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BREXPIPRAZOLE IN COMBINATION WITH SERTRALINE FOR THE TREATMENT OF ADULTS WITH POST-TRAUMATIC STRESS DISORDER

SPONSOR BRIEFING DOCUMENT

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

MEETING DATE: 18 JULY 2025

AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
AUC_t	area under the concentration-time curve calculated to the last observable concentration at time t
AUC_∞	area under the concentration-time curve from time zero to infinity
B-IPF	Brief Inventory of Psychosocial Function
BMI	body mass index
C-SSRS	Columbia Suicide Severity Rating Scale
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
$C_{avg,ss}$	average concentration at steady state
CGI-S	Clinical Global Impression - Severity
CI	confidence interval
C_{max}	maximum (peak) plasma concentration of the drug
CPK	creatine phosphokinase
CYP	cytochrome P450
DBP	diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	Electrocardiogram
E_{max}	maximum effect
EMDR	eye movement desensitization and reprocessing
EMS	Emergency Medical Services
EPS	extrapyramidal symptoms
FAS	Full Analysis Set
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale - Depression subscale
HIV	human immunodeficiency virus

IDDM	insulin-dependent diabetes mellitus
LOE	loss of efficacy
LS	least squares
LSMD	least squares mean difference
MAR	missing at random
MCID	minimal clinically important difference
MDD	major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model repeated measurements
MWPC	meaningful within-patient change
NDA	New Drug Application
OR	odds ratio
PCL-5	PTSD Checklist for DSM-5
PK	pharmacokinetic(s)
PT	preferred term
PTSD	post-traumatic stress disorder
QT	QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF-36v2	36-item Short-Form Health Survey Version 2
sNDA	supplemental New Drug Application
SNRI	serotonin and norepinephrine reuptake inhibitor
SOTS	Symptoms of Trauma Scale
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

1 EXECUTIVE SUMMARY

1.1 Introduction

Post-traumatic stress disorder (PTSD) is a serious psychiatric disorder that can develop after a person experiences or witnesses a traumatic event. With only 2 treatments approved by the Food and Drug Administration (FDA) in the past 25 years, both with moderate and inconsistent efficacy, many people continue suffering from PTSD and its severe consequences.

Brexpiprazole (REXULTI®), to be used in combination with sertraline, was co-developed by Otsuka Pharmaceutical Co. and H. Lundbeck A/S for the treatment of adults with PTSD. The PTSD clinical development program for brexpiprazole is the largest clinical development program within PTSD to date and includes three 12-week, multicenter, randomized, double-blind trials – Trials 061, 071, and 072 – to support the efficacy and safety of brexpiprazole in combination with sertraline. Combination treatment with brexpiprazole plus sertraline was more effective in relieving symptoms of PTSD and demonstrated better response rates than sertraline alone in 2 of the 3 trials. Additionally, the combination treatment was well tolerated, and the safety profile is consistent with the large database of brexpiprazole from clinical trials and extensive real-world usage in a variety of psychiatric indications.

As described throughout this briefing document, the brexpiprazole PTSD clinical development program supports a positive benefit-risk profile for brexpiprazole in combination with sertraline for the treatment of PTSD in adults, addressing a critical unmet need for individuals suffering from PTSD.

1.2 Background and Unmet Need

PTSD is a highly prevalent trauma-based psychiatric disorder characterized by 4 core symptom clusters: intrusion, avoidance, negative alterations in mood and cognition, and arousal (American Psychiatric Association 2022). In the United States (US), PTSD impacts an estimated 13 million adults each year (National Center for PTSD 2025), and approximately 6 out of every 100 people will have PTSD at some point in their lives (Goldstein et al 2016). Notably it has been reported that 86% of people who experience PTSD in the US are in the civilian population (Davis et al 2022). PTSD is often stigmatized (Parrott 2023) and is associated with considerable public health, humanistic and clinical burden (Al Jowf et al 2022).

Current US PTSD treatment guidelines recommend trauma-focused psychotherapies as first-line treatments for PTSD and pharmacotherapies where indicated or as second-line treatments (American Psychological Association 2025; US Department of Veterans Affairs 2023). In the US, only two medications, sertraline and paroxetine, are approved for the treatment of PTSD. However, these selective serotonin reuptake inhibitors (SSRIs) have demonstrated only modest efficacy in managing PTSD

symptom clusters (ie, negative mood and cognition). Moreover, individual trials fail to show consistent efficacy across all 4 PTSD symptom clusters, particularly intrusion and arousal (Williams et al 2022), with many patients responding inadequately to treatment (Williams et al 2022).

Due to modest efficacy achieved by approved pharmacotherapy options, PTSD symptoms are often managed using off-label pharmacotherapies, including other SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, anxiolytics or sedative hypnotics, alpha blockers, and antipsychotics (Cook et al 2021). Most trials evaluating use of these agents involved a small number of patients and demonstrated inconsistent results (Braun et al 1990; Carey et al 2012; Cates et al 2004; Dowd et al 2020; Germain et al 2012; Padala et al 2006; Pollack et al 2011; Raskind et al 2007; Stein et al 2002); other larger trials did not differentiate from placebo treatment (Krystal et al 2011; Raskind et al 2018). These options are prescribed for symptom-specific management, and providers may utilize a trial-and-error approach which may contribute to an increased adverse event (AE) burden and safety concerns (Krystal et al 2017; Williams et al 2022).

With only 2 FDA-approved treatment options, many people continue suffering from PTSD and its severe consequences. Overall, these treatment patterns highlight an unmet need for effective and safe options that better address patients' burdensome, heterogeneous, and complex symptoms.

1.3 Product Description

Brexpiprazole was first approved by the FDA in 2015 for the treatment of schizophrenia and as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults; brexpiprazole was approved for schizophrenia in adolescents in 2021. Most recently in 2023, the FDA-approved brexpiprazole for the treatment of agitation associated with dementia due to Alzheimer's disease. Dose ranges for the approved indications are shown in Table 7. Brexpiprazole has been approved in more than 60 countries worldwide, including in Canada and countries in the European Union.

The proposed supplemental indication is for the treatment of PTSD in adults, in combination with sertraline. The recommended starting brexpiprazole dosage for PTSD is 0.5 mg/day in combination with sertraline 50 mg/day. The target daily dose of brexpiprazole is 2 mg/day plus sertraline 150 mg/day, with a maximum recommended daily dosage of brexpiprazole 3 mg/day plus sertraline 200 mg/day.

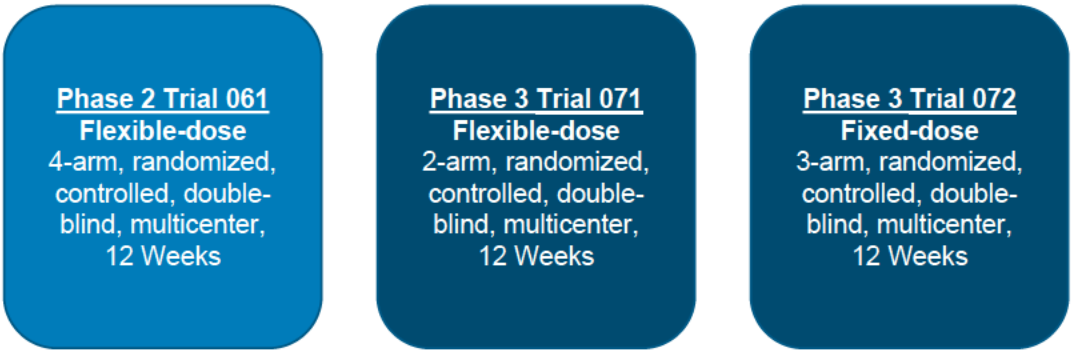
Brexpiprazole has a high and similar binding affinity for noradrenergic, serotonergic, and dopaminergic receptors, leading to decreased norepinephrine, increased serotonin, and partial agonism of the dopamine receptor. Additionally, during combination therapy with sertraline, the regulation of neurotransmitter activity by sertraline may be augmented through blockade of excitatory norepinephrine receptors

and partial agonism of serotonin and dopamine receptors by brexpiprazole. Collectively, these effects may normalize monoamine neurotransmitter activity, reducing the fear response and restoring reward system function. By targeting multiple neurotransmitter systems, brexpiprazole in combination with sertraline addresses a wider range of PTSD symptoms than sertraline alone.

1.4 PTSD Development Program and Trial Design

The brexpiprazole PTSD clinical development program for brexpiprazole in combination with sertraline consists of 3 completed 12-week, multicenter, randomized, double-blind trials: 2 flexible-dose trials, Trials 061 and 071, and 1 fixed-dose trial, Trial 072 (Figure 1). Based on the outcome of Phase 2 Trial 061, the Phase 3 program with Trials 071 and 072 was designed in collaboration with the FDA to compare the combination treatment of brexpiprazole plus sertraline to sertraline plus placebo.

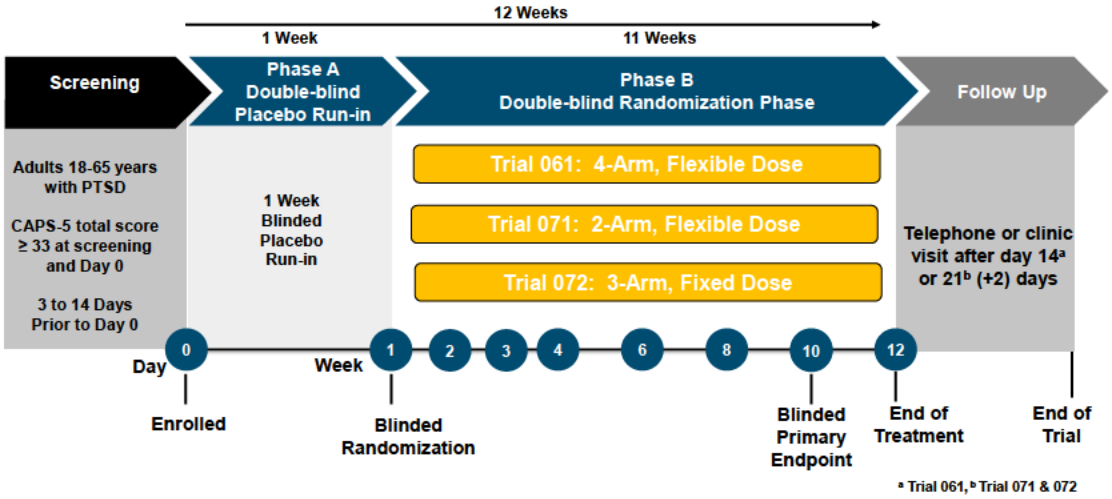
Figure 1: Overview of PTSD Phase 2 and Phase 3 Trials



The PTSD trials enrolled more than 1,200 patients in the US. Each trial enrolled outpatients with a diagnosis of PTSD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and confirmed by the Mini International Neuropsychiatric Interview (MINI). Patients were required to have been symptomatic for at least 6 months prior to Screening and to have a Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total Symptom Severity Score ≥ 33 at Screening and Day 0 in order to be considered for enrollment (see Appendix Section 10.1 for full inclusion/exclusion criteria).

All 3 trials utilized a 1-week double-blind placebo run-in period (Phase A) prior to randomization followed by an 11-week, double-blind, active treatment period (Phase B). To reduce potential bias in efficacy outcomes, aspects of the trial design were blinded to patients and trial personnel. Specifically, the existence of the placebo run-in period, the timing of randomization (Week 1) and the timing of the primary efficacy endpoint (Week 10) was not revealed such that the trial appeared to comprise a single, 12-week, double-blind treatment period (Figure 2).

Figure 2: Schematic of PTSD Phase 2 and Phase 3 Trial Design



CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder.

All trials utilized the same primary endpoint:

- Change from Baseline to Week 10 in CAPS-5 Total Score

The CAPS-5 is a validated, clinician-reported outcome measure completed via a structured interview by trained and certified interviewers. Twenty items are used to assess the severity of PTSD symptoms, each rated on a scale of 0 to 4 (0 = absent; 1 = mild/subthreshold; 2 = moderate/threshold; 3 = severe/markedly elevated; 4 = extreme/incapacitating). These 20 symptoms align with the 4 symptom clusters that characterize PTSD, and the sum reflects the total symptom severity score or CAP-5 Total Score.

Trials 071 and 072 also included 2 key secondary endpoints:

- Change from Baseline to Week 10 in Clinical Global Impression - Severity (CGI-S) Score
- Change from Baseline to Week 12 in Brief Inventory of Psychosocial Function (B-IPF) Score

Other clinician- and patient-reported endpoints included in the 3 trials are summarized in Table 1. See Section 6 for complete trial design details.

Table 1: Summary of Phase 2 and 3 Efficacy Endpoints

Efficacy Assessment	Endpoint Assessments	Description
Clinician-Reported		
CAPS-5 Total Score	Primary Endpoint: Change from Baseline to Week 10	Assessment of PTSD status and severity of symptoms
CAPS-5 Subscale Intrusion (Re-Experiencing) Symptoms	Change from Baseline to Week 10	Assessment of severity of symptoms by cluster
CAPS-5 Subscale Avoidance	Change from Baseline to Week 10	Assessment of severity of symptoms by cluster
CAPS-5 Subscale Negative Cognitions/ Mood	Change from Baseline to Week 10	Assessment of severity of symptoms by cluster
CAPS-5 Subscale Arousal and Reactivity	Change from Baseline to Week 10	Assessment of severity of symptoms by cluster
CGI-S Score	Key Secondary Endpoint[a]: Change from Baseline to Week 10	Assessment of severity of illness
CAPS-5 Response Rate	Change from Baseline to Week 10	Assessment of individual patient response to treatment
Patient-Reported		
B-IPF Score	Key Secondary Endpoint[b]: Change from Baseline (Day 0) to Week 12	Assessment of psychosocial functioning related to PTSD
PCL-5 Score	Change from Baseline to Week 10	Assessment of PTSD status and severity of symptoms
HADS Subscale Scores: • HADS-Anxiety • HADS-Depression	Change from Baseline to Week 10	Screening for symptoms of anxiety and depression

B-IPF = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression – Severity; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder.

[a.] CGI-S was included as "other efficacy endpoint" in Trial 061.

[b.] B-IPF was not assessed in Trial 061.

Other exploratory efficacy endpoints included the 36-item Short-Form Health Survey Version 2 (SF-36v2), the Symptoms of Trauma Scale (SOTS), sleep-specific CAPS-5 items and sleep-specific PCL-5 items. The SF-36v2 was evaluated as exploratory efficacy endpoint in the Phase 3 trials and not in the Phase 2 trial. The SOTS was evaluated as other endpoint in the Phase 2 trial but was not included in Phase 3 trials (see Appendix Section 10.5.6).

Of note, to maintain the blind, not all scales were performed at each visit so 2 different Baseline and endpoint timepoints resulted depending on the endpoint:

- The last assessment collected prior to first dose of active double-blind treatment at the Week 1 visit served as the baseline measure and Week 10 served as the

main timepoint for the CAPS-5, CGI-S, PCL-5 and Hospital Anxiety and Depression Scale (HADS) endpoints.

- The last assessment collected prior to first dose of placebo run-in at Day 0 Visit serves as the baseline measure and Week 12 served as the main timepoint for the B-IPF, SF-36, and SOTS endpoints, which were not assessed at the Week 1 and Week 10 visits.

For the remainder of the document, Baseline will refer to Week 1 for the CAPS-5, CGI-S, PCL-5, and HADS and to Day 0 for the B-IPF, SF-36, and SOTS.

Statistical Considerations

In general, similar statistical considerations were applied to Trials 061, 071, and 072. A brief summary is provided below; additional details are included in Section 6.

Sample size: Each trial was sized to have adequate statistical power to assess their respective primary objective.

Efficacy population: For all efficacy endpoints, the Efficacy Sample was used and was defined similarly across the trials. The Efficacy Sample comprised randomized patients who 1) took at least 1 dose of double-blind trial drug, 2) had a Baseline value and, 3) at least 1 post-Baseline evaluation for the CAPS-5 Total Score. For Trials 071 and 072, as per the trial protocol, the Efficacy Sample was enriched to contain patients with CAPS-5 Total Score of 27 or greater at the randomization visit (Week 1) and less than 50% improvement in CAPS-5 Total Score from Day 0 to Week 1. This excluded patients who responded to placebo during the placebo run-in period.

Statistical analyses of the primary endpoint: The primary analysis of change from Baseline to Week 10 in CAPS-5 for all trials was based on a mixed model repeated measurements (MMRM) model, which handled missing data under the missing at random (MAR) assumption. To evaluate the robustness of this assumption for the primary analyses, prespecified sensitivity analyses were planned for all trials under various missing data assumptions.

Supportive analyses: Trial 061 was a multifactorial trial with the primary objective of evaluating the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adult patients with PTSD. Trial 061 was powered (80%) to evaluate pairwise comparisons with a 2-sided significance level of 0.05 without multiplicity adjustment across these pairwise comparisons. To further evaluate the robustness of the effect demonstrated by brexpiprazole plus sertraline, retrospective multiplicity adjustments were applied for the 3 comparisons related to the primary objective as described further in Section 6.

Supportive analyses for Trials 071 and 072 are also described in Section 6.

1.5 Efficacy Findings

This section presents results from the 3 clinical trials: Phase 3 trial (071) that met its primary and key secondary endpoints, Phase 3 trial (072) that did not meet its primary endpoint, and Phase 2 trial (061) that met its primary endpoint and supports the findings of Trial 071. The studies are presented in chronological order.

1.5.1 Phase 2 Trial 061 Efficacy Results

Trial Population

A total of 321 patients were randomized (1:1:1:1) in Trial 061:

- 82 patients to brexpiprazole (1 - 3 mg/day) plus sertraline (100 - 200 mg/day)
- 75 patients to brexpiprazole (1 - 3 mg/day) plus placebo
- 81 patients to sertraline (100 - 200 mg/day) plus placebo
- 83 patients to placebo plus placebo

Demographics and Baseline characteristics were generally balanced across treatment groups and representative of the intended population (see Section 6.1.2).

By treatment group, the mean dose at each patient's last visit was brexpiprazole 2.2 mg + sertraline 161 mg, brexpiprazole 2.1 mg + placebo and sertraline 158 mg + placebo. The modal (most frequent) brexpiprazole dose was 2 mg/day for 64% of patients and 3 mg/day for 25% of patients.

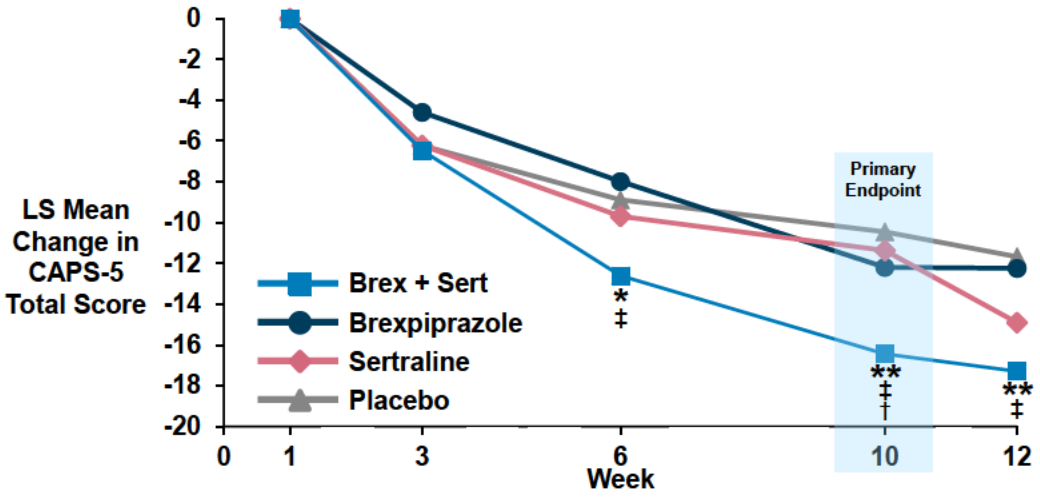
Primary Endpoint Results

The primary objective of Trial 061 was to evaluate the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adult patients with PTSD by assessing the change in CAPS-5 Total Score from Baseline to Week 10. As a multifactorial design, the Statistical Analysis Plan for Trial 061 prespecified 5 pairwise comparisons, 3 of which are relevant to the primary objective (Figure 3):

- The combination of brexpiprazole 1-3 mg/day plus sertraline demonstrated clinically meaningful improvements versus placebo (treatment difference: −5.99 [95% confidence interval (CI): −9.79, −2.19]; p = 0.0021)
- The combination of brexpiprazole 1-3 mg/day plus sertraline demonstrated clinically meaningful improvements versus sertraline plus placebo (treatment difference: −5.08 [95% CI: −8.96, −1.20]; p = 0.0106)
- Monotherapy treatment with brexpiprazole plus placebo did not demonstrate improvement versus placebo at Week 10 (treatment difference: −1.74 [95% CI: −5.70, 2.22]; p = 0.3868)

In addition to the primary assessments, the combination of brexpiprazole 1-3 mg/day plus sertraline demonstrated clinically meaningful improvements versus brexpiprazole plus placebo (treatment difference: −4.24 [95% CI: −8.26, −0.23]; p = 0.0384). However, treatment with sertraline plus placebo did not demonstrate improvement from placebo at Week 10 (LS mean difference −0.91 (95% CI: −4.74, 2.92; p = 0.6399). Note that sertraline has been extensively studied in PTSD, and, while a number or trials support its efficacy, several did not demonstrate significant efficacy versus placebo, meaning the lack of efficacy for sertraline in the present trial was not unanticipated.

Figure 3: Trial 061 LS Mean Change in CAPS-5 Total Score Over Time (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; Sert = sertraline.
p-values Brex + Sert vs placebo: * <0.05, ** <0.01.
p-values Brex + Sert vs Sertraline: † <0.05.
p-values Brex + Sert vs Brex + placebo: ‡ p <0.05.
The Efficacy Sample comprises 308 patients, 299 were included in the primary efficacy analysis since 9 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.
Baseline CAPS-5 Total Score: Placebo = 35.14, n = 78; Brex = 33.88, n = 69; Sertraline = 36.51, n = 75; Brex + Sert = 35.73, n = 77.

To further evaluate the robustness of the effect demonstrated by brexpiprazole plus sertraline, retrospective multiplicity adjustment was applied for the 3 comparisons relevant to the primary objective. Statistical significance of the combination of brexpiprazole plus sertraline when compared to each, placebo and sertraline alone, was demonstrated even under multiplicity adjustment.

Additional Efficacy Endpoints

The clinician- and patient-reported secondary endpoints results in Trial 061 further support the efficacy of combination treatment with brexpiprazole plus sertraline for treatment of PTSD (Table 2).

