to a minimum of 1 mg/d) were permitted until Week 6. Sertraline: Week 1, 50 mg/d; Week 2, 100 mg/d; Week 3, 150 mg/d. At Week 4, based on efficacy and tolerability, options were to stay at 150 mg/d, increase to 200 mg/d, or decrease to 100 mg/d. Dose decreases (to a minimum of 100 mg/d) were permitted until Week 6. Participants in the brexpiprazole + sertraline arm who required a dose increase/decrease had the doses changed for both drugs.

Abbreviations: CAPS-5=Clinician-Administered PTSD Scale for DSM-5; PTSD=post-traumatic stress disorder.

Supplementary Figure 2. Change in CAPS-5 Total Score From Randomization (Week 1) to Week 10 by Subgroup, For Brexpiprazole + Sertraline Vs Sertraline + Placebo (Efficacy Sample)



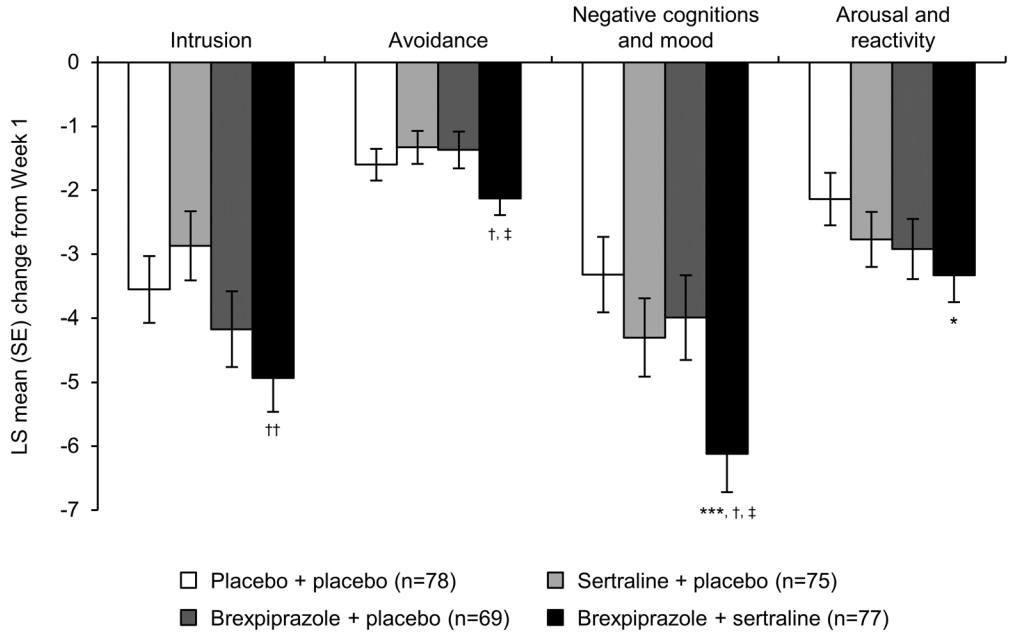
[a]<20% improvement during Period A (placebo run-in) and CAPS-5 total score ≥27 at randomization (Week 1).

[b]<25% improvement during Period A (placebo run-in) and CAPS-5 total score ≥27 at randomization (Week 1).

[c]<30% improvement during Period A (placebo run-in) and CAPS-5 total score ≥27 at randomization (Week 1).

Abbreviations: B+S=brexpiprazole + sertraline; CAPS-5=Clinician-Administered PTSD Scale for DSM-5; PTSD=post-traumatic stress disorder; S+P=sertraline + placebo. N-values are for participants with measurements at randomization (Week 1).