Table 2: Trial 061 Other Efficacy Endpoints: Summary of Mean Change from Baseline to Week 10 in Clinician- and Patient-Reported Outcomes (Efficacy Sample)

	Brex + Sert vs Sert + Placebo	
Endpoint	**Treatment Difference[a] (95% CI)**	**Nominal p-value[a]**
Clinician-Reported		
CGI-Severity	−0.42 (−0.76, −0.08)	0.0167
CAPS-5 Subscale Intrusion (Re-Experiencing)	−2.06 (−3.51, −0.60)	0.0058
CAPS-5 Subscale Avoidance	−0.79 (−1.50, −0.09)	0.0273
CAPS-5 Subscale Negative Cognitions/ Mood	−1.82 (−3.44, −0.19)	0.0285
CAPS-5 Subscale Arousal and Reactivity	−0.56 (−1.69, 0.58)	0.3325
Patient-Reported		
PCL-5	−4.93 (−9.83, −0.03)	0.0487
HADS - Anxiety	−1.55 (−2.92, −0.17)	0.0274
HADS - Depression	−1.94 (−3.23, −0.65)	0.0033

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI = Clinical Global Impression; CI: confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; Sert = sertraline.

[a.] Mixed model repeated measures method with model terms: treatment, (pooled) trial site, type of trauma, visit, and treatment by visit and Baseline by visit interaction.

Based on the positive results for the brexpiprazole plus sertraline arm in Trial 061, the Phase 3 program was designed to evaluate whether treatment with brexpiprazole in combination with sertraline would be superior to treatment with sertraline plus placebo.

1.5.2 Phase 3 Trial 071 Efficacy Results

Trial Population

A total of 416 patients were randomized (1:1) to treatment (214 to brexpiprazole plus sertraline, 202 to sertraline plus placebo). The predefined Efficacy Sample included:

- 149 patients in the brexpiprazole 2-3 mg/day plus sertraline 150 mg/day group
- 137 patients in the sertraline 150 mg/day plus placebo group

Patient demographics were balanced across treatment groups and representative of the intended population. See Section 6.2.2 for complete demographics and patient Baseline characteristics.

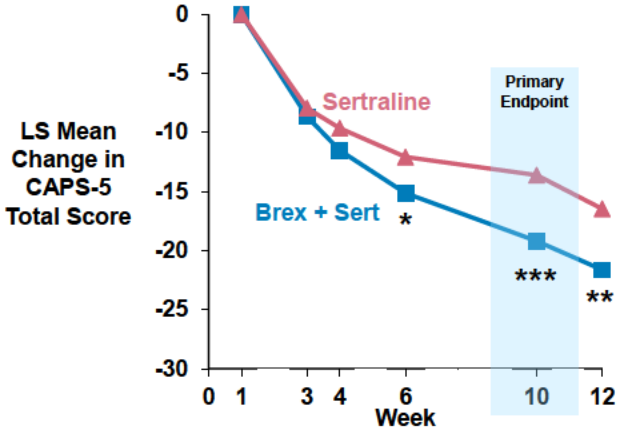
Of the patients treated in the brexpiprazole plus sertraline flexible-dose group, the mean (standard deviation [SD]) brexpiprazole dose at each patient's last visit was 2.2 (0.6) mg. The modal (most frequent) dose was 2 mg for 59% of patients and 3 mg for 31% of patients.

Primary Endpoint Results

The primary objective of Trial 071 was to evaluate the efficacy of brexpiprazole plus sertraline compared with sertraline plus placebo in patients with PTSD.

Trial 071 met its primary endpoint providing statistically significant and clinically meaningful evidence that brexpiprazole in combination with sertraline is superior to sertraline alone. The CAPS-5 treatment difference at Week 10 was −5.59 (95% CI: −8.79, −2.38; p = 0.0007; Figure 4).

Figure 4: Trial 071 LS Mean Change in CAPS-5 Total Score Over Time and at Week 10 (Efficacy Sample)



	Brexpiprazole + Sertraline	Sertraline
CAPS-5 Total Score at Week 1, Mean (SD)	**38.35** (7.18)	**38.68** (7.75)
Mean Change in CAPS-5 Total Score at Week 10, LS Mean (SE)	**-19.19** (1.17)	**-13.61** (1.24)
Treatment Difference at Week 10 (95% CI)	**-5.59 (-8.79, -2.38)**	
p-value	**0.0007**	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI: confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder SD = standard deviation; SE = standard error; Sert = sertraline.
*p-value <0.05, ** p-value <0.01, ***p-value <0.001.
The Efficacy Sample comprises 286 patients, 282 were included in the primary efficacy analysis since 4 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.
Baseline CAPS-5 Total Score: Brex + Sert = 38.35, n = 148; sertraline = 38.68, n = 134.

Secondary Endpoint Results

Both key secondary endpoints of change in CGI-S and B-IPF met statistical significance and support the clinical relevance of the primary endpoint results (Table 3). Additionally, brexpiprazole plus sertraline was more effective than sertraline alone for each of the CAPS-5 symptoms clusters and patient-reported outcomes

PCL-5, Hospital Anxiety and Depression Scale - Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale - Depression subscale (HADS-D).

The consistency of the results of the clinician-reported CAPS-5 and CGI-S and the patient-reported B-IPF and PCL-5 indicates that brexpiprazole plus sertraline treatment leads to noticeably larger clinical and functional improvement than treatment with sertraline alone.

Table 3: Trial 071 Clinician- and Patient-Reported Other Endpoint Results (Efficacy Sample)

	Brexpiprazole + Sertraline vs Sertraline + Placebo	
Endpoint	**Treatment Difference (95% CI)**	**p-value**
Clinician-Reported		
CGI-S [key secondary endpoint]	−0.47 (−0.76, −0.17)	0.0019
CAPS-5 Subscale Intrusion (Re-Experiencing)	−1.69 (−2.76, −0.62)	0.0022
CAPS-5 Subscale Avoidance	−0.74 (−1.32, −0.15)	0.0134
CAPS-5 Subscale Negative Cognitions/Mood	−1.94 (−3.33, −0.55)	0.0065
CAPS-5 Subscale Arousal and Reactivity	−1.35 (−2.25, −0.45)	0.0036
Patient-Reported		
B-IPF [key secondary endpoint]	−12.03 (−19.44, −4.62)	0.0016
PCL-5	−7.28 (−11.50, −3.06)	0.0008
HADS - Anxiety	−1.56 (−2.72, −0.41)	0.0083
HADS - Depression	−1.34 (−2.49, −0.19)	0.0223

B-IPF = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression – Severity; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder.

1.5.3 Phase 3 Trial 072 Efficacy Results

Trial Population

A total of 553 patients were randomized (1:1:1) to treatment (191 to brexpiprazole 2 mg/day plus sertraline, 185 to brexpiprazole 3 mg/day plus sertraline, and 177 to sertraline plus placebo). The Efficacy Sample included:

- 132 patients in the brexpiprazole 2 mg plus sertraline 150 mg/day group
- 126 patients in the brexpiprazole 3 mg plus sertraline 150 mg/day group
- 130 patients in the sertraline 150 mg/day plus placebo group

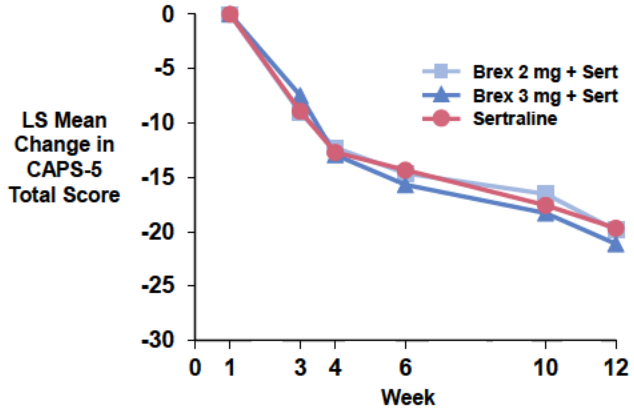
Demographics were balanced across all treatment groups and similar to Trial 071. See Section 6.3.2.

Primary Endpoint Results

The primary objective of Trial 072 was to confirm the efficacy of brexpiprazole plus sertraline compared with sertraline plus placebo in patients with PTSD.

The primary endpoint was not met in Trial 072 (Figure 5). The improvement observed on the CAPS-5 Total Score in the brexpiprazole plus sertraline groups was −16.53 (standard error [SE] 1.19) points for the 2 mg brexpiprazole dose and −18.28 (SE 1.23) for the 3 mg brexpiprazole dose. The improvement observed in the sertraline plus placebo group was −17.57 (SE 1.19) points on the CAPS-5 Total Score.

Figure 5: Trial 072 LS Mean Change in CAPS-5 Total Score Over Time and at Week 10 (Efficacy Sample)



	Brex 2 mg + Sert	Brex 3 mg + Sert	Sertraline
CAPS-5 Total Score at Week 1, Mean (SD)	38.80 (8.26)	37.88 (7.38)	39.30 (7.75)
Mean Change in CAPS-5 Total Score at Week 10, LS Mean (SE)	-16.53 (1.19)	-18.28 (1.23)	-17.57 (1.19)
Treatment Difference at Week 10 (95% CI)	1.03 (-2.09, 4.16) p = 0.52	-0.71 (-3.88, 2.46) p = 0.66	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI: confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; SD = standard deviation; SE = standard error; Sert = sertraline.
The Efficacy Sample comprises 388 patients, 386 were included in the primary efficacy analysis since 2 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.
Baseline CAPS-5 Brex 2 mg + Sert = 38.80, n = 132; Brex 3 mg + Sert = 37.88, n = 124; Sertraline = 39.30, n = 130.

Key Secondary Endpoint Results

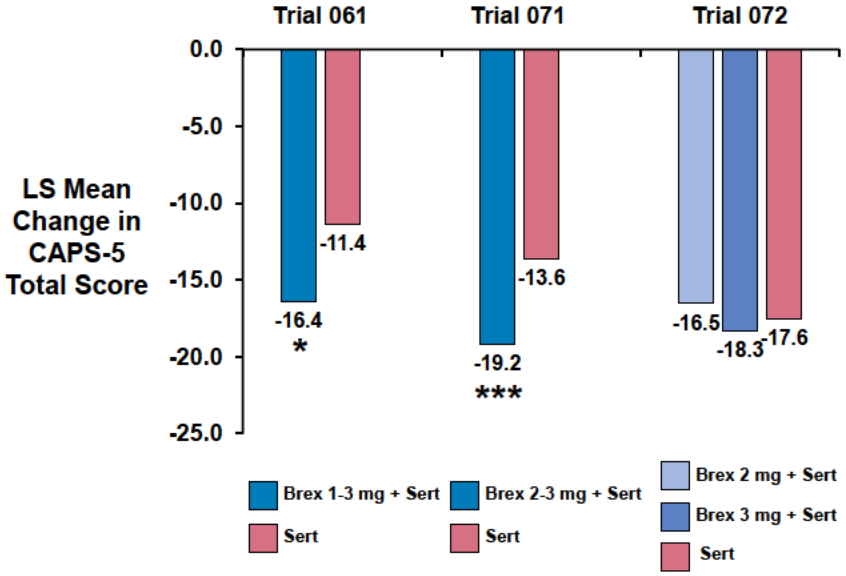
For the key secondary endpoint of change in CGI-S score, neither the 2 mg nor the 3 mg doses of brexpiprazole plus sertraline showed a difference versus sertraline alone. Numerical improvements were observed for the B-IPF key secondary endpoint in the brexpiprazole 3 mg plus sertraline group compared to the sertraline alone group (see Section 6.3.3.2).

Multiple post hoc analyses were conducted to identify a cause for the diverging results of Trial 072 compared to Trials 061 and 071. Evaluation of factors linked to trial methodology and patient characteristics, such as demographics, psychiatric history, substance use, and PTSD attributes, did not reveal a clear explanation for the divergence.

1.5.4 Efficacy Across Trials

The therapeutic benefit of combination treatment of brexpiprazole plus sertraline over sertraline alone has been observed within the 2 flexible-dose trials (Trial 071 and Trial 061) with similar treatment effect on the primary (CAPS-5 Total Score LS mean difference [LSMD] −5.59 and −5.08, respectively) and secondary endpoints. Trial 072 did not meet its primary endpoint. Post hoc analyses did not reveal a cause for the diverging results with respect to treatment differences versus sertraline. However, the LS mean changes from Baseline observed in the brexpiprazole plus sertraline arm were consistent across all 3 trials (LS mean change = −16.4 to −19.2 across all trials). The response observed in the sertraline plus placebo group in Trial 072 (LS mean change = −17.6) was higher than the response observed in Trials 071 and 061 (Trial 071 LS mean change = −13.6; Trial 061 LS mean change = −11.4). As such, data from the clinical program suggest that brexpiprazole in combination with sertraline has a consistent effect on PTSD symptoms (Figure 6).

Figure 6: Primary Endpoint Results Across Trials (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.
*nominal p <0.05, ***p <0.001.

Importantly, brexpiprazole plus sertraline demonstrated broad and consistent symptom improvements in the 4 clinician-reported CAPS-5 symptom clusters (ie, intrusion [re-experiencing], avoidance, negative cognitions and mood, and arousal and reactivity symptoms), addressing limitations of approved treatments, which have shown moderate and inconsistent efficacy across symptom clusters. In the 2 flexible-dose trials, brexpiprazole plus sertraline showed improvements (nominal $p < 0.05$) in all 4

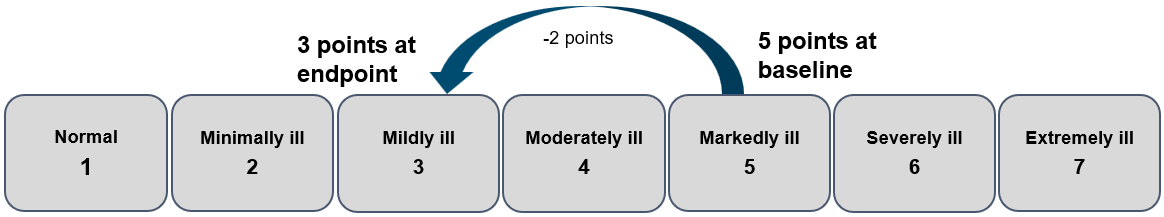
symptom clusters in Trial 071 and in 3 out of 4 symptom clusters in Trial 061. The changes in the symptom clusters in Trial 072 were of similar magnitude for brexpiprazole in combination with sertraline as that seen in Trials 071 and 061 (see Figure 30).

Consistency was also observed within and between the 3 trials across the clinical and patient-reported outcome assessments of PTSD symptom severity and psychosocial functioning. In Trials 071 and 061, the changes in CAPS-5, CGI-S, PCL-5, HADS-A, and HADS-D all showed benefit of brexpiprazole plus sertraline over sertraline alone, which further substantiates the robustness of the treatment effects of the combination.

Clinical Meaningfulness

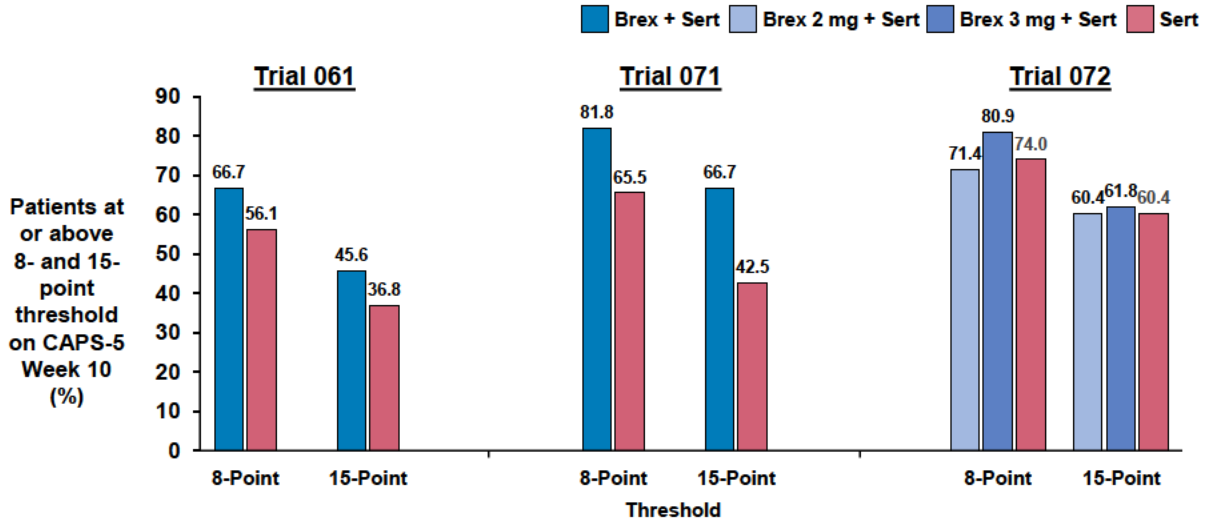
The clinical meaningfulness of the primary endpoint result was evaluated using individual-level meaningful change thresholds derived by triangulation of an anchor-based approach and a distribution-based approach from Trial 061 data. A threshold of −8 and −15 points, anchored to a 1-point and 2-point improvement on CGI-S, respectively, was identified as an appropriate meaningful score difference on the CAPS-5. As an example, a 2-point reduction in CGI-S would mean that a patient who was “markedly ill” at Baseline moved to “mildly ill” at endpoint (Figure 7).

Figure 7: Clinical Global Impression-Severity Scale



Across trials, greater proportions of patients in the brexpiprazole plus sertraline groups met the meaningful change thresholds of −8 and −15 points on the CAPS-5 Total Score compared to sertraline alone (Figure 8). These results support the interpretability of the score changes on the CAPS-5 in a manner consistent with the FDA’s Patient-Focused Drug Development Guidance (FDA 2023).

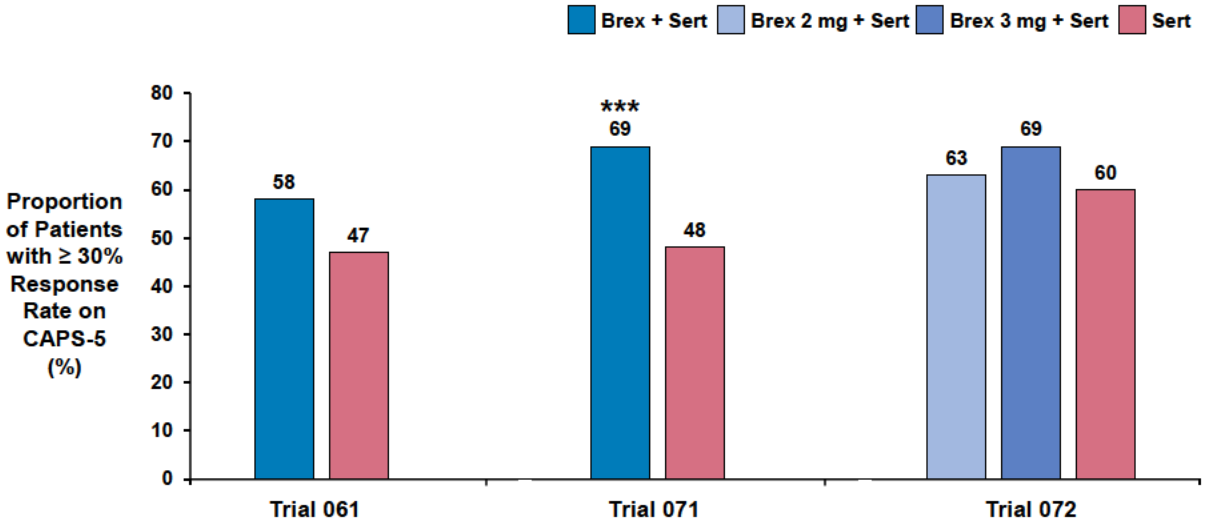
Figure 8: Patients Meeting Clinical Meaningfulness Thresholds on the Change in CAPS-5 Total Score at Week 10 (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder; Sert = sertraline.

Prespecified responder analyses showed that a higher proportion of patients treated with brexpiprazole in combination with sertraline achieved a response (≥ 30% decrease from Baseline) on the CAPS-5 Total Score compared to sertraline (Figure 9).

Figure 9: Proportion of Patients with CAPS-5 Response Rate (≥ 30%) at Week 10 in 12-Week Controlled Trials in PTSD (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder; Sert = sertraline
*** p <0.001.

Overall, brexpiprazole in combination with sertraline provided clinically meaningful reductions in PTSD symptoms beyond sertraline alone.

1.6 Safety Findings

The primary safety population supporting the PTSD indication includes patients from Trials 061, 071, and 072. To assess the safety of brexpiprazole in combination with sertraline, pooled analyses were performed, which included 650 patients in the all brexpiprazole plus sertraline group and 447 patients in the sertraline plus placebo group. Safety in the brexpiprazole (N = 75) and placebo monotherapy (N = 82) treatment groups from Trial 061 was assessed separately and not included in the pooled data; no safety concerns were identified. Safety data for the individual trials are summarized in Appendix Section 10.6.

Overall, the safety profile across all brexpiprazole plus sertraline dose groups was comparable to the sertraline plus placebo group, demonstrating that in patients with PTSD, combination treatment with brexpiprazole plus sertraline once daily was well tolerated.

Additionally, there is consistency with the well-established safety profile of brexpiprazole from clinical trials and extensive real-world usage across several indications.

The overall incidence of treatment-emergent AEs (TEAEs) were similar between the combination of brexpiprazole plus sertraline and the sertraline alone groups (Table 4). Rates of AEs observed in the brexpiprazole 3 mg plus sertraline treatment group were consistent with those observed in the brexpiprazole 2 mg plus sertraline treatment group and with sertraline alone. The incidences of patients with serious AEs (SAEs) and of patients with AEs leading to discontinuation were lower in the all brexpiprazole plus sertraline group than in the sertraline plus placebo group. No single SAE was reported in more than 1 patient in the all brexpiprazole plus sertraline group or the sertraline plus placebo group.

One death occurred in the brexpiprazole 2 mg/day plus sertraline group, and 1 death occurred in the sertraline plus placebo group. Both deaths were considered to be not related to the trial treatment by the investigator. One additional death occurred in placebo group in Trial 061 (not included in the pooled data).

Additional pooled safety data by treatment group are presented in Section 7.

Table 4: Summary of Adverse Events in the 12-Week Controlled Trials in PTSD (Safety Sample)

Category, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
Patients with AEs	95 (51.4)	87 (48.3)	179 (62.8)	**361 (55.5)**	**251 (56.2)**	612 (55.8)
Patients with SAEs	1 (0.5)	1 (0.6)	3 (1.1)	**5 (0.8)**	**7 (1.6)**	12 (1.1)
Patients discontinued trial drug due to AE	5 (2.7)	8 (4.4)	13 (4.6)	**26 (4.0)**	**31 (6.9)**	57 (5.2)
Deaths	1 (0.5)	0 (0.0)	0 (0.0)	**1 (0.2)**	**1 (0.2)**	2 (0.2)

Brex = brexpiprazole; AE = adverse event; PTSD = post-traumatic stress disorder; SAE = serious adverse event; Sert = sertraline.
Note: All AEs presented started after start of trial treatment; or if the event was continuous from Baseline and was serious, trial treatment-related, or resulted in death, discontinuation, interruption, or reduction of trial drug.

Identified safety topics of interest included extrapyramidal symptoms (EPS)-related events; orthostatic hypotension, dizziness, and syncope; effects on weight, lipid, and glucose; somnolence; and suicidality. Overall, with the exception of effects on weight, the other safety topics were generally balanced across the treatment groups with no new safety signals identified in the clinical program (Table 5). The effect on body weight was consistent with the known profile of brexpiprazole. The mean change from Baseline to last visit in body weight was small and not considered clinically meaningful (+1.0 kg with brexpiprazole plus sertraline, and −0.2 kg with sertraline plus placebo). A complete listing of safety topics of interest is provided in Section 7.8.

Table 5: Overview of Key Safety Topics of Interest in the All Brexpiprazole Plus Sertraline and Sertraline Plus Placebo of 12-Week Controlled Trials in PTSD (Safety Sample)

Safety Topic, n (%)	All Brex + Sert N = 650	Sert + Placebo N = 447
EPS-related adverse events	60 (9.2)	39 (8.7)
Effect on weight	43 (6.6)	10 (2.2)
Somnolence	34 (5.2)	20 (4.5)
Orthostatic hypotension, dizziness, and syncope	21 (3.2)	22 (4.9)
Suicidality	4 (0.6)	5 (1.1)
Effect on glucose	3 (0.5)	1 (0.2)
Effect on lipids	2 (0.3)	1 (0.2)

Brex = brexpiprazole; EPS: extrapyramidal symptoms; PTSD = post-traumatic stress disorder; Sert = sertraline.

There were no clinically relevant differences between the brexpiprazole plus sertraline group and the sertraline plus placebo group in any other laboratory test values or in any vital sign or electrocardiogram (ECG) measurements.

Overall, the safety results show that the addition of brexpiprazole to sertraline was well tolerated compared to sertraline alone, and the safety profile in the PTSD program is consistent with the well-established profile of brexpiprazole.

1.7 Benefit-Risk Conclusions

A summary of the benefit-risk assessment for brexpiprazole as treatment for PTSD is shown in Table 6. Overall, the evidence supports a positive benefit-risk profile for brexpiprazole in combination with sertraline for the treatment of PTSD in adults.

Table 6: Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Current guidelines recommend psychotherapy and pharmacotherapy as first-line treatments for PTSD. • Approved agents (sertraline and paroxetine) have demonstrated modest efficacy in managing PTSD symptoms across all symptom clusters, with most patients responding inadequately to treatment. • Consequently, PTSD symptoms are often managed using off-label treatments (eg, other SSRIs, SNRIs, benzodiazepines, anxiolytics or sedative hypnotics, antipsychotics, and alpha blockers).	A significant proportion of patients with PTSD continue to have an unmet need for effective, evidence-based treatment despite being treated with pharmacotherapy.
Benefit	• In Trial 071, statistically significant and clinically meaningful benefits were observed across all endpoints. • Trial 072 did not meet its primary endpoint. Absolute reductions in primary and key secondary endpoints in the brexpiprazole plus sertraline group were similar to those observed in Trials 061 and 071. • Trial 061 provides supportive evidence that brexpiprazole plus sertraline is superior to sertraline alone in the treatment of PTSD. • Clinician-reported CAPS-5 Total Score, its subscores (symptom clusters) and CGI-S and patient-reported B-IPF, PCL-5 and HADS showed consistency in clinical and functional benefit of brexpiprazole plus sertraline compared to sertraline alone. • The clinical relevance of the efficacy results was demonstrated by the higher proportion of responders, both on protocol-defined criteria and empirically derived individual change criteria, for patients treated with brexpiprazole plus sertraline compared to sertraline alone.	Based on the evidence generated, brexpiprazole in combination with sertraline is effective for the treatment of adults with PTSD. The combination of brexpiprazole and sertraline demonstrated statistically significant and clinically meaningful reductions in PTSD symptoms beyond those seen with sertraline alone in the treatment of PTSD.

Risk and Risk Management	• Overall, the incidences of reported AEs were similar in the brexpiprazole plus sertraline and the sertraline plus placebo treatment groups. A low incidence of serious AEs in the brexpiprazole plus sertraline group (0.8% vs 1.6% in the sertraline plus placebo group) was observed. There was 1 death in the brexpiprazole plus sertraline group and 1 death in the sertraline plus placebo group; both events were considered not related to trial drug. • The incidence of safety topics of interest were reported with similar frequency in the brexpiprazole plus sertraline group and the sertraline plus placebo group, except for effect on weight (6.6% vs 2.2%). • Brexpiprazole has a well-established safety profile in a variety of approved psychiatric indications. A comprehensive and detailed review of all the safety data from all available sources, such as nonclinical, published literature, clinical and post-marketing experience, suggests a favorable benefit-risk profile of brexpiprazole for PTSD.	Overall, no new risks were identified in the PTSD population and the safety results from these trials are consistent with the current overall safety profile of brexpiprazole. Use of brexpiprazole in combination with sertraline in patients with PTSD is associated with a favorable safety profile. Current risks can be managed with existing labeling with no additional risk minimization measures.

AE = adverse event; B-IPF = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression - Severity; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

2 BACKGROUND ON POST-TRAUMATIC STRESS DISORDER

Summary

- PTSD is a serious, long-term, psychiatric disorder characterized by 4 heterogenous core clusters of symptoms: intrusion (re-experiencing), avoidance, negative cognition and mood changes, and alterations in arousal or reactivity.
- PTSD is highly prevalent, affecting ~13 million adults during a given year in the US; 86% are in the civilian population.
- In the US, only 2 approved pharmacological treatments exist, which have modest and varied response rates.
- Physicians often rely on trial-and-error polypharmacy approaches that come with notable safety problems.
    - Only 20% of patients are receiving FDA-approved medications, and 7 out of 10 patients need to switch medicine usually in first 2 years of treatment.
    - PTSD treatment changes are most commonly due to inadequate or suboptimal symptom management.
- With only 2 FDA-approved treatments, with modest and inconsistent efficacy, many people continue suffering from PTSD and its severe consequences. Additional PTSD treatment options are needed that safely and effectively treat all 4 symptom clusters of PTSD.

2.1 Overview of Post-Traumatic Stress Disorder

PTSD is a highly prevalent trauma-based psychiatric disorder characterized by 4 core symptom clusters spanning (American Psychiatric Association 2022):

- Intrusive reexperiences of the trauma,
- Avoidance of internal and external associations with the trauma,
- Negative alterations in cognitions and mood, and
- Heightened arousal and reactivity.

PTSD impacts an estimated 13 million US adults during a given year (National Center for PTSD 2025) and approximately 6 out of every 100 people will have PTSD at some point in their lives, with the highest prevalence rates seen in females and individuals < 55 years old (Goldstein et al 2016; Kessler et al 2005; Koenen et al 2017). Notably it has been reported that 86% of people who experience PTSD in the US are in the

civilian population (Davis et al 2022), with rape and physical abuse by a partner being among the highest risk factors for developing PTSD (Kessler et al 2017).

2.2 Patient Experience

PTSD is often stigmatized (Parrott 2023) and is associated with considerable humanistic and clinical burden, resulting in impaired psychosocial functioning and lowered quality of life (Rodriguez et al 2012). In the US, PTSD is significantly associated with substance use disorder and increased suicide risk compared to individuals without a diagnosis of PTSD (Dell'Aquila and Berle 2023; Pietrzak et al 2011). Moreover, individuals with PTSD are at increased risk of external-cause and all-cause mortality, inclusive of somatic (such as cardiovascular, metabolic) and psychiatric comorbidities (Goldstein et al 2016; Sumner et al 2023). The public health burden of PTSD is also profound (Al Jowf et al 2022). Beyond direct health care costs, the impact of PTSD is substantial, exceeding costs for other mental health conditions such as anxiety and depressive disorders (Davis et al 2022).

Individuals with PTSD often suffer from long-term, fluctuating and heterogeneous PTSD symptoms, with symptom presentation varying throughout the disease course (American Psychiatric Association 2022). The relative predominance of the 4 PTSD symptom clusters differ with trauma characteristics and individual neurobiology, which can result in significant impairment in daily functioning necessitating treatment options that can target all 4 symptom clusters of PTSD (Rodriguez et al 2012; Yehuda et al 2015).

2.3 Current Treatment Options

Current US PTSD treatment guidelines recommend trauma-focused psychotherapies as first-line treatments for PTSD, and pharmacotherapies where indicated or as second-line treatments (American Psychological Association 2025; US Department of Veterans Affairs 2023). In the US, only 2 medications, sertraline and paroxetine, are approved for the treatment of PTSD. However, these SSRIs have demonstrated only modest efficacy in managing PTSD symptom clusters (ie, negative mood and cognition). Moreover, individual trials fail to show consistent efficacy across all 4 PTSD symptom clusters, particularly intrusion and arousal, with many patients responding inadequately to treatment (Williams et al 2022).

Although SSRIs increase serotonin levels, they have minimal effect on regulating other monoamines (norepinephrine and dopamine) that may be implicated in PTSD pathophysiology (Jain et al 2024; Strawn and Geracioti 2008; Torrisi et al 2019; Young and Breslau 2004).

Due to modest efficacy achieved by approved pharmacotherapy options, PTSD symptoms are often managed using off-label treatments including other SSRIs, SNRIs, benzodiazepines, anxiolytics or sedative hypnotics, alpha blockers, and antipsychotics

(Cook et al 2021). Most trials evaluating the use of these agents involved a small number of patients and demonstrated inconsistent results (Braun et al 1990; Carey et al 2012; Cates et al 2004; Dowd et al 2020; Germain et al 2012; Padala et al 2006; Pollack et al 2011; Raskind et al 2007; Stein et al 2002); other larger trials did not differentiate from placebo treatment (Krystal et al 2011; Raskind et al 2018). These options are prescribed for symptom-specific management, and providers may utilize a trial-and-error approach which may contribute to an increased AE burden (Krystal et al 2017; Williams et al 2022) and safety concerns such as drug abuse, dependence, and sedation (Leeies et al 2010).

Prescribing trends in patients with PTSD show that only 20% of patients receive SSRIs approved by the FDA (Holder et al 2021), and 41% of patients receive polypharmacy in their initial treatment regimen following their diagnosis (data on file). Remarkably, about 7 out of 10 patients will need to switch medications within the first 2 years (Davis et al 2024). The most common reasons for treatment changes include inadequate management of PTSD symptoms and the need to address residual symptoms (Davis et al 2024).

2.4 Unmet Medical Need

With only 2 FDA-approved treatments, many people continue suffering from PTSD and its severe consequences. Overall, these treatment patterns highlight an unmet need for effective and safe options that better address patients' burdensome, heterogeneous, and complex symptoms.

3 PRODUCT DESCRIPTION

Summary

- Brexpiprazole is an atypical antipsychotic that modulates norepinephrine, serotonin, and dopamine.
- In the US, brexpiprazole is currently approved for treatment of schizophrenia in adults and adolescents, adjunctive therapy to antidepressants for the treatment of MDD in adults, and treatment of agitation associated with dementia due to Alzheimer's disease.
- The proposed indication is for the treatment of PTSD in adults, in combination with sertraline. The target daily dose of brexpiprazole is 2 mg/day (max 3 mg/day) in combination with sertraline 150 mg/day (max 200 mg/day) for treatment of PTSD.
- Sertraline is a selective serotonin reuptake inhibitor. Brexpiprazole combines partial agonist activity at serotonergic 5-HT1A and at dopaminergic D2 receptors with antagonist activity at serotonergic 5-HT2A and noradrenergic α receptors.
- Combination therapy with brexpiprazole and sertraline may improve PTSD symptoms through synergistic activity in certain brain regions.

3.1 Product Overview

Brexpiprazole, co-developed by Otsuka and Lundbeck, is a well-known atypical antipsychotic that modulates norepinephrine, serotonin, and dopamine and is approved in the US (tradename REXULTI®) for 3 indications:

- As monotherapy for the treatment of schizophrenia in adults and pediatric patients ages 13 years and older
- As an adjunctive therapy to antidepressants for the treatment of MDD in adults
- As monotherapy for treatment of agitation associated with dementia due to Alzheimer's disease

Brexpiprazole has also been registered and approved in more than 60 countries, including Canada and countries in the European Union.

Therapy with brexpiprazole in combination with sertraline may improve PTSD symptoms through synergistic activity in the key brain regions to normalize fear processing in the amygdala (see Section 3.5).

3.2 Proposed Indication

The proposed indication of brexpiprazole is for the treatment of PTSD in adults, in combination with sertraline.

3.3 Recommended Dosing

Brexpiprazole should be administered orally once daily with or without food and should be titrated to the target daily dose of brexpiprazole 2 mg/day plus sertraline 150 mg/day for treatment of PTSD. The maximum recommended daily dosage of brexpiprazole is 3 mg/day plus sertraline 200 mg/day.

The PTSD dosing recommendation is consistent with the approved dosages for other brexpiprazole indications (Table 7).

Table 7: Brexpiprazole Dosing for Approved Indications

Indication	Starting Dosage	Recommended Target Dosage	Maximum Dosage
MDD – Adults	0.5 mg/day or 1 mg/day	2 mg/day	3 mg/day
Schizophrenia – Adults	1 mg/day	2 to 4 mg/day	4 mg/day
Schizophrenia – Pediatric (13 - 17 years)	0.5 mg/day	2 to 4 mg/day	4 mg/day
Agitation associated with dementia due to Alzheimer's disease	0.5 mg/day	2 mg/day	3 mg/day

MDD = major depressive disorder

3.3.1 Dose Titration

The recommended starting brexpiprazole dosage for PTSD is 0.5 mg once daily in combination with sertraline 50 mg on Days 1 to 7. Thereafter, titrate brexpiprazole to 1 mg once daily in combination with sertraline 100 mg once daily on Days 8 to 14, then titrate on Day 15 to the target dosage of brexpiprazole 2 mg once daily in combination with sertraline 150 mg once daily. Then, based on the patient's clinical response and tolerability, increase the brexpiprazole dosage at weekly intervals. The maximum recommended daily dosage of brexpiprazole is 3 mg in combination with maximum dosage of sertraline 200 mg once daily. Periodically reassess to determine the continued need and appropriate dosage for treatment.

3.4 Drug Interactions

Brexpiprazole is primarily metabolized by cytochrome P450 (CYP) 3A4 and CYP2D6 and the potential drug-drug interactions for brexpiprazole are well known. As shown in the US Prescribing Information, dosage modifications are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors, CYP2D6 inhibitors, or strong CYP3A4 inducers (Table 8).

Table 8: Dosage Modifications of Brexpiprazole for CYP2D6 Poor Metabolizers and for Concomitant Use with CYP3A4 Inhibitors, CYP2D6 Inhibitors, or CYP3A4 Inducers

Factors	Adjusted Brexpiprazole Dosage
CYP2D6 Poor Metabolizers	
CYP2D6 poor metabolizers	Administer half of the recommended dosage.
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Patients Taking CYP2D6 Inhibitors and/or CYP3A4 Inhibitors	
Strong CYP2D6 inhibitors[a]	Administer half of the recommended dosage.
Strong CYP3A4 inhibitors	Administer half of the recommended dosage.
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dosage.
Patients Taking CYP3A4 Inducers	
Strong CYP3A4 inducers	Double the recommended dosage over 1 to 2 weeks.

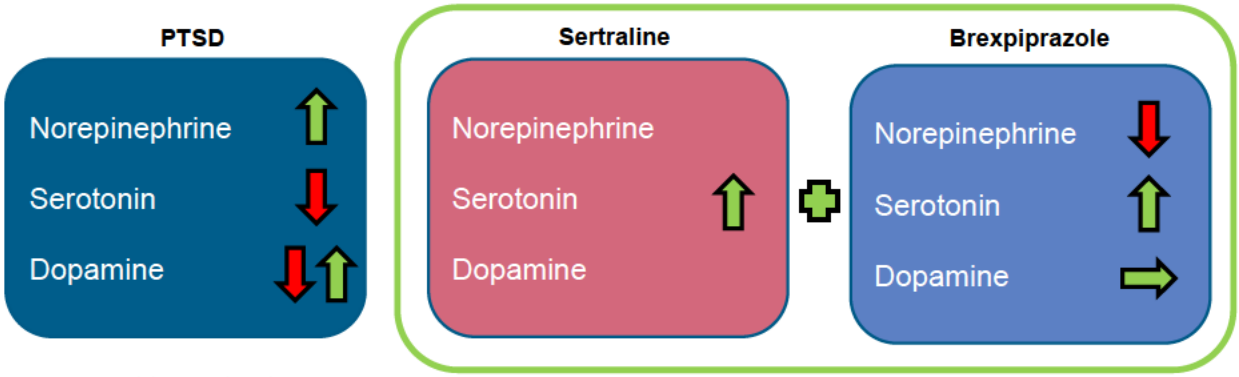
CYP = Cytochrome P450; MDD = major depressive disorder; PTSD = post-traumatic stress disorder.
[a] In the clinical studies examining the use of brexpiprazole for the adjunctive treatment of MDD, dosage was not adjusted for strong CYP2D6 inhibitors (eg, paroxetine, fluoxetine). Thus, CYP considerations are already factored into general dosing recommendations, and brexpiprazole may be administered without dosage adjustment in patients with MDD and PTSD.

3.5 Mechanism of Action

The mechanism of action of brexpiprazole is unknown. Combination therapy with brexpiprazole and sertraline is believed to improve PTSD symptoms through synergistic activity in key brain regions. In PTSD, elevated norepinephrine levels can lead to increased fear responses through overactivation of excitatory α1-adrenoceptors in the amygdala, while low serotonin levels can prevent proper regulation of amygdala activity (Arnsten 2015; Ferry et al 1999; Krystal and Neumeister 2009; Sherin and Nemeroff 2011). Therapy with an SSRI, such as sertraline, increases serotonin levels, leading to greater activation of both excitatory serotonin 5-HT2A receptors, which can increase fear responses, and inhibitory serotonin 5-HT1A receptors, which can decrease fear responses (de Paula and Leite-Panissi 2016; Li et al 2006; MacQueen et al 2001). During combination therapy with brexpiprazole and sertraline, the regulation of amygdala activity by sertraline may be augmented through blockade of α1-adrenoceptors and serotonin 5-HT2A receptors and partial agonism of serotonin 5-HT1A receptors and dopamine D2 receptors (Figure 10) (Cohen et al 2018; MacQueen et al 2001; Maeda et al 2014). Collectively, these effects may normalize fear processing in the amygdala. This is supported by preclinical evidence that combination

treatment with brexpiprazole and the SSRI escitalopram reduced stress responses and anxiety-like behavior in a rat model of PTSD-like symptoms (Cohen et al 2018).

Figure 10: Proposed Mechanism of Action Schematic



PTSD = post-traumatic stress disorder.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Brexpiprazole has been approved in the US since July 2015 for treatment of schizophrenia and for use as an adjunctive therapy to antidepressants for the treatment of MDD in adults. Additional approvals have been granted for the treatment of schizophrenia in adolescents and for treatment of agitation associated with dementia due to Alzheimer's disease.
- The PTSD clinical development program was designed with input from the FDA. The primary data contributing to the efficacy and safety in the PTSD population come from 1 Phase 2 trial (Trial 061) and 2 Phase 3 trials (Trials 071 and 072).
- Trial 071 was positive, meeting all primary, secondary, and exploratory endpoints whereas Trial 072 did not meet its primary endpoint. Trial 061 is a supportive trial providing independent substantiation of the results from Trial 071.

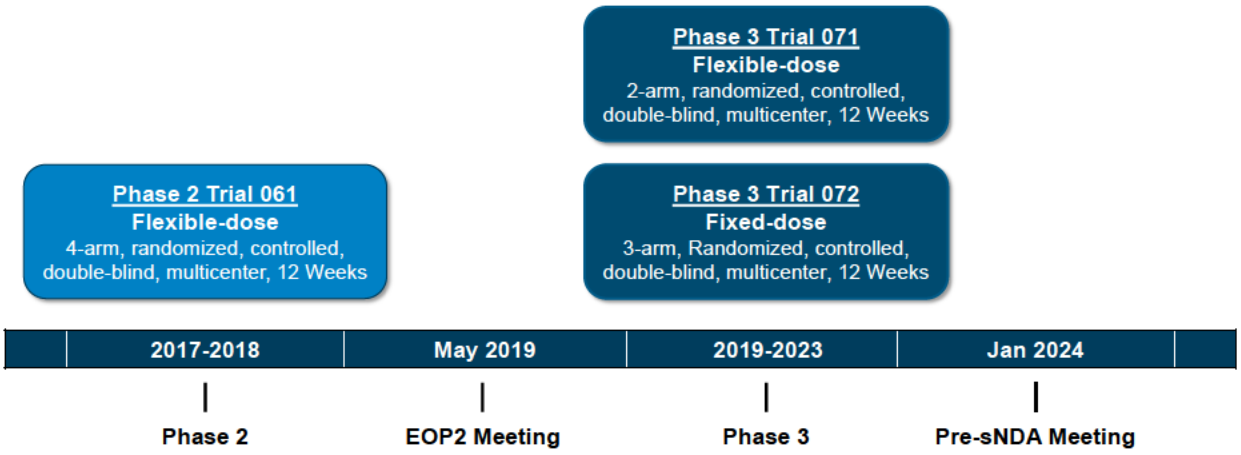
4.1 Regulatory Milestones

Otsuka and Lundbeck have sought FDA input at various stages of the brexpiprazole PTSD development program. A timeline and summary of the regulatory interactions are provided in Figure 11 and Table 9, respectively.

Brexpiprazole was approved by the FDA on 10 Jul 2015 for the treatment of schizophrenia and for use as an adjunctive therapy to antidepressants for the treatment of MDD in adults. In December 2021, brexpiprazole was approved in the US for the treatment of schizophrenia in adolescents. Most recently in May 2023, brexpiprazole was approved in the US for treatment of agitation associated with dementia due to Alzheimer's disease.

The supplemental New Drug Application (sNDA) for the PTSD indication was submitted on 08 April 2024. The submission includes two Phase 3, adequate well-controlled trials. Trial 071 was positive whereas Trial 072 did not meet its primary endpoint. Trial 061 is a supportive trial providing independent substantiation of the results from Trial 071.

Figure 11: Brexpiprazole PTSD Development Timeline



EOP2 = End of Phase 2 Meeting; PTSD = post-traumatic stress disorder; sNDA = supplemental New Drug Application.