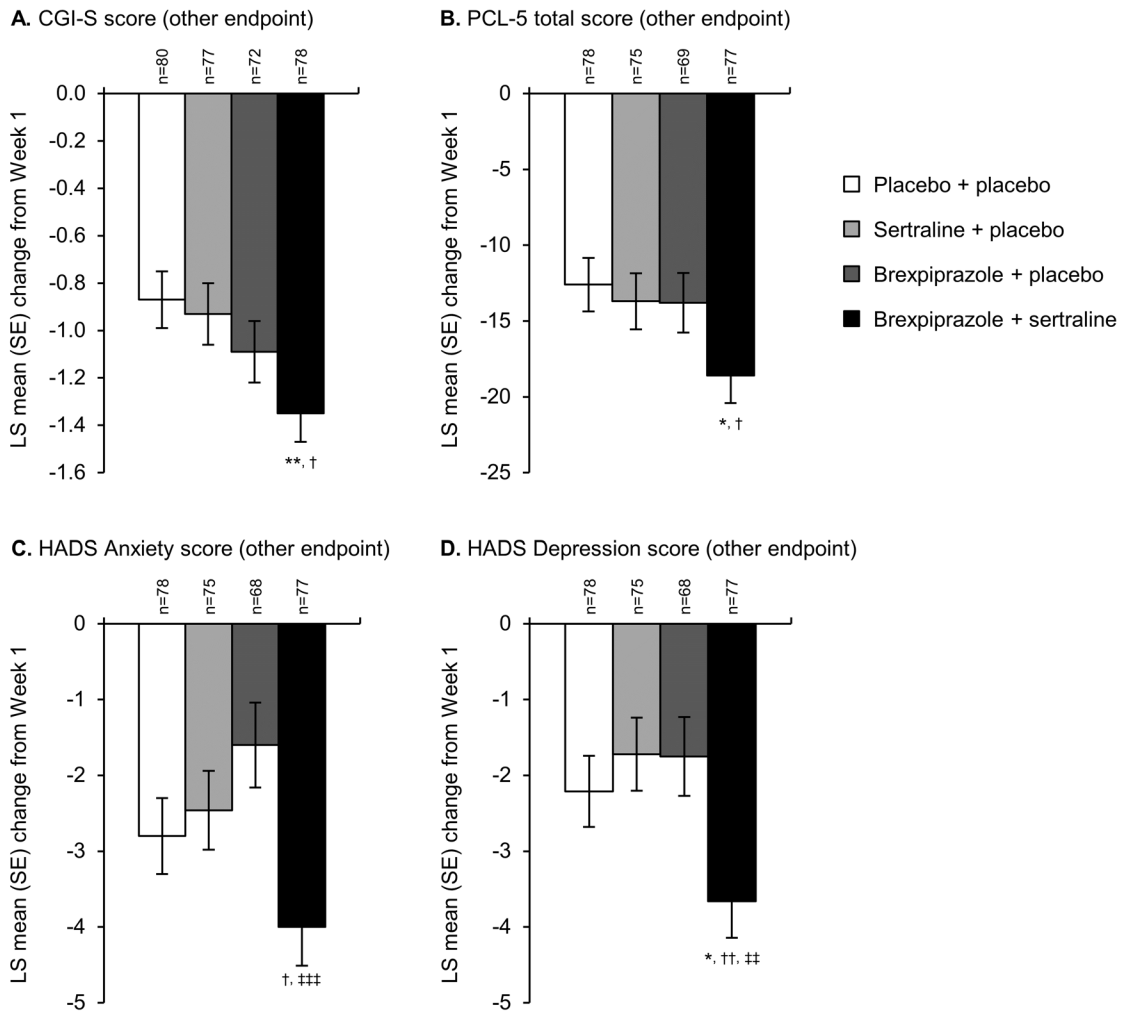
Supplementary Figure 3. Change in CAPS-5 Symptom Cluster Scores From Randomization (Week 1) to Week 10



*P<.05, ***P<.001 vs placebo + placebo; †P<.05, ††P<.01 vs sertraline + placebo; ‡P<.05 vs brexpiprazole + placebo (nominal P values with no adjustment for multiplicity); mixed model for repeated measures; efficacy sample.

Abbreviations: CAPS-5=Clinician-Administered PTSD Scale for DSM-5; PTSD=post-traumatic stress disorder. N-values are for participants with measurements at randomization (Week 1).

Supplementary Figure 4. Change in CGI-S, PCL-5 Total, HADS Anxiety, and HADS Depression Scores From Randomization (Week 1) to Week 10



*P<.05, **P<.01 vs placebo + placebo; †P<.05, ††P<.01 vs sertraline + placebo; ‡‡P<.01, ‡‡‡P=.001 vs brexpiprazole + placebo (nominal P values with no adjustment for multiplicity); mixed model for repeated measures; efficacy sample.

Abbreviations: CGI-S=Clinical Global Impression – Severity of illness; HADS=Hospital Anxiety and Depression Scale; PCL-5=PTSD Checklist for DSM-5; PTSD=post-traumatic stress disorder. N-values are for participants with measurements at randomization (Week 1).

Supplementary Table 1. List of Principal Investigators and Trial Sites

Site #	Principal Investigator Name	Address	# Screened	# Enrolled	# Discon-tinued
001	Sarah D Atkinson	Finger Lakes Clinical Research, 885 South Winton Road, Rochester, NY 14618-1609	14	11	3
002	Michael D Banov	Northwest Behavioral Research Center, 11755 Pointe Pl, Suite A-1, Roswell, GA 30076-4657	15	11	4
003	Ronald Loewy Brenner	Neurobehavioral Research, Inc., 74 Carman Avenue, Cedarhurst, NY 11516	23	14	3
004	Armen K Goenjian	Collaborative Neuroscience Network, Inc, 19401 S. Vermont Ave, Suite F-100, Torrance, CA 90502-4432	19	8	0
005	Lee Ann Kelley	Noesis Pharma Research, 16601 N 40th St, Suite 101, Phoenix, AZ 85032	3	1	0
006	Louise M Thurman	IPS Research Company, 1111 North Lee Avenue, Suite 400, Oklahoma City, OK 73103	31	3	1
007	Benny L Barnhart	Grayline Clinical Drug Trials, 3300 Seymour Highway, Wichita Falls, TX 76309	16	9	1
008	David Purselle	iResearch Atlanta, LLC, 125 Clairemont Avenue, Suite 470, Decatur, GA 30030	25	11	6
009	Howard R Hassman	Hassman Research Institute, 175 Cross Keys Rd, Bldg 300B, Berlin, NJ 08009	12	8	2
010	Rishi Kakar	Innovative Clinical Research, Inc., 7481 W Oakland Park Blvd, Suite 205, Lauderhill, FL 33319	11	4	1
013	Vishaal Mehra	Artemis Institute for Clinical Research, LLC, 770 Washington St, Suite 300, San Diego, CA 92103	19	7	2
014	Sejal Patel	Compass Research North, LLC, 100 West Gore Street, Suite 202, Orlando, FL 32806	10	4	1
016	James J Whalen	Lincoln Research, 640 George Washington Hwy, Bldg C, Suite 202, Lincoln, RI 02865-4207	5	1	0
017	Sherry A Soefje	Excell Research, Inc., 3998 Vista Way, Suite 100, Oceanside, CA 92056	22	15	4
018	Nandita Joshi (Jones)	Clinical Neuroscience Solutions, P.A., 5200 Belfort Rd, Suite 420, Jacksonville, FL 32256	18	8	3
019	Anita S Varma	Research Strategies of Memphis, LLC, 5395 Estate Office Park Dr, Suite 2, Memphis, TN 38119	2	1	0
020	Nick G Vatakis	Social Psychiatry Research Institute (SPRI), 3044 Coney Island Ave, Suite 201, Brooklyn, NY 11235	8	6	1

Site #	Principal Investigator Name	Address	# Screened	# Enrolled	# Discon-tinued
021	Kelly Yokum	Olympian Clinical Research, 2919 W Swann Ave, Suite 205, Tampa, FL 33609-4038	10	4	4
022	Daniel Francis Chueh	Neuropsychiatric Research Center of Orange County, 1010 W Chapman Ave, Orange, CA 92868-2847	15	9	3
023	Andrew J Cutler	Meridien Research, 8043 Cooper Creek Blvd, Suite 107, Bradenton, FL 34201-2142	17	4	1
025	Valerie K Arnold	Clinical Neuroscience Solutions, P.A., 1340 Poplar Ave, Suite 420, Memphis, TN 38119	13	5	2
026	Courtney D Nixon	Paradigm Research Professionals, 5400 N Classen Blvd, Suite 110, Oklahoma City, OK 73118	8	4	0
027	Michael Liebowitz	The Medical Research Network, LLC, 134 East 93rd Street, Suite 201A, New York, NY 10128-1704	9	5	1
028	Andrew C Sedillo	MCB Clinical, 110 S Parkside Dr, Colorado Springs, CO 80910	24	12	5
029	Angelo Sambunaris	The Institute for Advance Medical Research, 3015 Flowers Road South, Atlanta, GA 30341	3	2	2
030	Beal G Essink	Oregon Center for Clinical Investigations, Inc., 905 SE 14th Ave, Portland, OR 97214	20	15	4
031	Drissana Tran	Oregon Center for Clinical Investigations, Inc., 702 Church St. NE, Salem, OR 97301-2404	27	22	3
032	Diane M Highum	CiTrials, 17800 Woodruff Ave, Suite B, Bellflower, CA 90706	54	32	6
033	Robert Molpus	Clinical Neuroscience Solutions, P.A., Dba CNS Healthcare, 618 E South St, Suite 100, Orlando, FL32801-2987	23	11	2
034	Don Anderson	Anderson Clinical Research, 2068 Orange Tree Lane, Suite 226, Redlands, CA 92374	5	5	1
035	Jeffrey Apter	Global Medical Institute, LLC, Woodlands Professional Building, 256 Bunn Dr, Suite 6, Princeton, CA 08540	19	11	3
036	Jim G Aukstuolis	Woodland International Research Group, 910 Autumn Road, Suite 3, Little Rock, AR 72211	13	4	0
037	Daniel Gruener	St. Louis Clinical Trials LLC, 10330 Old Olive Road, St. Louis, MO 63118	6	2	0
038	Jelena A Kunovac	Altea Research Institute, 3012 W Charleston Blvd, Suite 100, Las Vegas, NV 89102-1972	35	16	5
039	Fayz Hudefi	Woodland Research Northwest, LLC, 609 E Dyke Rd, Rogers, AZ 72758-0132	17	8	4