Table 9: Key Regulatory Interactions in Brexpiprazole Clinical Development for the Treatment of PTSD

Regulatory Interaction Date	Key Outcomes
End of Phase 2 Meeting 02 May 2019	• Agreement on designs of Phase 3 trials based on Trial 061 results. • Agreement that long-term safety data in PTSD was not considered warranted for the submission, as justified by the existing brexpiprazole safety database. • The Sponsor originally proposed 2 identical flexible-dose trials, however, the Division requested at least 1 trial be fixed-dose trial to better characterize the safety and tolerability of 2 mg versus 3 mg doses of brexpiprazole in the PTSD population. • Alignment in terms of adequacy of conducting combination therapy with sertraline, and the exclusion of brexpiprazole monotherapy and placebo only arms. • Agreement on CAPS-5 as primary endpoint with recommendation to provide prespecified threshold for a clinically meaningful within-patient change score using an anchor-based approach (preferably using the Phase 2 trial data).
Type C Meeting – Written Responses: Clinical Outcome Assessments 11 Aug 2023	• Alignment on planned analyses to evaluate MWPC thresholds for CAPS-5 and B-IPF. • The Division generally agreed with the proposed approach of conducting clinically meaningful change analysis to support the interpretation of score changes.
Pre-sNDA Meeting – Written Responses 05 Jan 2024	• The Division indicated use of efficacy findings from Trial 061 as confirmatory evidence will be a matter of review. The Division noted that Trial 061 was not designed (eg, lack of control for multiple comparisons) with the intent to serve as an adequate and well-controlled trial. In addition, there was concern with lack of assay sensitivity given the lack of separation between the sertraline vs placebo.
sNDA Submission – 08 Apr 2024	• Standard review classification (PDUFA 08 Feb 2025)
PDAC Meeting Request – 08 Jan 2025	• FDA request for Psychopharmacologic Drugs Advisory Committee Meeting

B-IPF = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; FDA = Food and Drug Administration; MWPC = meaningful within-patient change; PDAC = Psychopharmacologic Drugs Advisory Committee Meeting; PDUFA = Prescription Drug User Fee Act; PTSD = post-traumatic stress disorder; sNDA = supplemental New Drug Application.

4.2 Clinical Development Program

4.2.1 PTSD Clinical Development Program Overview

The brexpiprazole PTSD clinical development program for brexpiprazole in combination with sertraline was designed in collaboration with the FDA and is the largest PTSD program conducted to date, consisting of over 1200 patients in 3 completed 12-week, multicenter, randomized, double-blind trials conducted in the US (Table 10).

Table 10: Completed Controlled Clinical Trials Supporting Brexpiprazole Efficacy in Adult Patients with PTSD

Trial Number (Start and End Date)	Trial Design	Trial Population	Regimen/ Schedule No. of Patients Randomized (n)	Treatment Duration/ Follow-Up	Primary Efficacy Endpoint
331-201-00061 (Jan 2017 - Nov 2018)	R, DB, PC, AC, MC	Adults aged 18-65 years with PTSD	Flexible dose (n = 321) • Brex (1-3 mg/day) + Sert (100-200 mg/day): n = 82 • Brex (1-3 mg/day) + placebo: n = 75 • Sert (100-200 mg/day) + placebo: n = 81 • Placebo + placebo[a]: n = 83	One-week placebo run-in, followed by 11-week DB Treatment/ Telephone contact or clinic visit 14 (+2) days after last dose	Change in CAPS-5 Total Score from Baseline to Week 10 in Efficacy Sample[b]
331-201-00071 (Oct 2019 - Aug 2023)	R, DB, AC, MC	Adults aged 18-65 years with PTSD	Flexible dose (n = 416) • Brex (2-3 mg/day) + Sert (150 mg/day): n = 214 • Sert (150 mg/day) + placebo: n = 202	One-week placebo run-in, followed by 11-week DB Treatment/ Telephone contact or clinic visit 21 (+2) days after last dose	Change in CAPS-5 Total Score from Baseline to Week 10 in Efficacy Sample[c]
331-201-00072 (Oct 2019 - Aug 2023)	R, DB, AC, MC	Adults aged 18-65 years with PTSD	Fixed dose (n = 553) • Brex (2 mg/day) + Sert (150 mg/day): n = 191 • Brex (3 mg/day) + Sert (150 mg/day): n = 185 • Sert (150 mg/day) + placebo: n = 177	One-week placebo run-in, followed by 11-week DB Treatment/ Telephone contact or clinic visit 21 (+2) days after last dose	Change in CAPS-5 Total Score from Baseline to Week 10 in Efficacy Sample[c]

AC = active control; Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DB = double-blind; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; MC = multicenter; PC = placebo-controlled; PTSD = post-traumatic stress disorder; R = randomized; Sert = sertraline.

[a] Placebo + placebo will be referred to as placebo for Trial 061 thereafter.

[b] Efficacy Sample for Trial 061 comprises all randomized patients who took at least 1 dose of double-blind trial drug and had a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score.

[c] Efficacy Sample for Trials 071 and 072 comprises all randomized patients who took at least 1 dose of double-blind trial drug and had a Baseline and at least 1 post-Baseline evaluation for the CAPS-5 Total Score PLUS: CAPS-5 Total Score of ≥ 27 at the randomization visit (Week 1) and an improvement in terms of reduction in CAPS-5 Total Score of less than 50% at end of the placebo run-in phase (Phase A) to exclude patients who responded to placebo during the placebo run-in phase.

All 3 trials utilized a 1-week double-blind placebo run-in period (Phase A) prior to randomization followed by an 11-week, double-blind, active treatment period (Phase B). To reduce potential bias in efficacy outcomes, aspects of the trial design were blinded to patients and trial site personnel. Specifically, the existence of the placebo run-in period, the timing of randomization (Week 1) and the timing of the primary efficacy endpoint (Week 10) was not revealed such that the trial appeared to comprise a single, 12-week, double-blind treatment period. Visits occurred weekly from Day 0 to Week 4, then every 2 weeks (Figure 2). The schedule of events for efficacy assessments is provided in Appendix Section 10.2.

Each trial enrolled adult outpatients with a diagnosis of PTSD as defined in the DSM-5 and confirmed by the MINI. Patients were required to have been symptomatic for at least 6 months prior to Screening and to have a CAPS-5 Total Score ≥ 33 at Screening and Day 0 to be considered for enrollment. In Trial 061, the index traumatic event that led to the development of PTSD was required to have taken place within the 15 years prior to Screening. In Trials 071 and 072, the index traumatic event was required to have taken place within the 9 years prior to Screening. Full inclusion and exclusion criteria are provided in Appendix Section 10.1.

During the screening period, prohibited medications (including antipsychotics and antidepressants) were washed out. Limited use of benzodiazepines and non-benzodiazepine sleep aids were permitted only for short-term management of TEAEs of anxiety and agitation, or insomnia, respectively. Patients were permitted to continue pre-existing psychotherapy, provided they had participated in this therapy regularly for ≥ 28 days prior to Screening and agreed to maintain their participation for the duration of the trial. Information on prior PTSD treatments was collected using the Emory Treatment Resistance Interview for PTSD, which consists of clinician-administered questions to assess the adequacy and benefit derived from prior pharmacologic or psychotherapeutic treatments.

Three additional trials conducted contribute to the sNDA:

- Trial 14865A (terminated early): a flexible-dose trial of brexpiprazole as adjunctive treatment to paroxetine or sertraline in adults suffering from PTSD; the trial was terminated early due to challenges with patient eligibility, not based on any safety concerns.
- Trial 331-201-00245 (completed): Phase 1, open-label, drug-drug-interaction trial to assess the effect of sertraline on the pharmacokinetics (PK) of orally administered brexpiprazole in healthy adults.
- Trial 331-201-00246 (terminated early): Phase 1 trial to assess the blood pressure effects of single-dose prazosin or propranolol administered in the presence of steady-state brexpiprazole and sertraline; the trial was terminated early due to software-related quality issues and not based on safety concerns.

4.2.2 Efficacy Outcome Measures

4.2.2.1 Phase 2 and 3 Primary and Key Secondary Endpoints

Similar evaluation instruments were used to assess efficacy in all 3 clinical trials (Table 11). These clinician- and patient-reported outcomes are further described in Sections 4.2.2.2 and 4.2.2.3, respectively.

Table 11: Summary of Phase 2 and Phase 3 Efficacy Endpoints

Efficacy Assessment	Endpoint Assessments	Endpoint Type		
		Flexible-Dose		Fixed-Dose
		Trial 061	Trial 071	Trial 072
Clinician-Reported				
CAPS-5 Total Score	Change from Baseline to Week 10	Primary	**Primary**	**Primary**
CAPS-5 Subscale Intrusion (Re-Experiencing) Symptoms	Change from Baseline to Week 10	Other efficacy	Other efficacy	Other efficacy
CAPS-5 Subscale Avoidance	Change from Baseline to Week 10	Other efficacy	Other efficacy	Other efficacy
CAPS-5 Subscale Negative Cognitions/Mood	Change from Baseline to Week 10	Other efficacy	Other efficacy	Other efficacy
CAPS-5 Subscale Arousal and Reactivity	Change from Baseline to Week 10	Other efficacy	Other efficacy	Other efficacy
CGI-S Score	Change from Baseline to Week 10	Other efficacy	**Key secondary**	**Key secondary**
CAPS-5 Response Rate[a]	Change from Baseline to Week 10	Other efficacy	Other efficacy	Other efficacy
Patient-Reported				
B-IPF Score	Change from Baseline (Day 0) to Week 12	-	**Key secondary**	**Key secondary**
PCL-5 Score	Change from Baseline to Week 10	Other efficacy	Other efficacy	Other efficacy
HADS Subscale Scores: • HADS-A (Anxiety) • HADS-D (Depression)	Change from Baseline to Week 10	Other efficacy	Other efficacy	Other efficacy

B-IPF = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression - Severity; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale - Depression subscale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder.
[a] Response rate defined as ≥ 30% reduction in CAPS-5 Total Score from Baseline.

Other exploratory efficacy endpoints included the SF-36v2, the SOTS, sleep-specific CAPS-5 items and sleep-specific PCL-5 items. The SF-36v2 was evaluated as exploratory efficacy endpoint in the Phase 3 trials and not in the Phase 2 trial. The SOTS was evaluated as an exploratory endpoint in the Phase 2 trial but was not included in Phase 3 trials. Results for these exploratory endpoints are provided in Appendix Section 10.5.6.

4.2.2.2 Clinician-Reported Outcomes

4.2.2.2.1 CAPS-5

The CAPS-5 is a clinician-reported outcome measure completed via a structured interview by trained and certified interviewers designed to assess PTSD diagnostic status and symptoms severity as defined by the DSM-5 (Figure 12) (Weathers et al 2015; Weathers et al 2018a). Symptoms severity is assessed on a scale of 0-4: 0 = absent; 1 = mild/subthreshold; 2 = moderate/threshold; 3 = severe/markedly elevated; 4 = extreme/incapacitating.

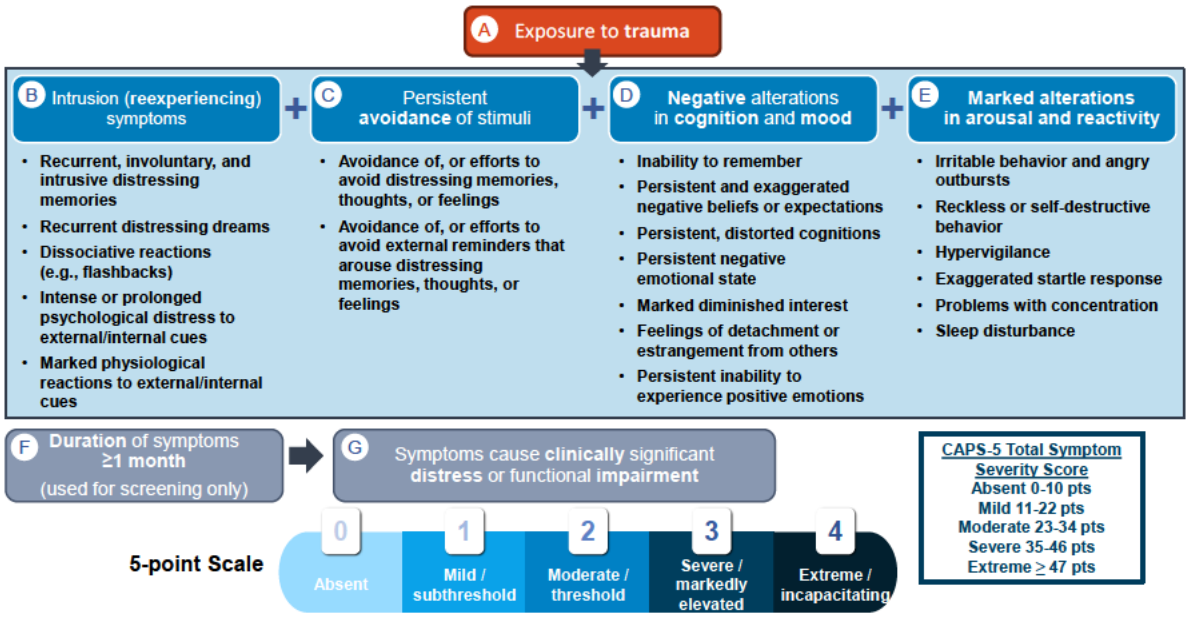
The CAPS instrument has been extensively validated and widely used with good internal consistency, inter-rater reliability and test-retest reliability (Weathers et al 2018a; Weathers et al 2018b), with the latest CAPS-5 involving an expert panel review to ensure content validity.

The CAPS-5 comprises 30 questions that target the onset and duration of symptoms (‘past month’ version for establishing diagnostic status only), subjective distress, impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS-5 administration, overall response validity, overall PTSD severity, and specifications for the dissociative subtype (depersonalization and derealization). CAPS-5 Total Score for symptom severity is calculated by summing the 20 DSM-5 PTSD symptom items for a maximal possible score of 80, with higher scores reflecting increased PTSD severity. In addition to the total severity score, scores representing 4 symptom clusters can be derived; intrusion/re-experiencing (items 1-5), avoidance (items 6-7), negative cognitions and mood (items 8-14), and arousal and reactivity (items 15-20).

In order to rate each item, the rater asks a series of standardized prompts for each item, combines information obtained from the frequency and intensity of each symptom, and makes a single severity rating for each (range 0 – 4).

Clinical meaningfulness of the CAPS-5 is further described in Section 4.2.3.

Figure 12: Overview of CAPS-5 Assessment



CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder.
Source: Source: Weathers et al 2013a; Weathers et al 2018a.

4.2.2.2.2 Clinical Global Impression - Severity

The severity of illness for each patient was rated using the CGI-S (Guy 1976). To perform this assessment, the rater or investigator answered the following question: "Considering your total clinical experience with this particular population, how mentally ill is the subject at this time?" Response choices were 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most extremely ill subjects.

4.2.2.3 Patient-Reported Outcomes

4.2.2.3.1 PTSD Checklist for DSM-5

The PCL-5 is a patient-rated instrument intended to assess the degree to which individual DSM-5 PTSD symptoms have influenced a patient's daily life (Weathers et al 2015). Unlike the CAPS-5, which is a clinical research tool, the PCL-5 is used in clinical practice to evaluate the progress over time in discussions between clinicians and patients to come to shared decision-making on treatment interventions. Patients assign a number to the right of each problem to indicate how much they had been bothered by that problem in the past week. The scale rates items from 0 (not at all), 1 (a little bit), 2 (moderately), 3 (quite a bit), and 4 (extremely). The PCL-5 were administered on the visits as specified in each trial.

4.2.2.3.2 Hospital Anxiety and Depression Scale

The HADS is a patient-rated scale designed to screen for anxiety and depressive states in people with a medical condition, consisting of 2 subscales: The D-scale measures depression and the A-scale measures symptoms of anxiety (Zigmond and Snaith 1983). Each subscale contains 7 items, and each item is rated from

0 (absent) to 3 (maximum severity). The score of each subscale ranges from 0 to 21, and the subscales are analyzed separately.

4.2.2.3.3 Brief Inventory of Psychosocial Function

The B-IPF is a short patient-reported questionnaire consisting of 7 questions that measure PTSD-specific psychosocial function on a 7-point Likert scale (0 = not at all to 6 = very much, and a "not applicable" option), with a recall period of 30 days. The B-IPF measures the concepts of romantic relationships, parenting, family, friendships and socializing, work, education, and self-care (Kleiman et al 2020).

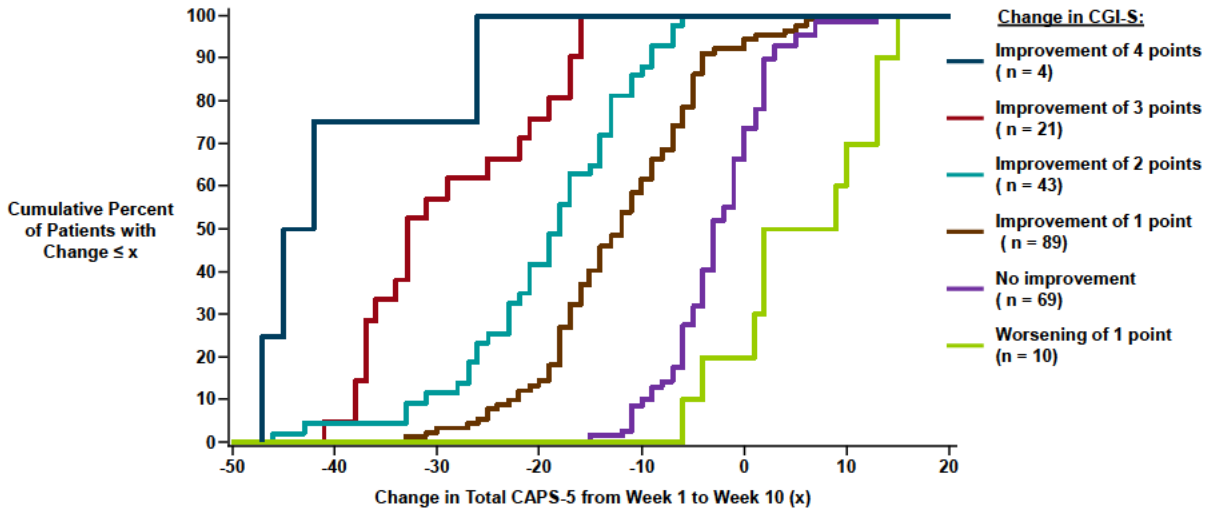
4.2.3 Determination of Clinical Meaningfulness

While past publications have reported on Minimal Clinically Important Difference (MCID) for the CAPS-IV (Krystal et al 2011; Stefanovics et al 2018), meaningful within-patient change (MWPC) estimates for the CAPS-5 had not been published. MCID estimates help interpret whether statistically significant change observed between groups (eg, treatment vs placebo/control) are clinically relevant. The FDA, however, recommends that Sponsors look beyond group mean change by defining MWPC thresholds at the individual patient level, further noting that the meaningful change thresholds for individual responders would likely be higher than the between-group MCID (Coon and Cappelleri 2016).

In consultation with the FDA, a triangulated approach was used to estimate MWPC thresholds with Trial 061 data. Two analytic approaches were used to estimate the thresholds using CGI-S as the primary anchor:

- The first approach involved calculating the mean change in CAPS-5 total severity scores from Week 1 to Week 10 anchored to a 1-point or 2-point decrease on the CGI-S over the same period (Figure 13).

Figure 13: Cumulative Distribution Function of Change in CAPS-5 from Week 1 to 10 based on CGI-S Anchor from Trial 061



CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression - Severity; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder.

- The second approach involved an adjusted predictive modelling approach classifying patients into those showing improvement on CGI-S (eg, decrease of ≥ 2 points) and those not showing improvement (Hunt et al 2018). The dichotomized anchor was regressed on the CAPS-5 change score using a logistic regression model to identify the optimal cut-point.

Thresholds of −8 and −15 points in individual-level reduction in CAPS-5 Total Score (absolute reduction from Baseline), anchored to a 1- to 2-point improvement on the CGI-S, respectively, were identified as an appropriate range of MWPC thresholds on the CAPS-5. Responder analyses based on these thresholds were performed using observed cases.

While MWPC thresholds were empirically derived using Trial 061 data and applied to Trials 071 and 072 as responder definitions, these responder analyses were not prespecified. A separate prespecified analysis was conducted with a response defined as a decrease ≥ 30% in CAPS-5 Total Score from Week 1 to the end of the efficacy period during the double-blind randomization period (Halvorsen 2016; Varker et al 2020). Responder analysis based on this criterion was performed using last-observation-carried-forward.

4.2.4 Safety Outcome Measures

Safety was assessed via standard variables including TEAEs, body weight, laboratory tests, vital signs, electrocardiograms, the Columbia Suicide Severity Rating Scale (C-SSRS)(Posner K et al 2008), and 3 EPS rating scales: Simpson-Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale (Barnes 1989; Guy 1976; Simpson and Angus 1970).

5 CLINICAL PHARMACOLOGY

Summary

- The clinical pharmacology characteristics of brexpiprazole have been established in an extensive program.
- For PTSD development program, two Phase 1 trials were conducted to examine drug interactions of brexpiprazole and sertraline.
- Mean brexpiprazole maximum (peak) plasma concentration (C_{max}) and area under the concentration-time curve (AUC) were the same or slightly lower following a single oral dose of 2 mg brexpiprazole with multiple 200 mg doses of sertraline compared to brexpiprazole alone.
- Based on the exposure-efficacy analysis, 2 and 3 mg/day doses of brexpiprazole in combination with 150 mg sertraline in patients with PTSD is sufficient to achieve maximum reduction in CAPS-5 Total Score.
    - This finding is consistent with the dosing recommendation of a daily dose of 2 to 3 mg/day brexpiprazole plus sertraline 150 mg once/day and aligns with the results of the brexpiprazole PTSD clinical development program.
- The significant relationship between brexpiprazole exposure and treatment response assessed by CAPS-5 Total Score provides supportive evidence that brexpiprazole in combination with sertraline is effective in the treatment of PTSD.
- There were no clinically meaningful changes in plasma concentration of any analyte due to treatment period or coadministration of prazosin or propranolol in the presence of brexpiprazole plus sertraline.

5.1 Overview

The brexpiprazole PTSD clinical pharmacology program for brexpiprazole in combination with sertraline consisted of two Phase 1 trials:

- Trial 245: a single-center, open-label, drug-interaction trial to assess the effect of sertraline (200 mg) at steady state on the PK of brexpiprazole in healthy adults
- Trial 246: an open-label, fixed-sequence, cross-over trial to assess the blood pressure effects of single-dose prazosin or propranolol administered with steady-state brexpiprazole and sertraline in adults with MDD, PTSD, general anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, or panic disorder (terminated early).

5.2 Pharmacokinetics

The PK profile of brexpiprazole was previously assessed in an extensive clinical pharmacology program as part of the original New Drug Application (NDA). Briefly, after single-dose administration of brexpiprazole tablets, the peak plasma brexpiprazole concentrations occurred within 4 hours after administration, and the absolute oral bioavailability was 95%. Brexpiprazole steady-state concentrations were attained within 10 to 12 days of dosing. Fed/fasted studies showed that food does not significantly influence absorption of brexpiprazole.

In vivo, brexpiprazole is metabolized primarily by CYP3A4 and CYP2D6 enzymes and in vitro studies showed little to no inhibition of CYP450 isozymes. General information on other potential drug-drug interactions is already included within the approved prescribing information.

Trial 245 examined drug interactions of brexpiprazole and sertraline. Since sertraline is a weak CYP2D6 inhibitor, the FDA requested that Trial 245 be performed. A summary of brexpiprazole PK parameters following administration of a single 2-mg oral dose of brexpiprazole alone or with multiple 200 mg doses of sertraline in healthy adults is presented in Table 12.

Mean brexpiprazole C_{max}, area under the concentration-time curve calculated to the last observable concentration at time t ($AUC_{t,}$) and area under the concentration-time curve from time zero to infinity (AUC_{∞}) were the same or slightly lower following a single oral dose of 2 mg brexpiprazole with multiple 200 mg doses of sertraline compared to brexpiprazole alone, while apparent clearance of drug from plasma after extravascular administration was higher following a single oral dose of 2 mg brexpiprazole with multiple 200 mg doses of sertraline compared to brexpiprazole alone. The decrease in brexpiprazole C_{max} and exposure is not expected to be clinically relevant, thus supporting the proposed dosing recommendations for patients with PTSD with no dose adjustment.

Table 12: Summary of Brexpiprazole Pharmacokinetic Parameters Following a Single 2 mg Oral Dose of Brexpiprazole Alone or With Multiple 200 mg Doses of Sertraline in Healthy Adults

PK Parameter	Brexpiprazole Alone N = 14	Brexpiprazole with Sertraline N = 14
C_{max} (ng/mL), mean (SD)	22.4 (5.70)	21.3 (7.22)
t_{max} (h) [a]	4.99 (2.00 - 7.99)	5.01 (1.99 - 5.04)
AUC_t (ng·h/mL) [b], mean (SD)	1690 (485)	1350 (493)
AUC_∞ (ng·h/mL) [c], mean (SD)	2000 (557)	1300 (453)
$t_{1/2,z}$ (h) [c], mean (SD)	99.7 (32.5)	86.1 (27.9)
CL/F (mL/min) [c], mean (SD)	18.2 (6.47)	29.6 (13.7)
CL/F/BW ([mL/min]/kg) [c], mean (SD)	0.222 (0.0720)	0.367 (0.126)

AUC_t = area under the concentration-time curve calculated to the last observable concentration at time t; AUC_∞ = area under the plasma concentration-time curve from time zero extrapolated to infinity; BW = body weight; Cmax = maximum (peak) plasma concentration of the drug; CL/F = apparent clearance of drug from plasma after extravascular administration; PK = pharmacokinetic; r^2 = coefficient of determination; SD = standard deviation; $t_{1/2,z}$ = terminal-phase elimination half-life; t_{max} = time to maximum (peak) plasma concentration.

[a] Median (minimum-maximum).

[b] AUC_t is considered equal to area under the concentration-time curve from time zero to 288 hours post-dose.

[c] The terminal-phase elimination rate constant (λz) was estimated for each participant by a log-linear regression of at least 3 nonzero concentrations; participants with regressions with r^2 values < 0.8 or non-negative slopes were not reported, thus n = 11 for brexpiprazole alone and n = 8 for brexpiprazole with sertraline.

Trial 246 (terminated early) assessed the hemodynamic changes associated with the effects of a single-dose of prazosin (1 mg) or propranolol (40 mg) in the presence of brexpiprazole (1 to 3 mg/day) plus sertraline (50 to 150 mg/day) at steady state. Mean sertraline, brexpiprazole, prazosin, and propranolol plasma concentrations were as expected throughout the trial. There were no clinically meaningful changes in plasma concentration of any analyte due to treatment period or coadministration of the trial drugs.

5.3 Exposure-Efficacy Analysis

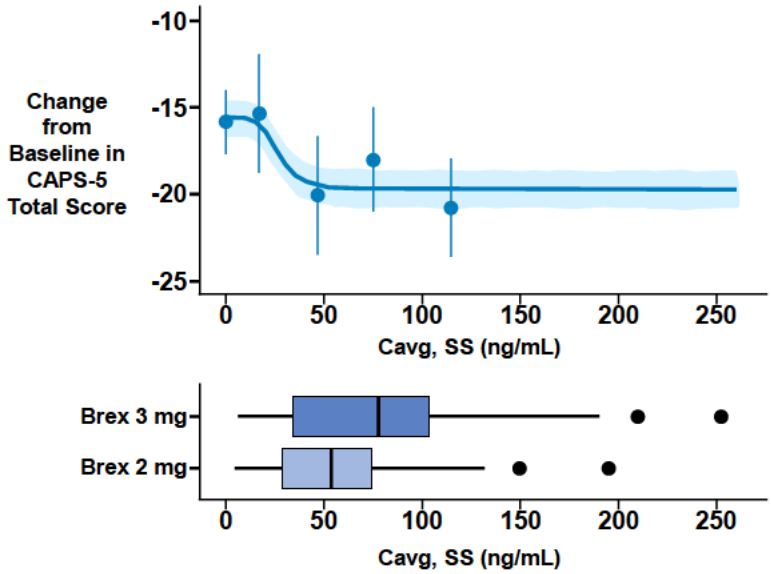
An exposure-efficacy analysis was conducted for the two Phase 3 trials to describe the relationship between brexpiprazole systemic exposure and the change from Baseline in CAPS-5 Total Score at Week 10. A total of 403 patients enrolled in Trials 071 and 072 were included in the analysis.

A sigmoid maximum effect (E_{max}) model adequately described the effect of brexpiprazole exposure as the average concentration at steady state ($C_{avg,ss}$) on the change from Baseline in CAPS-5 Total Score at Week 10. The model predicted a mean sertraline plus placebo effect of −15.6 (90% CI: −17.1, −14.1) change from Baseline in CAPS-5 Total Score, and a mean maximum brexpiprazole effect of −4.1 (90% CI: −8.82, −2.25) on top of the sertraline plus placebo effect. The model-

predicted mean brexpiprazole $C_{avg,ss}$ to achieve half-maximal brexpiprazole effect on change from Baseline was 26.7 ng/mL (90% CI: 10.2, 97.2; Figure 14).

The sigmoid E_{max} model adequately described the effect of brexpiprazole $C_{avg,ss}$ on the change from Baseline in CAPS-5 Total Score at Week 10 in the overall population, as well as in low and high sertraline concentration groups (Figure 14). The results show that the daily dose of brexpiprazole 2 to 3 mg in combination with sertraline 150 mg is expected to be efficacious.

Figure 14: Observed and Model-Predicted Mean and 95% Confidence Interval of Change from Baseline in CAPS-5 Total Score versus Brexpiprazole $C_{avg,ss}$



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CFB = Change from Baseline; $C_{avg,ss}$ = average brexpiprazole concentration at steady state; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder.
Note: Data points and error bars on top panel represent the observed mean and 95% confidence interval of change from Baseline in CAPS-5 Total Score at Week 10 by sertraline + placebo treatment group and brexpiprazole $C_{avg,ss}$ quartiles. The blue line and shaded region on top panel represent the model-predicted mean and 95% confidence interval of CFB in CAPS-5 Total Score at Week 10.
Boxplots show the brexpiprazole $C_{avg,ss}$ distribution at 2, and 3 mg/day doses in this PTSD adult population.

While sertraline exposure was not incorporated in the final exposure-efficacy model because patients in all treatment arms in Trials 071 and 072 received the same fixed-dose of sertraline (150 mg/day), exploratory analyses suggested that 1) distributions of observed sertraline concentrations were similar across all treatment arms, 2) the relationship between observed sertraline concentrations and change from Baseline in CAPS-5 Total Score was not consistent in the two Phase 3 trials, and 3) the relationship between brexpiprazole $C_{avg,ss}$ and change from Baseline in CAPS-5 Total Score was consistent and not influenced by differences in sertraline concentrations.

6 CLINICAL EFFICACY

Summary

- In the largest program in PTSD to date, combination treatment with brexpiprazole plus sertraline was more effective in relieving symptoms of PTSD and demonstrated larger response rates than sertraline alone in 2 of 3 studies, addressing a critical unmet need for these patients.
- Trial 071 provides statistically significant and clinically meaningful evidence that brexpiprazole plus sertraline is superior to sertraline plus placebo in the treatment of PTSD.
    - Flexible dose (2-3 mg/day) brexpiprazole plus sertraline was statistically superior to sertraline plus placebo on the primary efficacy endpoint of change in CAPS-5 Total Score from Week 1 to Week 10.
    - The benefit of brexpiprazole plus sertraline was also demonstrated across multiple clinician- and patient-reported efficacy scales.
- Trial 072 did not meet its primary endpoint.
- Trial 061 provides supportive evidence that brexpiprazole plus sertraline is superior to sertraline plus placebo in the treatment of PTSD.
    - Flexible dose (1-3 mg/day) brexpiprazole plus sertraline was more effective in relieving PTSD symptoms than sertraline alone, brexpiprazole alone, and placebo.
    - Consistent support for the efficacy of brexpiprazole plus sertraline therapy was seen in clinician- and patient-reported other endpoints.
- Brexpiprazole plus sertraline demonstrated broad and consistent symptom improvements across the 4 clinician-reported CAPS-5 symptom clusters in Trials 071 and 061.

6.1 Trial 331-201-00061: Phase 2 Flexible-Dose Trial

6.1.1 Trial 061: Trial Design

6.1.1.1 Overview

Trial 061 was a Phase 2, randomized, double-blind, placebo- and active-controlled, 4-arm, multifactorial flexible-dose trial. The trial evaluated the efficacy, safety, and tolerability of brexpiprazole (1 to 3 mg/day) as a combination therapy with sertraline and as monotherapy in adult patients with PTSD across 48 sites in the US. The trial was conducted between Jan 2017 and Nov 2018 and is registered at ClinicalTrials.gov (identifier: NCT03033069).

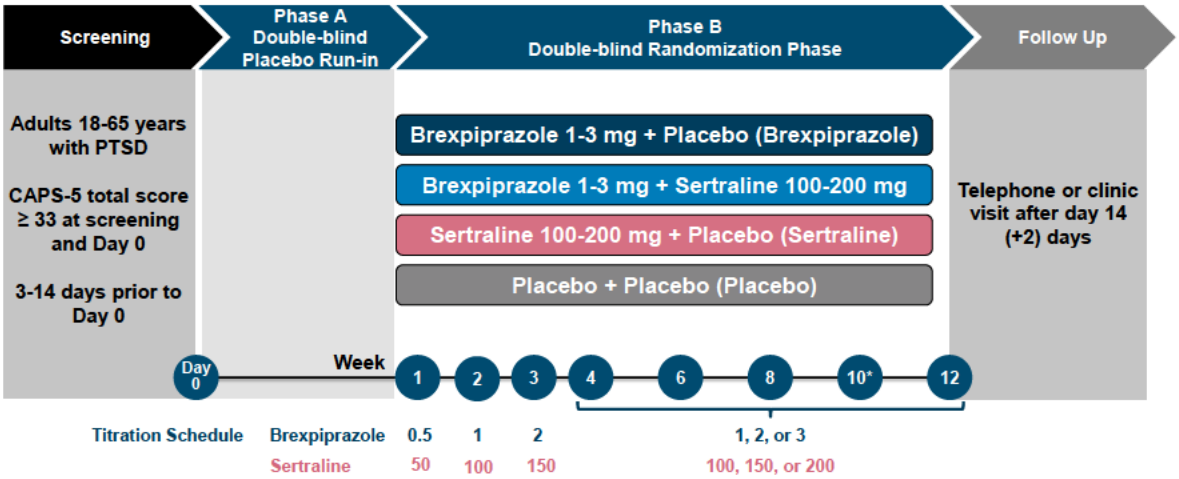
Trial 061 included a 14-day screening period, 1-week double-blind placebo run-in period (Phase A), 11-week double-blind treatment period (Phase B), and 14-day

safety follow-up period (Figure 15). After the 1-week placebo run-in period (Phase A), eligible patients were randomized into 1 of 4 treatment arms:

- Brexpiprazole (1 to 3 mg/day) plus sertraline (100 to 200 mg/day)
- Brexpiprazole (1 to 3 mg/day) plus placebo
- Sertraline (100 to 200 mg/day) plus placebo
- Placebo plus placebo (referred to as placebo)

Brexpiprazole and sertraline were flexibly dosed at 1-3 mg/day and 100-200 mg/day, respectively. Trial drugs were taken orally, together, once daily, without regard to meals. Brexpiprazole tablets (or matched placebo) and sertraline capsules (or matched placebo) were provided by the Sponsor or designee in blinded blister cards. Patients were titrated to the respective target doses over 3 weeks. Trial drugs were taken orally, together, once daily, without regard to meals. Trial visits occurred at Day 0 and Weeks 1, 2, 3, 4, 6, 8, 10, and 12. The primary endpoint was assessed at Week 10.

Figure 15: Trial 061 Design Schematic



CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; PTSD = post-traumatic stress disorder.
*Primary assessment
Target dose was 1-3 mg/day for brexpiprazole and 100-200 mg/day for sertraline.

6.1.1.2 Enrollment Criteria

The trial population included male and female outpatients between 18 and 65 years of age at the time of consent, inclusive, with a DSM-5 diagnosis of PTSD with a CAPS-5 Total Score ≥ 33 at Screening and Day 0 visits. The index trauma leading to the PTSD diagnosis should not have happened more than 15 years before Screening or before the age of 16 and symptoms of PTSD should have been present for at least 6 months prior to Screening.

Full enrollment criteria are provided in Appendix Section 10.1.

6.1.1.3 Efficacy Endpoints

The primary efficacy endpoint was the change from Baseline to the Week 10 visit in CAPS-5 Total Score. Other efficacy endpoints included, but were not limited to, change from Baseline in CAPS-5 symptom cluster scores, change from Baseline in CGI-S score; change from Baseline in PCL-5 score, change from Baseline in HADS score; and response defined by decrease ≥ 30% from Baseline to Week 10 in the CAPS-5 Total Score.

6.1.1.4 Statistical Methods

6.1.1.4.1 Sample Size

The primary objective of this trial was to evaluate the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adults with PTSD. The sample size was powered to detect a treatment difference of the primary endpoint of CAPS-5 change from Baseline at Week 10. Sixty-eight patients per arm provided at least 80% power at a 2-sided alpha level of 0.05 to detect the treatment difference of −6.5 points in the primary efficacy endpoint for active arm (Brex + Sert or Brex) vs placebo with an SD of 13. Adjusting for 10% non-evaluable patients, and 10% dropout between Day 0 and randomization, approximately 332 patients (83 per arm) were planned to be enrolled in the trial.

6.1.1.4.2 Analysis Populations

The primary efficacy population for Trial 061 was the Efficacy Sample, which comprised all randomized patients who took at least 1 dose of double-blind trial drug and had a CAPS-5 Total Score evaluation at Baseline and at least 1 post-Baseline evaluation.

Disposition and demographics are summarized using the Randomized Sample, which included all randomized patients who were assigned a treatment group at randomization. The Safety Sample was analyzed based on all randomized patients who received at least 1 dose of double-blind trial drug.

6.1.1.4.3 Statistical Analyses for the Primary Endpoint

As a multifactorial design, the Statistical Analysis Plan for Trial 061 prespecified 5 pairwise comparisons, 3 of which are relevant to the primary objective of evaluating the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adults with PTSD:

- Brexpiprazole plus sertraline versus placebo
- Brexpiprazole plus sertraline versus sertraline
- Brexpiprazole versus placebo (as monotherapy treatment)

The other 2 treatment group comparisons were:

- Brexpiprazole plus sertraline versus brexpiprazole
- Sertraline versus placebo (as assay sensitivity)

Statistical analyses were conducted for each pairwise comparison, with significance level of 2-sided alpha of 0.05.

The primary analysis was based on an MMRM analysis under MAR assumption. The dependent variable is change from Baseline to Week 10 in CAPS-5 Total Score, with fixed effects of treatment, site, type of trauma (combat-related Yes/No), visit week, and interaction terms of treatment by visit week and Baseline CAPS-5 Total Score by week. The unstructured variance covariance structure was used.

To evaluate the robustness of the primary analysis assumption of MAR, prespecified sensitivity analyses were performed under different methods of handling missing data, described in Appendix Section 10.5.1.

6.1.1.4.4 Retrospective Multiplicity Adjustment to Evaluate Statistical Significance

To assess robustness of the detected treatment effect, retrospective adjustment was applied to control for multiplicity in relation to the 3 pairwise comparisons of the primary endpoint. The following retrospective multiplicity adjustments were used:

- Bonferroni adjustment (Dunn 1961)
- Holm step-down method (Holm 1979)
- Hochberg step-up method (Hochberg 1988)

See Appendix Section 10.5.2 for additional details.

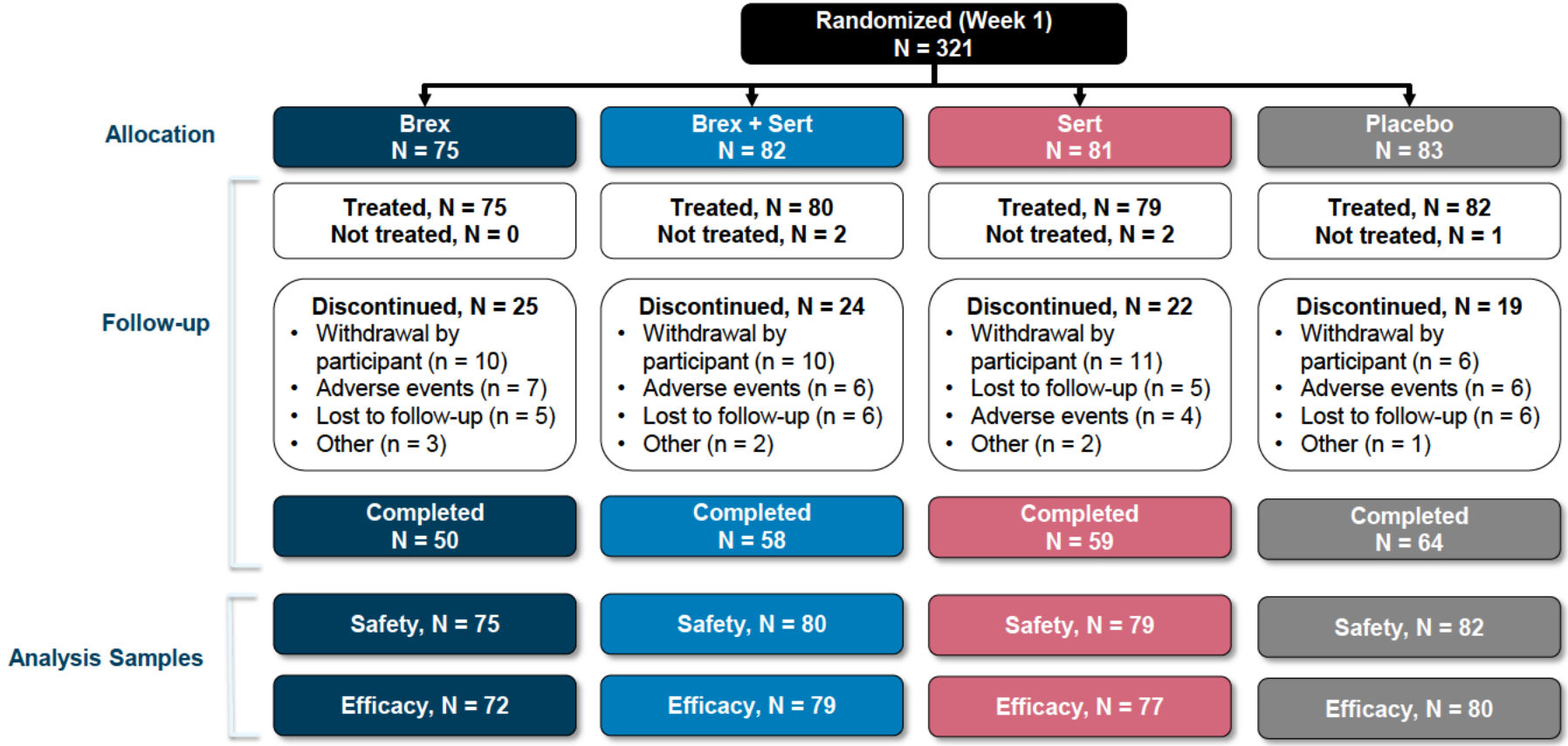
6.1.2 Trial 061: Enrolled Patients

6.1.2.1 Disposition

A total of 336 patients enrolled into the placebo run-in period. Following the placebo run-in period, 321 patients were randomized into the treatment period at Week 1 into 1 of the 4 treatment groups as illustrated in Figure 16.

Overall, 72.0% of randomized patients completed the trial. The most common reasons for discontinuation were withdrawal by patient, AE, and lost to follow-up.

Figure 16: Trial 061 Patient Disposition (Randomized Sample)



Brex = brexpiprazole; Sert = sertraline.
Note: "Other" includes all of the remaining discontinuation categories.

6.1.2.2 Demographic and Patient Characteristics

Patient demographics were generally balanced across treatment groups and representative of the intended population (Table 13). The mean age was approximately 39 years (range 18 – 65 years), and patients were predominately female, white, and not Hispanic or Latino.

Table 13: Trial 061 Key Demographic Characteristics (Randomized Sample)

Parameter	Brex 1-3 mg +Sert N = 82	Brex 1-3 mg + Placebo N = 75	Sert + Placebo N = 81	Placebo + Placebo N = 83
Age (years)				
Mean (SD)	38.4 (11.9)	39.3 (10.6)	38.6 (10.9)	40.3 (11.0)
Median (min, max)	35.0 (18, 65)	38.0 (20, 61)	39.0 (20, 62)	39.0 (19, 65)
Age Group, n (%)				
< 55	71 (86.6)	66 (88.0)	72 (88.9)	71 (85.5)
≥ 55	11 (13.4)	9 (12.0)	9 (11.1)	12 (14.5)
Sex, n (%)				
Male	31 (37.8)	26 (34.7)	30 (37.0)	35 (42.2)
Female	51 (62.2)	49 (65.3)	51 (63.0)	48 (57.8)
Race, n (%)				
White	55 (67.1)	43 (57.3)	53 (65.4)	46 (55.4)
Black or African American	21 (25.6)	23 (30.7)	22 (27.2)	26 (31.3)
American Indian or Alaska Native	1 (1.2)	1 (1.3)	0 (0.0)	2 (2.4)
Asian	1 (1.2)	2 (2.7)	0 (0.0)	1 (1.2)
Native Hawaiian or Other Pacific Islander	1 (1.2)	1 (1.3)	0 (0.0)	0 (0.0)
Other	3 (3.7)	5 (6.7)	6 (7.4)	8 (9.6)
Ethnicity, n (%)				
Hispanic or Latino	13 (15.9)	11 (14.7)	11 (13.6)	14 (16.9)
Not Hispanic or Latino	68 (82.9)	64 (85.3)	70 (86.4)	69 (83.1)
BMI (kg/m^2)				
Mean (SD)	29.9 (7.0)	29.8 (7.1)	30.0 (7.5)	30.3 (6.1)
Median (min, max)	29.2 (16.9, 50.3)	29.1 (16.0, 51.0)	28.7 (18.3, 63.4)	29.9 (17.7, 45.7)

BMI = body mass index; Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

The average time since the index trauma was 6.4 years, with an average age at index trauma of 32.8 years. Combat-related trauma events were present in 21.5% of the overall population, with the majority of the population having a noncombat-related

trauma index event (Table 14). Of the patients with prior treatment, 44.2% received pharmacotherapy and 36.4% received psychotherapy.