Site #	Principal Investigator Name	Address	# Screened	# Enrolled	# Discon-tinued
040	Jesse M Carr	Behavioral Research Specialists, LLC, 230 N. Maryland Avenue, Suite 207, Glendale, CA 91206	14	8	1
041	Stacey Layle	Artemis Institute for Clinical Research, LLC, 365 S Rancho Santa Fe Rd, Suite 202, San Marcos, CA 92078-2338	6	2	1
042	Richard Weisler	Richard H. Weisler, MD, PA, 700 Spring Forest Rd, Suite 125, Raleigh, NC 27609-9148	19	8	0
043	Jason Clay Miller	Clinical Trials of Texas, Inc., 7940 Floyd Curl Drive, Suite 700, San Antonio, TX 78229	15	2	0
045	Steven Szabo	Duke University Medical Center, 40 Duke Medicine Circle, Durham, NC 27710	5	2	0
046	Patricia Pilkinton	Tuscaloosa VA Medical Center, 3701 Loop Rd, Tuscaloosa, AL 35404-5015	5	1	1
051	Zaheer Aslam	Gulf Coast Clinical Research Center, 6150 Diamon Centre Court, Suite 500, Fort Myers, FL 33912	6	6	1
052	James Alan Knutson	Management Core Clinical Research, 2918 Colby Avenue, Suite 101, Everett, WA 98201	14	6	5
053	Brock H Summers	Southern California Research, LLC, 436 N. Roxbury Dr, Suite 222, Beverly Hills, CA 90210	3	2	1
054	Paul E Wylie	Preferred Research Partners, 11219 Financial Centre Pkwy, Suite 320, Little Rock, AR 72211-3800	3	2	1
055	Shivkumar Hatti	Suburban Research Associates, 107 Chesley Drive, Unit 4, Media, PA 19063	4	2	1
057	Gerald Maguire	CITrials, Inc. – Riverside & San Bernardino County, 5700 Division Street, Suite 101, Riverside, CA 92506	2	1	0

Supplementary Table 2. CAPS-5 Total Score Sensitivity Analysis – MNAR Using Pattern Mixture Model With Multiple Imputation – Assume All Dropouts as MNAR (Efficacy Sample)