Table 14: Trial 061 Post-Traumatic Stress Disorder Disease History (Randomized Sample)

Category, n (%)	Brex 1-3 mg + Sert N = 82	Brex 1-3 mg + Placebo N = 75	Sert + Placebo N = 81	Placebo + Placebo N = 83
Years since trauma				
Mean (SD)	6.8 (4.3)	6.3 (4.4)	5.5 (4.1)	6.9 (4.5)
Median (min, max)	6.9 (0.5, 14.4)	6.0 (0.5,15.0)	4.8 (0.3, 14.5)	7.0 (0.5, 14.9)
Age at Index Trauma, years				
Mean (SD)	31.5 (12.6)	33.1 (11.2)	33.1 (11.2)	33.5 (11.1)
Median (min, max)	27.0 (16, 61)	32.5 (15, 57)	33.0 (16, 56)	33.0 (17, 58)
Trauma Type, n (%)				
Non-combat-related trauma	60 (73.2)	63 (84.0)	65 (80.2)	64 (77.1)
Combat-related Trauma	22 (26.8)	12 (16.0)	16 (19.8)	19 (22.9)
Previous Medication Treatment, n (%)	36 (43.9)	26 (34.7)	39 (48.1)	41 (49.4)
Previous Psychotherapy, n (%)	29 (35.4)	27 (36.0)	31 (38.3)	30 (36.1)

Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

At randomization (Week 1), patients had mean CAPS-5 and CGI-S scores that were similar across treatment groups and representative of moderate-to-severe PTSD severity (Table 15).

Table 15: Trial 061 Summary of Baseline Efficacy Scale Scores (Efficacy Sample)

Score	Brex 1-3 mg + Sert N = 79	Brex 1-3 mg + Placebo N = 72	Sert + Placebo N = 77	Placebo + Placebo N = 80
CAPS-5 Total Severity Score				
Mean (SD)	35.5 (11.4)	34.2 (13.2)	36.8 (10.2)	35.3 (10.6)
Min, Max	5, 69	0, 58	5, 56	4, 58
CAPS-5 Subscale Intrusion Score				
Mean (SD)	8.4 (3.4)	7.8 (4.7)	8.9 (3.8)	8.5 (3.9)
Min, Max	0, 18	0, 16	0, 18	0, 15
CAPS-5 Subscale Avoidance Score				
Mean (SD)	4.5 (1.8)	4.2 (2.0)	4.7 (1.9)	4.6 (1.8)
Min, Max	0, 8	0, 6	0, 8	0, 8
CAPS-5 Subscale Cognitions and Mood Score				
Mean (SD)	12.9 (5.3)	12.3 (6.1)	13.2 (5.2)	12.2 (4.4)
Min, Max	0, 27	0, 23	0, 22	1, 23
CAPS-5 Subscale Arousal and Reactivity Score				
Mean (SD)	9.7 (3.7)	9.8 (3.8)	10.0 (2.7)	9.9 (3.4)
Min, Max	2, 17	0, 18	4, 15	0, 16
CGI-Severity of Illness Score				
Mean (SD)	4.4 (0.9)	4.3 (1.0)	4.4 (1.0)	4.4 (0.8)
Min, Max	2, 6	1, 6	2, 6	2, 6
HADS-Anxiety Score				
Mean (SD)	12.5 (4.0)	12.1 (4.5)	12.5 (4.4)	12.6 (3.9)
Min, Max	1, 20	4, 21	1, 21	3, 21
HADS-Depression Score				
Mean (SD)	10.2 (4.4)	9.4 (4.5)	9.6 (4.4)	9.0 (3.7)
Min, Max	1, 20	0, 20	0, 18	2, 16
PCL-5 Total Score				
Mean (SD)	43.9 (14.7)	44.3 (16.8)	44.6 (16.2)	42.7 (13.1)
Min, Max	7, 78	5, 78	14, 80	6, 74

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; SD = standard deviation; Sert = sertraline.

6.1.2.3 CAPS-5 Performance During Placebo Run-in Period

During the placebo run-in period, mean (SD) CAPS-5 Total Score change from enrollment (Day 0) to randomization (Week 1) was −7.7 (9.3) points.

6.1.2.4 Treatment Received

By group, the mean dose at each patient's last visit was brexpiprazole 2.2 mg plus sertraline 161 mg, brexpiprazole 2.1 mg plus placebo, and sertraline 158 mg plus placebo. The modal (most frequent) brexpiprazole dose was 2 mg/day for 64% of patients and 3 mg/day for 25% of patients.

6.1.3 Trial 061: Efficacy Results

6.1.3.1 Primary Endpoint Results

6.1.3.1.1 Change in CAPS-5 Total Score from Baseline to Week 10

The primary objective of Trial 061 was to evaluate the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adult patients with PTSD by assessing the change in CAPS-5 Total Score from Baseline to Week 10. As a multifactorial design, the Statistical Analysis Plan for Trial 061 prespecified 5 pairwise comparisons, 3 of which are relevant to the primary objective:

- The combination of brexpiprazole 1- 3 mg/day plus sertraline demonstrated clinically meaningful improvements versus placebo (treatment difference −5.99 [95% confidence interval (CI): −9.79, −2.19]; p = 0.0021)
- The combination of brexpiprazole 1- 3 mg/day plus sertraline demonstrated clinically meaningful improvements versus sertraline plus placebo (treatment difference −5.08 [95% CI: −8.96, −1.20]; p = 0.0106)
- Monotherapy treatment with brexpiprazole plus placebo did not demonstrate improvement versus placebo at Week 10 (treatment difference: −1.74 [95% CI: −5.70, 2.22]; p = 0.3868).

In addition to the primary assessments, the combination of brexpiprazole 1- 3 mg/day plus sertraline demonstrated clinically meaningful improvements versus brexpiprazole plus placebo (treatment difference: −4.24 [95% CI: −8.26, −0.23]; p = 0.0384.) However, treatment with sertraline plus placebo did not demonstrate improvement from placebo at Week 10 (treatment difference −0.91 [95% CI: −4.74, 2.92]; p = 0.6399) (Table 16). Note that sertraline has been extensively studied in PTSD, and, while a number or trials support its efficacy, several did not demonstrate significant efficacy versus placebo, meaning the lack of efficacy for sertraline in the present trial was not unanticipated.

The benefit over the other treatment groups in CAPS-5 Total Score was observed from Week 6 onward for brexpiprazole in combination with sertraline (Figure 17).

Subgroup analyses are presented in Appendix Section 10.5.4.

Table 16: Trial 061 Primary Endpoint: Change in CAPS-5 Total Score from Baseline to Week 10 (Efficacy Sample)

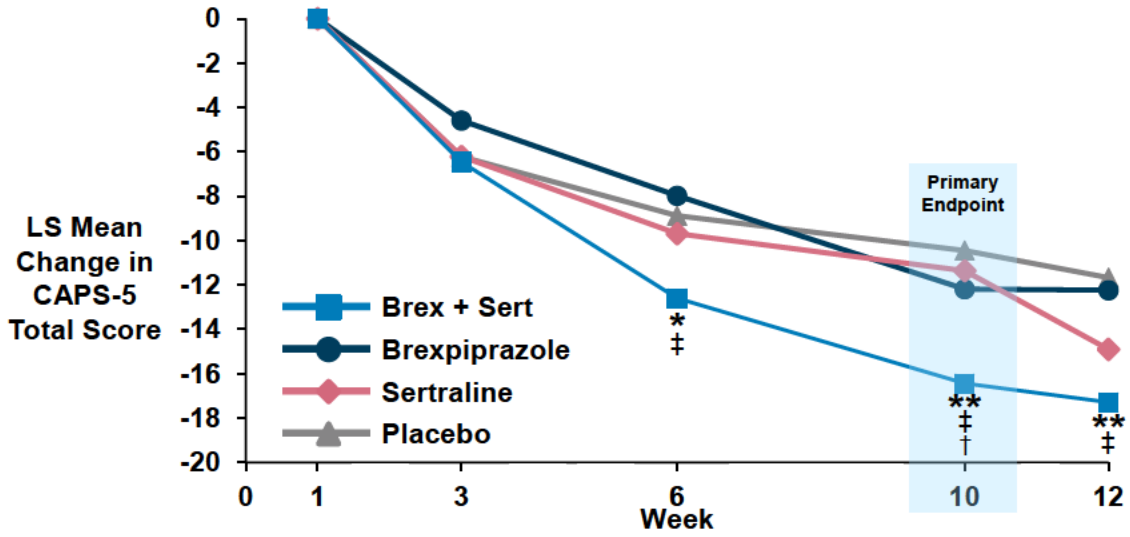
Variable	Brex 1-3 mg + Sert N = 77	Brex 1-3 mg + Placebo N = 69	Sert + Placebo N = 75	Placebo + Placebo N = 78
Mean CAPS-5 Total Score at Baseline (SD)	35.73 (11.50)	33.88 (13.31)	36.51 (10.19)	35.14 (10.68)
LS Mean Change at Week 10 (SE)	−16.44 (1.43)	−12.19 (1.57)	−11.36 (1.46)	−10.45 (1.40)
vs placebo				
Treatment Difference (95% CI)[a]	−5.99 (−9.79, −2.19)	−1.74 (−5.70, 2.22)	−0.91 (−4.74, 2.92)	-
p-value[a]	0.0021	0.3868	0.6399	-
Brex + Sert vs Sert + placebo				
Treatment Difference (95% CI) [a]	−5.08 (−8.96, −1.20)	-	-	-
p-value [a]	0.0106	-	-	-
Brex + Sert vs Brex+ placebo				
Treatment Difference (95% CI) [a]	−4.24 (−8.26, −0.23)	-	-	-
p-value [a]	0.0384	-	-	-

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; MMRM = Mixed Model Repeated Measurements; PTSD = post-traumatic stress disorder; SD = standard deviation; SE = standard error; Sert = sertraline.

[a] MMRM analysis for CAPS-5 TOTAL; treatment difference = difference in LS mean changes for MMRM.

The Efficacy Sample comprises 308 patients; however, 299 were included in the primary efficacy analysis since 9 patients who discontinued did not have a CAPS-5 value within the permitted visit window.

Figure 17: Trial 061 LS Mean Change in CAPS-5 Total Score Over Time (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.
Nominal p-value vs placebo: *p <0.05, ** p <0.01.
Nominal p-values vs sertraline + placebo: † p <0.05.
Nominal p-values vs Brex + placebo: ‡ p <0.05.
The Efficacy Sample comprises 308 patients, 299 were included in the primary efficacy analysis since 9 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.
Baseline CAPS-5 Total Score Placebo = 35.14, n = 78; Brex = 33.88, n = 69; Sertraline = 36.51, n = 75; Brex + Sert = 35.73, n = 77.

6.1.3.1.2 Prespecified Primary Endpoint Sensitivity Analyses and Retrospective Alpha Adjustment

Prespecified sensitivity analyses using different mechanisms of handling missing data showed robustness of the efficacy of brexpiprazole plus sertraline vs sertraline plus placebo regardless of the methods used for handling missing data (Appendix Table 50). As shown in Table 17, the Delta Adjustment (ie, Tipping Point) sensitivity analysis demonstrates the significance of the combination arm versus sertraline monotherapy is robust and maintained until the penalty on the combination arm reaches extreme values. For example, for discontinuation 'due to any reasons' it would require 8.5 points added to the imputed (based on multiple imputation under MAR) CAPS-5 for the missing observations in the combination arm to no longer be statistically significant versus the sertraline monotherapy arm, which is not penalized but has its missing values also imputed based on multiple imputation under MAR. Similarly, with missing due to AE or loss of efficacy (LOE) (7.8%), which is fewer than the due to any reasons category, a larger amount of delta/penalty (31.9 points) is required to shift the result to not be significant.

Results were consistent with other sensitivity approaches (Appendix Table 51).

Table 17: Trial 061 Prespecified Delta Adjustment Sensitivity Analysis Results for CAPS-5 Total Score

Reasons for Discontinuation, n (%)	LSMD Brex + Sert vs Sert + Placebo (95% CI) at Tipping Point	Tipping Point CAPS-5 Total Score Imputation
Due to AE or LOE, 24 (7.8%)	−3.88 (−7.79, 0.034)	Δ = 31.9 points
Due to AE or LOE or withdrew consent, 56 (18.2%)	−3.81 (−7.64, 0.021)	Δ = 13.0 points
Due to any reasons, 77 (25%)	−3.76 (−7.58, 0.058)	Δ = 8.5 points

AE = adverse event; Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LOE = loss of efficacy; LSMD = least squares mean difference; PTSD = post-traumatic stress disorder; Sert = sertraline.

Additionally, while there are multiple comparisons to be made with a multi-factorial design, no multiplicity adjustments were pre-specified. However, 3 of the most common retrospective multiplicity adjustments (Bonferroni, Holm, and Hochberg) were applied for the 3 pairwise comparisons related to the primary objective of Trial 061 to evaluate the robustness of the results when controlling for study-wise type 1 error. All of the methods demonstrated maintenance of statistical significance of the combination of brexpiprazole and sertraline when compared with placebo and when compared with sertraline (Table 18). Thresholds for the Holm and Hochberg adjustments are described in Appendix Section 10.5.2.

Table 18: Trial 061 Retrospective Multiplicity Adjustment Results

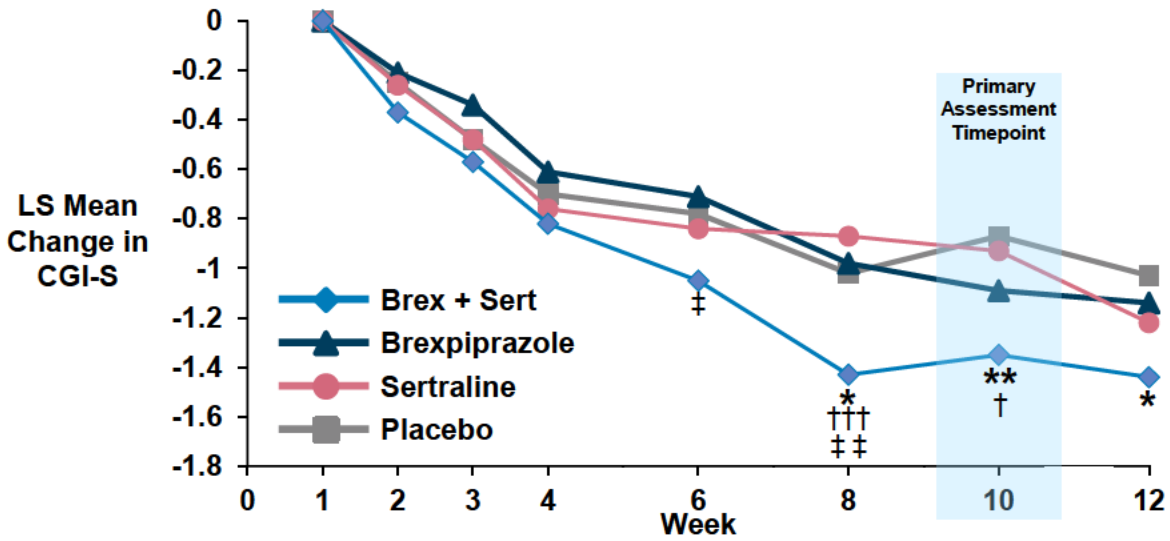
Comparison	Nominal p-value	Bonferroni Adjustment	Holm Step-up Adjustment	Hochberg Step-down Adjustment
Brex + Sert vs Sert	0.0106	Significant	Significant	Significant
Brex + Sert vs placebo	0.0021	Significant	Significant	Significant
Brex vs placebo	0.3868	Not significant	Not significant	Not significant

Brex = brexpiprazole; Sert = sertraline.

6.1.3.2 Other Efficacy Results

Clinician- and patient-reported other efficacy endpoints mirrored changes observed with the primary endpoint. Brexpiprazole plus sertraline combination therapy resulted in consistent improvement in change in CGI-Severity, with benefits over the other treatment groups (Figure 18).

Figure 18: Trial 061 LS Mean Change in CGI-S Over Time (Efficacy Sample)



Brex = brexpiprazole; CGI-S = Clinical Global Impression – Severity; LS = least squares; Sert = sertraline.
Nominal p-value vs placebo: *p <0.05, ** p <0.01.
Nominal p-values vs sertraline + placebo: †† p < 0.01; ††† p < 0.001.
Nominal p-values vs Brex + placebo: ‡ p < 0.05, ‡‡ p < 0.01.
Efficacy Sample comprises 308 patients, 307 were included in the CGI-S efficacy analysis since 1 patient who discontinued did not have a CGI-S value within the permitted visit window.
Baseline CGI-S score: Placebo = 4.38, n = 80; Brex = 4.26, n = 72; Sertraline = 4.38, n = 77; Brex + Sert = 4.42, n = 78.

Consistent benefits were also observed for PCL-5 Total Score, HADS-Anxiety, and HADS-Depression (Table 19). Additionally, treatment with brexpiprazole plus sertraline demonstrated numerical benefits on 3 of the 4 CAPS-5 symptom clusters versus sertraline plus placebo including improvements in CAPS-5 intrusion (re-experiencing), avoidance, negative cognitions and mood (all nominal p < 0.05).

Table 19: Trial 061 Other Efficacy Endpoints: Summary of Mean Change from Baseline to Week 10 in Clinician- and Patient-Reported Outcomes (Efficacy Sample)

	Brex + Sert vs Sert + Placebo	
Endpoint	**Treatment Difference [a] (95% CI)**	**Nominal P-value[a]**
Clinician-Reported		
CGI-Severity	−0.42 (−0.76, −0.08)	0.0167
CAPS-5 Subscale Intrusion (Re-Experiencing)	−2.06 (−3.51, −0.60)	0.0058
CAPS-5 Subscale Avoidance	−0.79 (−1.50, −0.09)	0.0273
CAPS-5 Subscale Negative Cognitions/Mood	−1.82 (−3.44, −0.19)	0.0285
CAPS-5 Subscale Arousal and Reactivity	−0.56 (−1.69, 0.58)	0.3325
Patient-Reported		
PCL-5	−4.93 (−9.83, −0.03)	0.0487
HADS - Anxiety	−1.55 (−2.92, −0.17)	0.0274
HADS - Depression	−1.94 (−3.23, −0.65)	0.0033

Brex = brexpiprazole; Brex + Sert = brexpiprazole plus sertraline; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI = Clinical Global Impression; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5 PTSD = post-traumatic stress disorder.

[a.] Mixed model repeated measures method with model terms: treatment, (pooled) trial site, type of trauma, visit, and treatment by visit and Baseline by visit interaction.

6.1.4 Trial 061: Efficacy Conclusions

Results of Trial 061 demonstrated that combination therapy with brexpiprazole plus sertraline was more effective in relieving PTSD symptoms (as determined by improvements in the CAPS-5 Total Score) than sertraline alone, brexpiprazole alone, and placebo. Consistent support for the efficacy of the combination of brexpiprazole plus sertraline therapy was also seen in the clinician- and patient-reported secondary endpoints.

6.1.5 Phase 3 Trial Design Considerations Based on Trial 061 Outcomes

Based on these findings of Trial 061, the Phase 3 program was designed to evaluate the combination treatment with brexpiprazole plus sertraline versus sertraline alone and was agreed upon with the FDA. Key points aligned upon with the FDA for the Phase 3 designs based on the outcomes of Trial 061 include:

- Removal of the brexpiprazole monotherapy and placebo arms in future trials as the pertinent question is whether brexpiprazole plus sertraline is superior to sertraline monotherapy

- Alignment on dose range and target dose for future trials to include 2-3 mg/day brexpiprazole compared to 150 mg/day sertraline based on Trial 061 modal dosing and sertraline prescribing information. To reduce the complexities of interpretation of the role of either drug in mediating efficacy and safety/tolerability, the FDA recommended after the titration period maintaining sertraline at 150 mg/day while allowing brexpiprazole doses to be 2 or 3 mg/day.
- The Sponsor proposed 2 identical flexible-dose trials given they are more reflective of real-world clinical practice; however, the FDA requested at least 1 trial be fixed dose to better characterize the safety and tolerability of 2 mg versus 3 mg doses of brexpiprazole in the PTSD population.
- The FDA agreed with the overall trial design, patient population, and endpoints for the Phase 3 trials.
- The FDA agreed that long-term safety data in PTSD was not needed for the submission given the extensive safety database for brexpiprazole, including when co-administered with sertraline.

6.2 Trial 331-201-00071: Phase 3 Flexible-Dose Trial

6.2.1 Trial 071: Trial Design

6.2.1.1 Overview

Trial 071 was a Phase 3, multicenter, 12-week, double-blind, randomized trial designed to evaluate the efficacy and safety of flexible-dose brexpiprazole plus sertraline or sertraline plus placebo combination treatment in adult patients with PTSD. The primary objective of this trial was to evaluate the efficacy of flexible dosing of brexpiprazole plus sertraline compared with the efficacy of sertraline plus placebo, as assessed by the change in the CAPS-5 Total Score from Baseline to Week 10. Patients were enrolled from 78 sites in the US. The trial was conducted between Oct 2019 and Aug 2023 and is registered at ClinicalTrials.gov (identifier: NCT04124614).

Trial 071 included a screening period (3- to 14-day medication washout period) followed by a 1-week, double-blind placebo only run-in period (Phase A), 11-week double-blind randomized treatment period (Phase B), and 3-week follow-up period (Figure 19). After the run-in period, eligible patients were randomized 1:1 to:

- Flexible dose (2-3 mg/day) brexpiprazole + sertraline (150 mg/day), or
- Sertraline (150 mg/day) + placebo

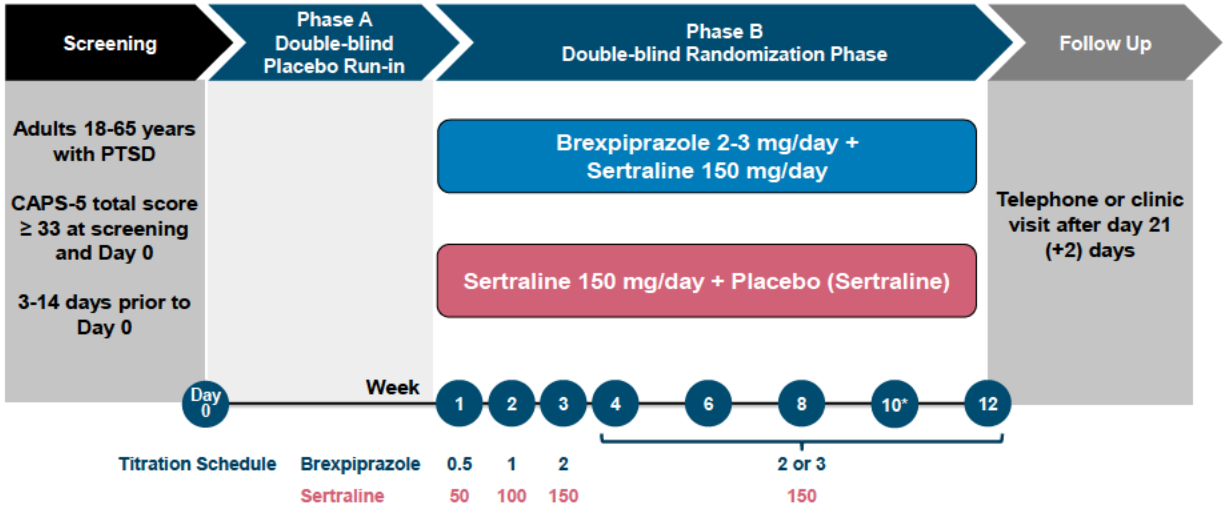
Randomization was stratified by site and whether a patient met the enriched patient criteria for the Efficacy Sample (CAPS-5 Total Score of at least 27 at the randomization visit [Week 1] and an improvement in terms of reduction in CAPS-5

Total Score of less than 50% at end of the placebo run-in phase [Phase A] to exclude patients who responded to placebo during the placebo run-in phase).

Trial drugs were taken orally, together, once daily, without regard to meals. Brexpiprazole tablets (or matched placebo) and sertraline capsules (or matched placebo) were provided by the Sponsor or designee in blinded blister cards. Patients were titrated to their respective target doses over 3 weeks as illustrated in Figure 19.

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

Figure 19: Trial 071 Design Schematic



CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder.
Titration schedule based on mg/day.
*Primary Assessment
CAPS-5 was assessed at each scheduled visit except for Week 2 and Week 8.

6.2.1.2 Enrollment Criteria

Trial 071 enrolled adult patients between 18 and 65 years of age (inclusive) with PTSD, diagnosed according to the DSM-5, with a CAPS-5 Total Score ≥ 33 at Screening and Day 0, and an onset of symptoms ≥ 6 months prior to Screening.

Exclusion criteria included, but were not limited to, an index traumatic event at an age of < 16 years, an index traumatic event > 9 years before Screening, and a traumatic event ≤ 3 months before Screening.

Full enrollment criteria are provided in Appendix Section 10.1.

6.2.1.3 Endpoints

Efficacy endpoints are described in Table 11.

6.2.1.4 Statistical Methods

6.2.1.4.1 Sample Size

A planned sample size of 284 patients in the Efficacy Sample was estimated to achieve 85% power at a 2-sided alpha level of 0.05 to detect a treatment difference of −5.0 points (SD, 14) in CAPS-5 Total Score change from randomization (Week 1) to Week 10, where −5.0 was derived from Trial 061 data and clinical experience with the PTSD patient population. This estimate was adjusted to 448 enrolled patients after accounting for up to 30% loss due to the enriched criteria and a 5% non-evaluability/dropout rate.

6.2.1.4.2 Analysis Populations

The primary efficacy analysis population in Trial 071 was the Efficacy Sample, which included all randomized patients who satisfied the enrichment criteria and took at least 1 dose of double-blind trial drug and had a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score. The Efficacy Sample excluded patients who responded during the placebo run-in period.

The Full Analysis Set (FAS), which included all randomized patients who took at least 1 dose of double-blind trial drug and had a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score, was used for prespecified supportive analyses.

The Randomized Sample and Safety Sample were defined as described in Section 6.1.1.4.2.

6.2.1.4.3 Endpoint Analyses

The primary analysis performed was based on Efficacy Sample.

The primary endpoint was analyzed using an MMRM model. The dependent variable was change from Baseline in CAPS-5 Total Score at Week 10, with fixed effects of treatment, site, visit, previous pharmacological treatment intervention for PTSD (Yes/No), and interaction terms of treatment by visit and Baseline CAPS-5 Total Score by visit as a covariate. The unstructured variance covariance structure was used. The primary comparison between the brexpiprazole plus sertraline versus sertraline plus placebo at the Week 10 visit during the double-blind period was estimated as the difference between LS means. The comparison between brexpiprazole plus sertraline versus sertraline plus placebo were tested at a significance level of 0.05 (2-sided).

The key secondary efficacy endpoints are the change from Baseline to Week 10 in the CGI-S score and the change from Baseline (Day 0) to Week 12 in B-IPF score. Both endpoints were analyzed using the MMRM model similar to that for the primary efficacy endpoint except the change of the dependent variable of the endpoint. The comparison between brexpiprazole plus sertraline versus sertraline plus placebo of

the key secondary efficacy endpoints were tested under hierarchical order at a significance level of 0.05 (2-sided).

6.2.1.4.4 Primary Endpoint Sensitivity Analyses

To evaluate the robustness of the results of the primary analysis across various assumption of missingness, prespecified sensitivity analyses were performed, described in Appendix Table 50.

6.2.1.4.5 Subgroup Analyses

Analyses for change from Baseline by week in CAPS-5 Total Score were conducted for the subgroups of sex at birth, race, age, and previous pharmacological treatment for PTSD.

6.2.1.4.6 Supportive Analyses

Using the same method as the primary analysis, a prespecified analysis of the primary endpoint was also performed for the FAS. These results are presented in Appendix Section 10.5.

6.2.2 Trial 071: Enrolled Patients

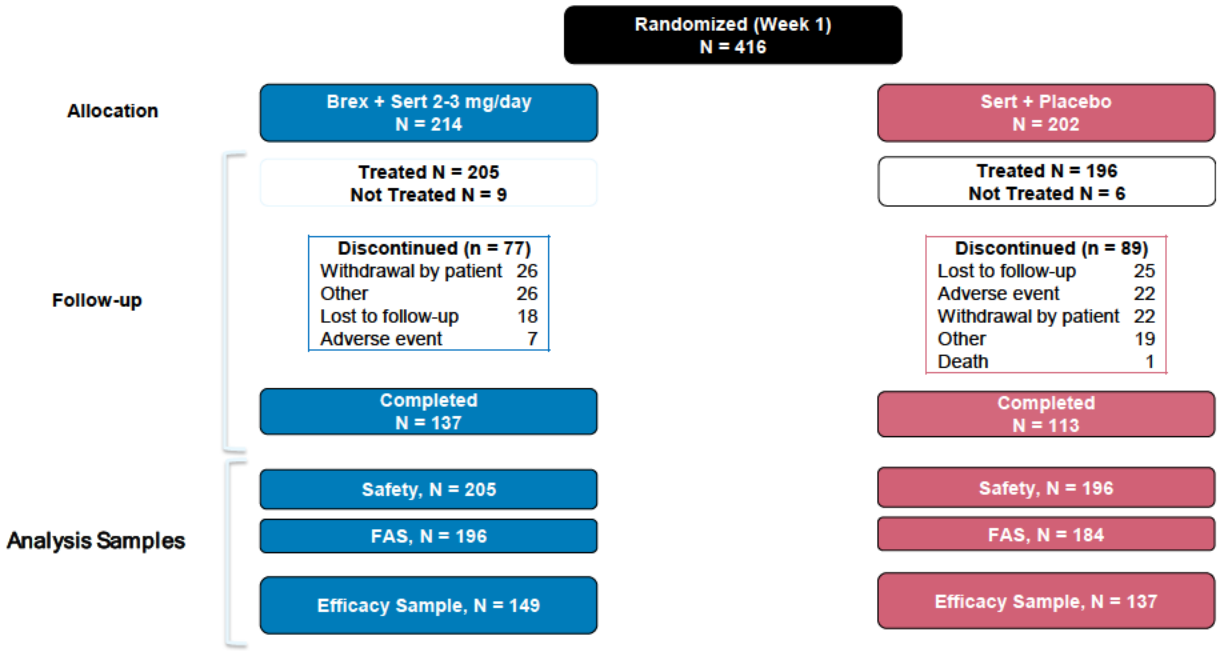
6.2.2.1 Disposition

A total of 450 patients were enrolled in the 1-week placebo run-in period. Of these 450 patients, 433 were treated with placebo during the 1-week placebo run-in period. At the end of the run-in period (Week 1), a total of 416 patients were randomized to double-blind treatment: 214 to 2 to 3 mg/day brexpiprazole plus sertraline and 202 to sertraline plus placebo (Figure 20).

In the Randomized Sample, 250 patients (60.1%) completed the trial. The most common reasons for discontinuation were withdrawal by patient, other, and lost to follow-up in the brexpiprazole plus sertraline group and lost to follow-up, withdrawal by patient, and AE in the sertraline plus placebo group.

The Efficacy Sample comprises 149 patients in the 2 to 3 mg/day brexpiprazole plus sertraline group and 137 patients in the sertraline plus placebo. Patient disposition for the Efficacy Sample is provided in Appendix Section 10.3.1.

Figure 20: Trial 071 Patient Disposition



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; FAS = Full Analysis Set; PTSD = post-traumatic stress disorder; Sert = sertraline.
Note: "Other" in the discontinuation boxes includes all categories (eg, noncompliance with study drug, protocol deviation, and other)
FAS criteria: all randomized patients who took at least 1 dose of double-blind trial drug and have a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score
Prespecified Efficacy Sample: all randomized patients who took at least 1 dose of double-blind trial drug and have a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score PLUS: CAPS-5 Total Score of ≥ 27 at the randomization visit (Week 1), and an improvement in terms of reduction in CAPS-5 Total Score of less than 50% at end of the placebo run-in period (Phase A) to exclude patients who responded to placebo during the placebo run-in phase.

6.2.2.2 *Demographic and Baseline Characteristics*

Demographic characteristics were similar across treatment groups (Table 20). The average age was 38 years (range 19 – 65 years) in the brexpiprazole plus sertraline group and 37 years (range 18 – 65 years) in the sertraline plus placebo group. The enrolled population was predominately female, white, and not Hispanic or Latino.

Demographic and Baseline characteristics for the Efficacy Samples were similar to the Randomized Sample. See Appendix Sections 10.3.2 and 10.3.3 for additional patient characteristics.

Table 20: Trial 071 Key Demographic Characteristics (Randomized Sample)

Parameter	Brex 2-3 mg + Sert N = 214	Sert + Placebo N = 202
Age (years)		
Mean (SD)	37.8 (11.7)	36.8 (12.1)
Median (min, max)	36.0 (19, 65)	34.0 (18, 65)
Age Group, n (%)		
< 55	193 (90.2)	179 (88.6)
≥ 55	21 (9.8)	23 (11.4)
Sex, n (%)		
Male	56 (26.2)	50 (24.8)
Female	158 (73.8)	152 (75.2)
Race, n (%)		
White	147 (68.7)	144 (71.3)
Black or African American	50 (23.4)	38 (18.8)
American Indian or Alaska Native	7 (3.3)	2 (1.0)
Asian	4 (1.9)	9 (4.5)
Native Hawaiian or Other Pacific Islander	1 (0.5)	0
Other	5 (2.3)	9 (4.5)
Ethnicity, n (%)		
Not Hispanic or Latino	183 (85.5)	167 (82.7)
Hispanic or Latino	29 (13.6)	32 (15.8)
Unknown	0	1 (0.5)
Other	2 (0.9)	2 (1.0)
BMI (kg/m^2)		
Mean (SD)	30.4 (6.7)	30.1 (7.1)
Median (min, max)	29.5 (18.2, 48.9)	29.5 (17.7, 50.2)

BMI = body mass index; Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

Patients in both treatment groups had a PTSD history with an approximate mean number of 4.0 years since onset of symptoms, and an approximate mean number of 4.2 years since the index trauma at Screening (Table 21). The most common trauma types were assault, sexual trauma, exposure to sudden death, and vehicle accident.

Table 21: Trial 071 Post-Traumatic Stress Disorder Disease History (Randomized Sample)

Parameter	Brex 2-3 mg + Sert N = 214	Sert + Placebo N = 202
Years Since Trauma		
Mean (SD)	4.2 (2.5)	4.1 (2.4)
Median (min, max)	4.0 (0.3, 9.5)	3.9 (0.5, 9.2)
Age at Index Trauma, years		
Mean (SD)	33.7 (12.0)	32.8 (12.3)
Median (min, max)	32.0 (15, 60)	30.0 (16, 62)
Previous Medication Treatment, n (%)	61 (28.5)	50 (24.8)
Previous Psychotherapy, n (%)	79 (36.9)	59 (29.2)
Index Trauma Type, n (%)		
Assault (With or Without Weapon)	75 (35.0)	79 (39.1)
Captivity	0 (0.0)	1 (0.5)
Combat or Exposure to War-Zone	5 (2.3)	5 (2.5)
Exposure To Sudden Death	33 (15.4)	21 (10.4)
Life-Threatening Illness or Injury	8 (3.7)	9 (4.5)
Motor Vehicle or Other Transportation Accident	16 (7.5)	28 (13.9)
Natural Disaster, Fire, Or Explosion	5 (2.3)	6 (3.0)
Serious Harm or Death for Which You Are Responsible	2 (0.9)	0 (0.0)
Serious Non-Transportation Accident	1 (0.5)	1 (0.5)
Sexual Trauma	55 (25.7)	39 (19.3)
Other	14 (6.5)	13 (6.4)

Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

Baseline efficacy scale scores were generally balanced between treatment groups (Table 22).

Table 22: Trial 071 Summary of Baseline Efficacy Scale Scores (Efficacy Sample)

	Brex 2-3 mg + Sert N = 149	Sert + Placebo N = 137
CAPS-5 Total Severity Score		
Mean (SD)	38.3 (7.2)	38.8 (8.0)
Min, Max	27, 61	27, 65
CAPS-5 Subscale Intrusion Score		
Mean (SD)	9.2 (3.3)	9.4 (3.4)
Min, Max	0, 17	0, 19
CAPS-5 Subscale Avoidance Score		
Mean (SD)	4.5 (1.6)	4.8 (1.6)
Min, Max	0, 7	0, 8
CAPS-5 Subscale Cognitions and Mood Score		
Mean (SD)	14.5 (3.8)	14.7 (4.0)
Min, Max	3, 26	5, 26
CAPS-5 Subscale Arousal and Reactivity Score		
Mean (SD)	10.1 (2.9)	10.0 (3.0)
Min, Max	3, 18	3, 16
CGI-Severity of Illness Score[a]		
Mean (SD)	4.6 (0.6)	4.6 (0.6)
Min, Max	3, 6	3, 6
B-IPF Total Score[b]		
Mean (SD)	65.2 (21.1)	64.3 (22.9)
Min, Max	16.7, 100.0	8.3, 100.0
HADS-Anxiety Score[c]		
Mean (SD)	14.0 (3.9)	14.1 (3.3)
Min, Max	3, 21	7, 21
HADS-Depression Score[c]		
Mean (SD)	11.0 (3.7)	10.7 (3.8)
Min, Max	2, 20	2, 20
PCL-5 Total Score[d]		
Mean (SD)	47.4 (12.9)	48.0 (13.4)
Min, Max	18, 74	14, 76

BIPF = Brief Inventory of Psychosocial Function; Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI = clinical global impressions; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; Flex = flexible; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; SD = standard deviation; PTSD = post-traumatic stress disorder; Sert = sertraline.

[a] Brex 2-3mg + Sert n=148; Sert + Placebo n=137

[b] Brex 2-3mg + Sert n=142; Sert + Placebo n=129

[c] Brex 2-3mg + Sert n=138; Sert + Placebo n=130
[d] Brex 2-3mg + Sert n=138; Sert + Placebo n=130

6.2.2.3 CAPS-5 Performance During Placebo Run-in Period

During the placebo run-in period, mean (SD) CAPS-5 Total Score change from enrollment (Day 0) to randomization (Week 1) was −8.8 (9.0) points, and −5.2 (5.8) in patients who met the Efficacy Sample criteria.

6.2.2.4 Treatment Received

In the brexpiprazole plus sertraline flexible-dose group, the mean (SD) brexpiprazole dose at each patient's last visit was 2.2 (0.6) mg. The modal (most frequent) brexpiprazole dose was 2 mg for 59% of patients and 3 mg for 31% of patients.

6.2.3 Trial 071: Efficacy Results

6.2.3.1 Primary Endpoint Results

6.2.3.1.1 Change from Baseline to Week 10 in the CAPS-5 Total Score

Brexpiprazole 2 to 3 mg/day plus sertraline showed a statistically significant improvement in CAPS-5 Total Score compared with the sertraline plus placebo group from Baseline through Week 10 (treatment difference = −5.59 [95% CI: −8.79, −2.38], p = 0.0007; Table 23).

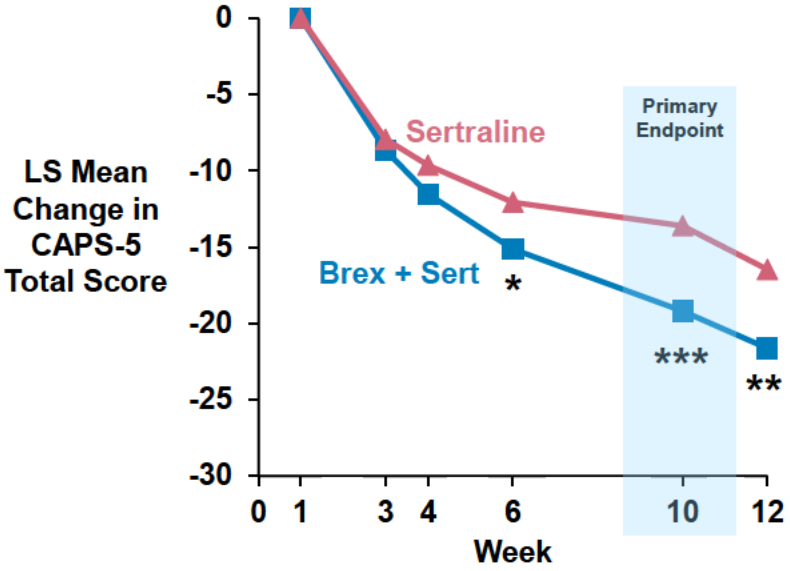
Greater improvement for brexpiprazole plus sertraline was observed from Week 6 onward (Figure 21).

Table 23: Trial 071 Primary Endpoint: Summary of Mean Change in CAPS-5 Total Score from Baseline to Week 10 (Efficacy Sample)

Variable	Brex + Sert N = 148	Sert + Placebo N = 134
CAPS-5 Total Score		
Mean at Baseline (SD)	38.35 (7.18)	38.68 (7.75)
LS Mean Change at Week 10 (SE)	−19.19 (1.17)	−13.61 (1.24)
Treatment Difference (95% CI)[a]	−5.59 (−8.79, −2.38)	
p-value[a]	0.0007	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least square; MMRM = Mixed Model Repeated Measurements; PTSD = post-traumatic stress disorder; SD = standard deviation; SE = standard error; Sert = sertraline.
[a] MMRM analysis; treatment difference = difference in LS mean changes for MMRM.
The Efficacy Sample comprises 286 patients, 282 were included in the primary efficacy analysis since 4 patients who discontinued did not have a CAPS-5 value within the permitted visit window.

Figure 21: Trial 071 LS Mean Change in CAPS-5 Total Score Over Time (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
The Efficacy Sample comprises of 286 patients, 282 were included in the primary efficacy analysis since 4 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.
Baseline CAPS-5 Total Score: Brex + Sert = 38.35, n = 148; Sertraline = 38.68, n = 134.

Analyses of the primary endpoint for the FAS were consistent with the primary analyses. These results are provided in Appendix Section 10.5.3.

6.2.3.1.2 Sensitivity Analyses

Prespecified sensitivity analyses were performed for the primary endpoint using different mechanisms of handling missing data. The observed separation at Week 10 was similar regardless of methods used for handling missing data and indicate robustness of the findings observed in the primary analysis (Table 24 and Appendix Table 52).

Table 24: Trial 071 Prespecified Delta Adjustment Sensitivity Analysis Results for CAPS-5 Total Score

Reasons for Discontinuation, n (%)	LSMD Brex + Sert vs Sert + Placebo (95% CI) at Tipping Point	Tipping Point CAPS-5 Total Score Imputation
Due to AE or LOE, 22 (7.7%)	−4.60 (−7.87, −1.33)	Δ* = 25.0 points
Due to AE or LOE or withdrew consent, 44 (15.4%)	−3.31 (−6.66, 0.05)	Δ = 17.5 points
Due to any reasons, 101 (35.3%)	−3.20 (−6.45, 0.06)	Δ = 8.0 points

AE = adverse event; Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LOE = loss of efficacy; LSMD = least squares mean difference; PTSD = post-traumatic stress disorder; Sert = sertraline.
*As prespecified, the delta was increased until conclusion of the primary analysis was overturned, or up to 500% of the expected treatment difference of 5 points.

6.2.3.2 Key Secondary Endpoints

Brexpiprazole 2 to 3 mg/day plus sertraline also demonstrated a statistically significant improvement compared with the sertraline plus placebo group on both the key secondary efficacy endpoints of change in the clinician-reported CGI-S Total Score from Baseline to Week 10 and change in the patient-reported B-IPF Total Score from Baseline (Day 0) to Week 12 (Table 25; Figure 23).

Consistent with the primary endpoint, greater improvement for brexpiprazole plus sertraline was observed from Week 6 onward for the CGI-S Total Score (Figure 22).

Table 25: Trial 071 Summary of Key Secondary Endpoint Results (Efficacy Sample)

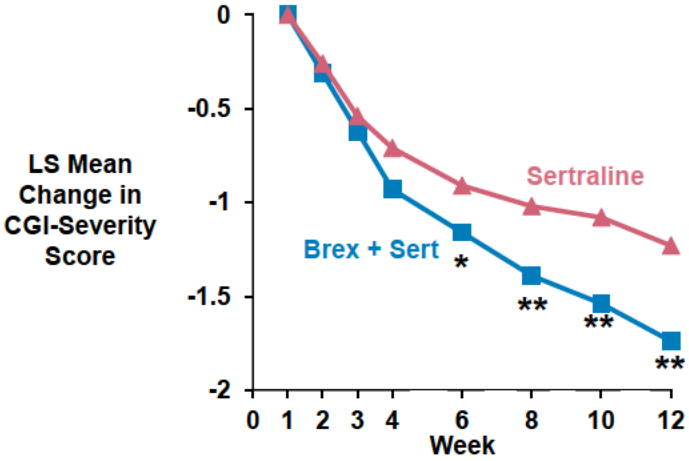
Treatment Group	Brex + Sert	Sert + Placebo
Change from Baseline to Week 10 in CGI-Severity Score		
N	148	137
LS Mean[a] (SE[a])	−1.54 (0.10)	−1.08 (0.11)
Diff[b] (95% CI)	−0.47 (−0.76, −0.17)	
p-value[b]	0.0019	
Change from Baseline (Day 0) to Week 12 in B-IPF Total Score		
N	104	97
LS Mean[a] (SE[a])	−33.80 (2.84)	−21.77 (2.97)
Diff[b] (95% CI)	−12.03 (−19.44, −4.62)	
p-value[b]	0.0016	

Brex = Brexpiprazole; B-IPF = Brief Inventory of Psychosocial Function; CGI = Clinical Global Impression; CI = confidence interval; LS = least square; PTSD = post-traumatic stress disorder; SE = standard error; Sert = sertraline.