Shifted from the MAR[a]	Treatment difference		
	Comparison	Difference (95% CI)[b]	*P* value[b]
0	Brex + sert vs placebo + placebo	-6.32 (-10.0 to -2.61)	.001
	Brex + sert vs sert + placebo	-5.46 (-9.26 to -1.67)	.005
	Brex + sert vs brex + placebo	-4.55 (-8.49 to -0.607)	.02
	Brex + placebo vs placebo + placebo	-1.78 (-5.71 to 2.16)	.38
	Sert + placebo vs placebo + placebo	-0.861 (-4.69 to 2.96)	.66
0.65	Brex + sert vs placebo + placebo	-6.19 (-9.91 to -2.47)	.001
	Brex + sert vs sert + placebo	-5.33 (-9.13 to -1.54)	.006
	Brex + sert vs brex + placebo	-4.41 (-8.35 to -0.472)	.03
	Brex + placebo vs placebo + placebo	-1.78 (-5.71 to 2.15)	.37
	Sert + placebo vs placebo + placebo	-0.858 (-4.68 to 2.97)	.66
1.3	Brex + sert vs placebo + placebo	-6.06 (-9.77 to -2.34)	.001
	Brex + sert vs sert + placebo	-5.20 (-8.99 to -1.41)	.007
	Brex + sert vs brex + placebo	-4.27 (-8.21 to -0.336)	.03
	Brex + placebo vs placebo + placebo	-1.78 (-5.71 to 2.15)	.37
	Sert + placebo vs placebo + placebo	-0.855 (-4.68 to 2.97)	.66
1.95	Brex + sert vs placebo + placebo	-5.92 (-9.64 to -2.21)	.002
	Brex + sert vs sert + placebo	-5.07 (-8.86 to -1.28)	.009
	Brex + sert vs brex + placebo	-4.14 (-8.08 to -0.200)	.04
	Brex + placebo vs placebo + placebo	-1.78 (-5.71 to 2.15)	.37
	Sert + placebo vs placebo + placebo	-0.852 (-4.67 to 2.97)	.66
2.6	Brex + sert vs placebo + placebo	-5.79 (-9.51 to -2.07)	.002
	Brex + sert vs sert + placebo	-4.94 (-8.73 to -1.15)	.01
	Brex + sert vs brex + placebo	-4.00 (-7.94 to -0.064)	.05
	Brex + placebo vs placebo + placebo	-1.79 (-5.72 to 2.15)	.37
	Sert + placebo vs placebo + placebo	-0.849 (-4.67 to 2.97)	.66
3.25	Brex + sert vs placebo + placebo	-5.65 (-9.37 to -1.94)	.003
	Brex + sert vs sert + placebo	-4.81 (-8.60 to -1.01)	.01
	Brex + sert vs brex + placebo	-3.87 (-7.81 to 0.073)	.05
	Brex + placebo vs placebo + placebo	-1.79 (-5.72 to 2.14)	.37
	Sert + placebo vs placebo + placebo	-0.846 (-4.67 to 2.98)	.66
3.9	Brex + sert vs placebo + placebo	-5.52 (-9.24 to -1.80)	.004

Shifted from the MAR[a]	Treatment difference		
	Comparison	Difference (95% CI)[b]	*P* value[b]
	Brex + sert vs sert + placebo	-4.68 (-8.47 to -0.883)	.02
	Brex + sert vs brex + placebo	-3.73 (-7.67 to 0.211)	.06
	Brex + placebo vs placebo + placebo	-1.79 (-5.72 to 2.14)	.37
	Sert + placebo vs placebo + placebo	-0.843 (-4.67 to 2.98)	.67
4.55	Brex + sert vs placebo + placebo	-5.39 (-9.11 to -1.67)	.005
	Brex + sert vs sert + placebo	-4.55 (-8.34 to -0.750)	.02
	Brex + sert vs brex + placebo	-3.59 (-7.54 to 0.349)	.07
	Brex + placebo vs placebo + placebo	-1.79 (-5.73 to 2.14)	.37
	Sert + placebo vs placebo + placebo	-0.840 (-4.67 to 2.99)	.67
5.2	Brex + sert vs placebo + placebo	-5.25 (-8.98 to -1.53)	.006
	Brex + sert vs sert + placebo	-4.41 (-8.21 to -0.616)	.02
	Brex + sert vs brex + placebo	-3.46 (-7.40 to 0.487)	.09
	Brex + placebo vs placebo + placebo	-1.79 (-5.73 to 2.14)	.37
	Sert + placebo vs placebo + placebo	-0.837 (-4.67 to 2.99)	.67
5.85	Brex + sert vs placebo + placebo	-5.12 (-8.84 to -1.39)	.007
	Brex + sert vs sert + placebo	-4.28 (-8.08 to -0.483)	.03
	Brex + sert vs brex + placebo	-3.32 (-7.27 to 0.626)	.10
	Brex + placebo vs placebo + placebo	-1.80 (-5.74 to 2.14)	.37
	Sert + placebo vs placebo + placebo	-0.834 (-4.67 to 3.00)	.67
6.5	Brex + sert vs placebo + placebo	-4.98 (-8.71 to -1.25)	.009
	Brex + sert vs sert + placebo	-4.15 (-7.96 to -0.348)	.03
	Brex + sert vs brex + placebo	-3.19 (-7.14 to 0.766)	.11
	Brex + placebo vs placebo + placebo	-1.80 (-5.74 to 2.14)	.37
	Sert + placebo vs placebo + placebo	-0.831 (-4.67 to 3.00)	.67
7.15	Brex + sert vs placebo + placebo	-4.85 (-8.58 to -1.12)	.01
	Brex + sert vs sert + placebo	-4.02 (-7.83 to -0.213)	.04
	Brex + sert vs brex + placebo	-3.05 (-7.00 to 0.906)	.13
	Brex + placebo vs placebo + placebo	-1.80 (-5.75 to 2.15)	.37
	Sert + placebo vs placebo + placebo	-0.828 (-4.67 to 3.01)	.67
7.8	Brex + sert vs placebo + placebo	-4.72 (-8.45 to -0.979)	.01
	Brex + sert vs sert + placebo	-3.89 (-7.70 to -0.078)	.05
	Brex + sert vs brex + placebo	-2.91 (-6.87 to 1.05)	.15
	Brex + placebo vs placebo + placebo	-1.80 (-5.75 to 2.15)	.37
	Sert + placebo vs placebo + placebo	-0.825 (-4.67 to 3.02)	.67

Shifted from the MAR[a]	Treatment difference		
	Comparison	Difference (95% CI)[b]	*P* value[b]
8.45	Brex + sert vs placebo + placebo	-4.58 (-8.32 to -0.840)	.02
	Brex + sert vs sert + placebo	-3.76 (-7.58 to 0.058)	.05
	Brex + sert vs brex + placebo	-2.78 (-6.74 to 1.19)	.17
	Brex + placebo vs placebo + placebo	-1.81 (-5.76 to 2.15)	.37
	Sert + placebo vs placebo + placebo	-0.822 (-4.67 to 3.02)	.68

[a]Analysis departs from MAR assumption by progressively increasing the delta (treatment effect) until the conclusion from the primary analysis is overturned. When delta is 0 the missing data are assumed to be MAR; when delta is >0 the missing data are assumed to be MNAR.

[b]Derived based on 100 imputations.

Abbreviations: CAPS-5=Clinician-Administered PTSD Scale for DSM-5; MAR=missing at random; MNAR=missing not at random.

Supplementary Table 3. Body Weight, Metabolic Parameters, Vital Signs, QT Interval, and Extrapyramidal symptoms (Safety Sample)

Endpoint[a]	Placebo + placebo		Sertraline + placebo		Brexpiprazole + placebo		Brexpiprazole + sertraline	
	Baseline (Day 0)	Change to last visit	Baseline (Day 0)	Change to last visit	Baseline (Day 0)	Change to last visit	Baseline (Day 0)	Change to last visit
Body weight, kg	86.7 (17.7) (n=82)[b]	0.3 (3.4) (n=82)	87.4 (23.2) (n=79)[b]	-0.2 (2.8) (n=79)	83.2 (22.7) (n=75)[b]	0.7 (2.8) (n=75)	85.6 (24.2) (n=80)[b]	1.4 (2.6) (n=80)
BMI, kg/m^2	30.3 (6.1) (n=82)[b]	0.1 (1.2) (n=82)	30.1 (7.5) (n=79)[b]	-0.1 (0.9) (n=79)	29.8 (7.1) (n=75)[b]	0.3 (1.0) (n=75)	30.0 (7.1) (n=80)[b]	0.5 (0.9) (n=80)
Fasting metabolic parameters, mg/dL								
Glucose	90.3 (10.0) (n=79)	0.7 (13.6) (n=71)	90.9 (14.1) (n=79)	1.4 (15.4) (n=70)	91.1 (9.8) (n=74)	1.3 (15.8) (n=62)	92.0 (12.7) (n=80)	-1.7 (15.5) (n=71)
HDL cholesterol	55.9 (14.3) (n=51)	0.9 (11.2) (n=45)	57.1 (17.9) (n=55)	0.5 (9.4) (n=50)	60.0 (18.3) (n=49)	-0.5 (10.0) (n=40)	53.2 (13.4) (n=45)	1.5 (5.8) (n=39)
LDL cholesterol	109.3 (33.2) (n=50)	2.6 (20.9) (n=44)	101.6 (31.1) (n=55)	0.5 (25.9) (n=49)	108.1 (35.6) (n=49)	-6.9 (15.8) (n=40)	108.2 (40.9) (n=45)	1.6 (19.2) (n=39)
Total cholesterol	187.6 (37.0) (n=79)	-1.7 (27.5) (n=71)	183.3 (41.8) (n=79)	7.8 (30.8) (n=70)	187.2 (41.0) (n=74)	-3.8 (20.0) (n=62)	188.3 (42.1) (n=80)	6.2 (26.6) (n=71)
Triglycerides	137.7 (116.1) (n=79)	-3.1 (93.4) (n=71)	136.3 (110.3) (n=79)	10.5 (101.9) (n=70)	109.4 (49.2) (n=74)	5.5 (34.1) (n=62)	122.3 (66.4) (n=80)	15.8 (64.3) (n=71)
Prolactin, ng/mL								
Females	7.3 (3.8) (n=48)	1.1 (4.4) (n=44)	8.9 (8.7) (n=50)	-0.3 (9.5) (n=46)	9.4 (6.4) (n=49)	4.6 (10.0) (n=47)	10.8 (7.2) (n=50)	6.1 (11.1) (n=48)
Males	7.3 (3.0) (n=34)	-0.6 (2.4) (n=32)	8.7 (4.4) (n=29)	-0.5 (2.8) (n=27)	7.0 (2.9) (n=26)	3.6 (6.7) (n=23)	7.6 (3.7) (n=30)	1.6 (3.5) (n=29)

Endpoint[a]	Placebo + placebo		Sertraline + placebo		Brexpiprazole + placebo		Brexpiprazole + sertraline	
	Baseline (Day 0)	Change to last visit	Baseline (Day 0)	Change to last visit	Baseline (Day 0)	Change to last visit	Baseline (Day 0)	Change to last visit
Prolactin >3x ULN, No. (%)[c]								
Females	–	0	–	0	–	0	–	0
Males	–	0	–	0	–	0	–	0
Orthostatic hypotension, No. (%)[d]	–	0	–	0	–	0	–	0
QTcF, ms	404.5 (19.7) (n=82)	-4.9 (16.9) (n=73)	406.2 (18.4) (n=79)	2.4 (18.1) (n=71)	401.2 (17.3) (n=75)	-1.6 (14.4) (n=66)	404.0 (19.7) (n=80)	1.5 (17.3) (n=73)
QTcF prolongation, No. (%)[e]	–	1/73 (1.4)	–	0	–	0	–	0
SAS total score	0.3 (0.6) (n=82)	-0.2 (0.6) (n=82)	0.3 (1.1) (n=78)	-0.2 (1.0) (n=78)	0.3 (0.9) (n=75)	-0.1 (1.0) (n=75)	0.3 (1.0) (n=80)	-0.1 (0.8) (n=80)
AIMS Movement rating score	0.1 (0.3) (n=82)	-0.1 (0.3) (n=82)	0.0 (0.2) (n=78)	0.0 (0.3) (n=78)	0.0 (0.2) (n=75)	0.0 (0.6) (n=75)	0.1 (0.7) (n=80)	-0.1 (0.7) (n=80)
BARS Global score	0.2 (0.5) (n=82)	-0.2 (0.5) (n=82)	0.2 (0.5) (n=78)	0.0 (0.7) (n=78)	0.2 (0.5) (n=75)	0.1 (0.8) (n=75)	0.3 (0.7) (n=80)	-0.1 (0.7) (n=80)

[a]Values are mean (SD) unless otherwise described as No. (%).

[b]Value at randomization (Week 1).

[c]At any post-baseline visit. ULN=13.13 ng/mL (males), 26.72 ng/mL (females).

[d]≥20 mmHg decrease in systolic blood pressure and ≥25 beats per minute increase in heart rate from supine to standing, at any post-baseline visit.

[e]New onset, >450 ms (men), >470 ms (women), at any post-baseline visit.

Abbreviations: AIMS=Abnormal Involuntary Movement Scale; BARS=Barnes Akathisia Rating Scale; BMI=body mass index; HDL=high-density lipoprotein; LDL=low-density lipoprotein; QTcF=QT interval as corrected by Fridericia's formula; SAS=Simpson–Angus Scale; ULN=upper limit of normal.