[a] Mixed model repeated measures method with model terms: treatment, (pooled) trial center, previous pharmacological treatment intervention for PTSD (yes/no), visit, treatment by visit and Baseline by visit interaction.

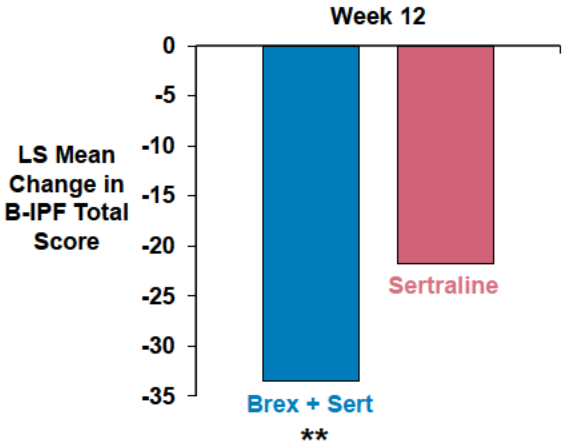
[b] Difference between Brexpiprazole + Sertraline and Sertraline + Placebo along with corresponding 95% CI and p-value.

Figure 22: Trial 071 LS Mean Change in Clinical Global Impression-Severity of Illness Scale Score Over Time (Efficacy Sample)



Brex = brexpiprazole; CGI = Clinical Global Impression; CGI-S = Clinical Global Impression Severity; LS = least squares; Sert = sertraline.
* $p < 0.05$, ** $p < 0.01$.
The Efficacy Sample comprises 286 patients, 285 were included in the CGI-S efficacy analysis since 1 patient who discontinued did not have a post-Baseline CGI-S value within the permitted visit window.
Baseline CGI-S score: Brex + Sert = 4.57, n = 148; sertraline = 4.64, n = 137.

Figure 23: Trial 071 LS Mean Change from Baseline to Week 12 in B-IPF Total Score (Efficacy Sample)



B-IPF = Brief Inventory of Psychosocial Function; Brex = brexpiprazole; LS = least squares; Sert = sertraline.
Brief Inventory of Psychosocial Function was assessed from Baseline (Day 0) to Week 12.
** $p < 0.01$.
The Efficacy Sample comprises 286 patients, 201 were included in the B-IPF efficacy analysis since 85 patients who discontinued did not have a post-Baseline B-IPF value within the permitted visit window.
Baseline B-IPF score: Brex + Sert = 64.78, n = 104; Sertraline = 63.53, n = 97.

6.2.3.3 *Other Secondary Efficacy Endpoint Results*

Brexpiprazole 2 to 3 mg/day plus sertraline resulted in improvements compared with sertraline plus placebo in all patient-reported endpoints (PCL-5, HADS-A, and HADS-D) for the respective change from Baseline to Week 10 (Table 26). Importantly, brexpiprazole plus sertraline demonstrated improvements in the 4 clinician-reported CAPS-5 subscales of intrusion, avoidance, negative cognitions and mood, and arousal and reactivity symptoms.

Table 26: Trial 071 Other Efficacy Endpoints: Summary of Mean Change from Baseline to Week 10 (Efficacy Sample)

	Brex + Sert vs Sert + Placebo	
Parameter	**Treatment Difference[a] (95% CI)**	**p-value[a]**
Change from Baseline to Week 10 in PCL-5 Total Score	−7.28 (−11.50, −3.06)	0.0008
Change from Baseline to Week 10 in HADS-Anxiety Subscale Score	−1.56 (−2.72, −0.41)	0.0083
Change from Baseline to Week 10 in HADS-Depression Subscale Score	−1.34 (−2.49, −0.19)	0.0223
CAPS-5 Subscale Intrusion (Re-Experiencing)	−1.69 (−2.76, −0.62)	0.0022
CAPS-5 Subscale Avoidance	−0.74 (−1.32, −0.15)	0.0134
CAPS-5 Subscale Negative Cognitions/ Mood	−1.94 (−3.33, −0.55)	0.0065
CAPS-5 Subscale Arousal and Reactivity	−1.35 (−2.25, −0.45)	0.0036

Brex = brexpiprazole; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; Sert = sertraline.
[a] Mixed model repeated measures method with model terms: treatment, (pooled) trial center, previous pharmacological treatment intervention for PTSD (yes/no), visit, treatment by visit and Baseline by visit interaction.

6.2.3.4 *Efficacy in Subgroups (CAPS-5)*

Subgroup analyses results were generally consistent with the results of the overall CAPS-5 Total Score analysis (see Appendix Figure 38).

6.2.4 Trial 071: Efficacy Conclusions

Flexible-dose (2-3 mg/day) brexpiprazole plus sertraline was statistically superior to sertraline plus placebo on the primary efficacy endpoint and across multiple clinician- and patient-reported efficacy scales. Treatment with brexpiprazole plus sertraline resulted in statistically significant improvement of PTSD symptoms versus treatment with sertraline alone as measured by change in CAPS-5 Total Score (primary endpoint) and supported by all key secondary and other efficacy endpoints including both clinician-reported (CGI-S, CAPS-5 symptoms clusters, CAPS-5 response) and patient-reported (B-IPF, PCL-5, HADS-Anxiety, HADS-Depression). Importantly,

brexpiprazole plus sertraline treatment showed improvements across the 4 CAPS-5 symptom clusters, as well as HADS depressive and anxious symptoms, which have not been consistently demonstrated for currently approved treatments. Finally, brexpiprazole plus sertraline treatment was associated with improvements in B-IPF psychosocial functioning (key secondary endpoint).

6.3 Trial 331-201-00072: Phase 3 Fixed-Dose Trial

6.3.1 Trial 072: Trial Design

6.3.1.1 Overview

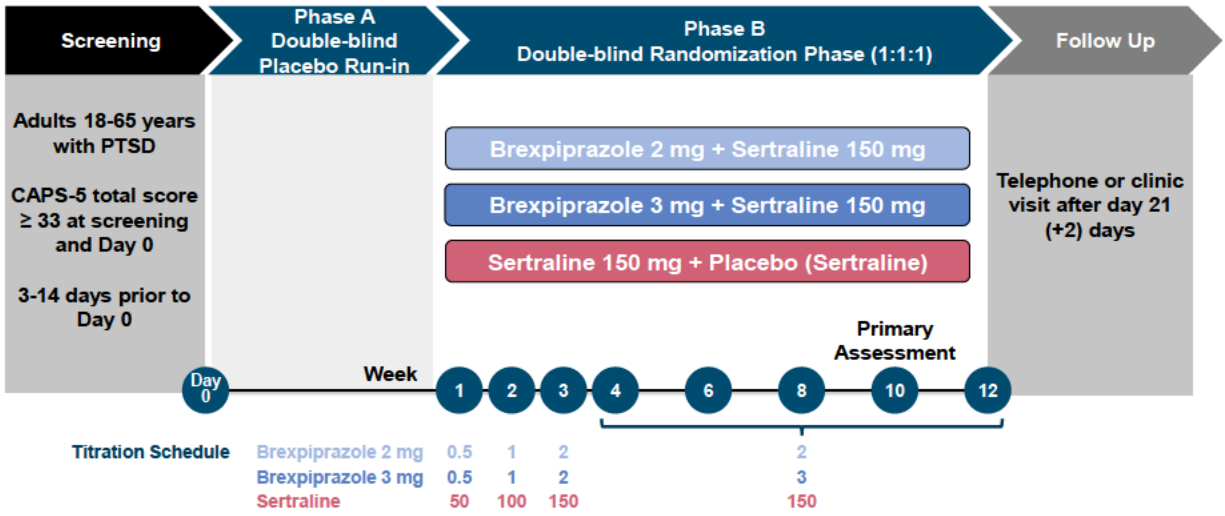
Trial 072 was a Phase 3, multicenter, 12-week, double-blind, randomized, fixed-dose, 3-arm trial to evaluate the efficacy and safety of brexpiprazole (2 or 3 mg/day) plus sertraline in adult patients with PTSD. The primary objective of this trial was to evaluate the efficacy of the fixed dosing of brexpiprazole plus sertraline compared with the efficacy of sertraline plus placebo, as assessed by the change in the CAPS-5 Total Score from Baseline to Week 10. Patients were enrolled from 91 sites in the US. The trial was conducted between October 2019 and August 2023 and is registered at ClinicalTrials.gov (identifier: NCT04174170).

With the exception of the dosing regimen, the design of Trial 071 was identical to Trial 071. The design schematic is shown in Figure 24. After the 1-week double-blind placebo run-in period, eligible patients were randomized (1:1:1) into 1 of 3 treatment groups:

- Brexpiprazole 2 mg/day plus sertraline
- Brexpiprazole 3 mg/day plus sertraline
- Sertraline plus placebo

Please refer to Section 6.2.1 for additional trial design details.

Figure 24: Trial 072 Design Schematic



CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder.
Titration schedule based on mg/day.

6.3.1.2 Enrollment Criteria

Enrollment criteria for Trial 072 were identical to the criteria for Trial 071, described in Section 6.2.1.2. Full enrollment criteria are provided in Appendix Section 10.1.

6.3.1.3 Endpoints

The efficacy endpoints in Trial 072 were identical to the endpoints in Trial 071, described in Table 11.

6.3.1.4 Statistical Methods

6.3.1.4.1 Sample Size

Sample size calculation was considered to have sufficient power for the primary endpoint based on the Efficacy Sample. The sample size calculation was based on the below hierarchical testing procedure designed to control the familywise type 1 error. Similar to Trial 071, the sample size calculation assumed the same treatment difference of –5.0 points in the primary efficacy endpoint with an SD of 14 for each of the combination arm vs sertraline monotherapy. The difference of −5.0 points is based on Phase 2 data and clinical experience with the population of patients with PTSD.

- First testing the average of the 2 combination treatment arms vs sertraline monotherapy
- Second testing each of the combination treatment arms vs sertraline monotherapy

A total of 375 patients (125 patients in each of the 2 combination arms and the sertraline arm) will provide 90% power for the average effect of 2 mg and 3 mg of brexpiprazole + sertraline combination versus sertraline monotherapy. Considering the hierarchical testing procedure, there is 80% power to compare each of the combination treatment arms vs sertraline mono arm at a 2-sided alpha level of 0.05. Considering up to 30% of randomized patients would not meet the enrichment criteria and further adjusting for a 5% non-evaluability/dropout impact, a total of 549 patients (183 patients in each of the 2 combination arms and the sertraline arm) were planned to be randomized. It is expected that approximately 585 patients (195 in each group) will be enrolled at Week 0 in order to randomize 549 patients.

6.3.1.4.2 Analysis Populations

The analysis populations in Trial 072 were defined identically to those in Trial 071, described in Section 6.2.1.4.2.

6.3.1.5 Endpoint Analyses

The endpoint analyses in Trial 072 were similar to those in Trial 071, except the change in treatment arms, described in Section 6.2.1.4.3.

The comparison between brexpiprazole plus sertraline group and sertraline group was tested at a significance level of 0.05 (2-sided). The family-wise error rate of multiple comparisons was controlled by testing the difference between the average effect of 2 mg and 3 mg of brexpiprazole plus sertraline combination versus sertraline monotherapy first, at an alpha level of 0.05. If this global test was significant, then comparisons for each group (2 mg of brexpiprazole plus sertraline combination and 3 mg of brexpiprazole plus sertraline combination) versus sertraline monotherapy would be performed at significant level 0.05, separately.

6.3.2 Trial 072: Enrolled Patients

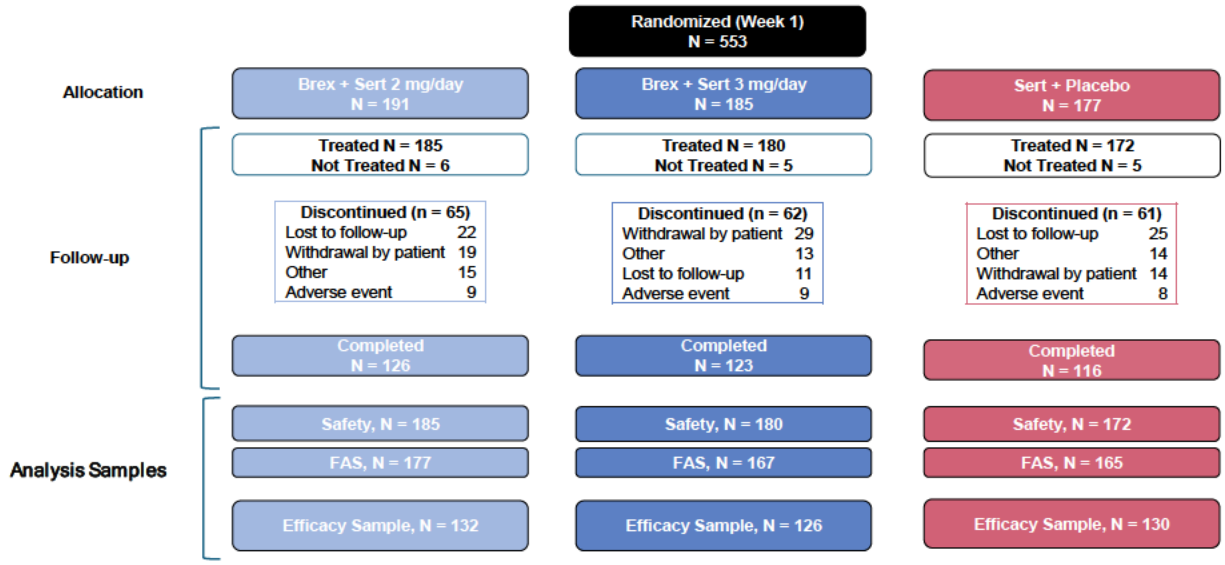
6.3.2.1 Disposition

A total of 591 were enrolled in the 1-week placebo run-in period (Phase A). Of the 591 patients enrolled in the 1-week placebo run-in, 553 patients were randomized to double-blind treatment: 191 to brexpiprazole 2 mg/day plus sertraline, 185 patients to brexpiprazole 3 mg/day plus sertraline, and 177 patients to sertraline plus placebo (Figure 25).

In the Randomized Sample, 365 patients (66.0%) completed the trial. In each treatment group, the most common reasons for discontinuation were lost to follow-up, withdrawal by patient, and AE (Figure 25).

The Efficacy Sample comprised 132 patients in the 2 mg/day brexpiprazole plus sertraline group, 126 patients in the 3 mg/day brexpiprazole plus sertraline group, and 130 patients in the sertraline plus placebo group. Patient disposition for the Efficacy Sample is provided in Appendix Section 10.4.1.

Figure 25: Trial 072 Patient Disposition



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; FAS = Full Analysis Set; PTSD = post-traumatic stress disorder; Sert = sertraline.
FAS criteria: all randomized patients who took at least 1 dose of double-blind trial drug and have a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score.
Prespecified Efficacy Sample: all randomized patients who took at least 1 dose of double-blind trial drug and have a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score PLUS: CAPS-5 Total Score of ≥ 27 at the randomization visit (Week 1), and an improvement in terms of reduction in CAPS-5 Total Score of less than 50% at end of the placebo run-in period (Phase A) to exclude patients who responded to placebo during the placebo run-in phase.

6.3.2.2 Demographic and Baseline Characteristics

Demographic characteristics were similar across treatment groups (Table 27). The average age was 37 years (range: 18-85 years) in the brexpiprazole 2 mg plus sertraline group, 36 years (range: 18-62) in the brexpiprazole 3 mg plus sertraline group, and 38 years (range: 18-65 years) in the sertraline plus placebo group. The enrolled population was predominately female, white, and not Hispanic or Latino.

See Appendix Section 10.4.2 for additional patient characteristics.

Table 27: Trial 072 Key Demographic Characteristics (Randomized Sample)

Parameter	Brex 2 mg + Sert N = 191	Brex 3 mg + Sert N = 185	Sert + Placebo N = 177
Age (years)			
Mean (SD)	37.1 (12.1)	36.3 (11.7)	37.7 (12.3)
Median (min, max)	36.0 (16, 85)	34.0 (18, 62)	36.0 (18, 65)
Age Group, n (%)			
< 55	168 (88.0)	168 (90.8)	154 (87.0)
≥ 55	23 (12.0)	17 (9.2)	23 (13.0)
Sex, n (%)			
Female	142 (74.3)	141 (76.2)	126 (71.2)
Male	49 (25.7)	44 (23.8)	51 (28.8)
Race, n (%)			
White	130 (68.1)	124 (67.0)	121 (68.4)
Black or African American	46 (24.1)	45 (24.3)	44 (24.9)
Asian	6 (3.1)	8 (4.3)	5 (2.8)
American Indian or Alaska Native	3 (1.6)	1 (0.5)	2 (1.1)
Native Hawaiian or Other Pacific Islander	2 (1.0)	1 (0.5)	0 (0.0)
Other	4 (2.1)	6 (3.2)	5 (2.8)
Ethnicity, n (%)			
Not Hispanic or Latino	143 (74.9)	146 (78.9)	140 (79.1)
Hispanic or Latino	48 (25.1)	37 (20.0)	37 (20.9)
Unknown	0 (0.0)	1 (0.5)	0 (0.0)
BMI (kg/m^2)			
Mean (SD)	29.5 (6.6)	29.2 (6.8)	28.3 (6.1)
Median (min, max)	28.6 (15.9, 53.1)	27.7 (16.3, 50.8)	27.8 (15.8, 46.8)

BMI = body mass index; Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

Patients in all treatment groups had a PTSD history with a mean number of 3.8-4.0 years since onset of symptoms, and a mean number of 3.9-4.1 years since the index trauma at Screening (Table 28). The most common trauma types were assault, sexual trauma, exposure to sudden death, and vehicle accident. The majority of patients had not previously received pharmacotherapy treatment or psychotherapy for PTSD.

Table 28: Trial 072 Post-Traumatic Stress Disorder Disease History (Randomized Sample)

Parameter	Brex 2 mg + Sert N = 191	Brex 3 mg + Sert N = 185	Sert + Placebo N = 177
Years Since Trauma			
Mean (SD)	4.1 (2.5)	4.1 (2.4)	3.9 (2.3)
Median (min, max)	3.9 (0.5, 9.0)	3.6 (0.5, 9.4)	3.7 (0.6, 8.9)
Age at Index Trauma, years			
Mean (SD)	33.0 (12.0)	32.2 (11.6)	33.9 (12.1)
Median (min, max)	32.0 (16, 64)	29.0 (17, 61)	31.0 (16, 64)
Previous Medication Treatment, n (%)	39 (20.4)	35 (18.9)	36 (20.3)
Previous Psychotherapy, n (%)	51 (26.7)	62 (33.5)	52 (29.4)
Index Trauma Type, n (%)			
Assault (With or Without Weapon)	65 (34.0)	60 (32.4)	70 (39.5)
Captivity	9 (4.7)	1 (0.5)	1 (0.6)
Combat or Exposure to War-Zone	2 (1.0)	2 (1.1)	2 (1.1)
Exposure to Sudden Death	31 (16.2)	39 (21.1)	28 (15.8)
Exposure to Toxic Substance	0	0	1 (0.6)
Life-Threatening Illness or Injury	9 (4.7)	6 (3.2)	6 (3.4)
Motor Vehicle or Other Transportation Accident	21 (11.0)	17 (9.2)	18 (10.2)
Natural Disaster, Fire, or Explosion	2 (1.0)	3 (1.6)	7 (4.0)
Serious Non-Transportation Accident	2 (1.0)	1 (0.5)	0 (0.0)
Serious Harm or Death for Which You Are Responsible	1 (0.5)	1 (0.5)	0 (0.0)
Sexual Trauma	38 (19.9)	42 (22.7)	34 (19.2)
Other	11 (5.8)	13 (7.0)	10 (5.6)

Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

Baseline efficacy scale scores were generally balanced between treatment groups (Table 29).

Table 29: Trial 072 Summary of Baseline Efficacy Scale Scores (Efficacy Sample)

Score	Brex 2 mg + Sert N = 132	Brex 3 mg + Sert N = 126	Sert + Placebo N = 130
CAPS-5 Total Severity Score			
Mean (SD)	38.8 (8.3)	37.8 (7.3)	39.3 (7.8)
Min, Max	26, 63	25, 60	21, 64
CAPS-5 Subscale Intrusion Score			
Mean (SD)	9.6 (3.5)	9.6 (3.5)	9.9 (3.4)
Min, Max	0, 18	0, 16	3, 18
CAPS-5 Subscale Avoidance Score			
Mean (SD)	5.0 (1.5)	4.7 (1.5)	4.7 (1.7)
Min, Max	0, 8	0, 7	0, 8
CAPS-5 Subscale Cognitions and Mood Score			
Mean (SD)	14.4 (3.9)	13.9 (3.6)	14.4 (3.9)
Min, Max	6, 26	5, 24	4, 23
CAPS-5 Subscale Arousal and Reactivity Score			
Mean (SD)	9.9 (3.2)	9.8 (3.0)	10.3 (2.9)
Min, Max	2, 19	3, 19	2, 19
CGI-Severity of Illness Score[a]			
Mean (SD)	4.6 (0.7)	4.5 (0.7)	4.7 (0.7)
Min, Max	30, 7	3, 6	3, 6
B-IPF[b]			
Mean (SD)	63.5 (20.1)	62.5 (22.4)	59.9 (20.5)
Min, Max	0, 100.0	0, 100.0	9.5, 100.0
HADS Subscale Anxiety Score[c]			
Mean (SD)	13.3 (3.6)	13.3 (3.6)	13.1 (3.9)
Min, Max	5, 21	2, 21	1.0, 21
HADS Subscale Depression Score[c]			
Mean (SD)	10.5 (3.4)	9.9 (4.1)	9.6 (3.9)
Min, Max	3, 19	0, 19	0, 21
PCL-5 Total Score[d]			
Mean (SD)	45.8 (12.1)	44.9 (12.0)	44.3 (12.2)
Min, Max	18, 80	22, 71	17, 79

BIPF = Brief Inventory of Psychosocial Function; Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI = clinical global impressions; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-

traumatic stress disorder; SD = standard deviation; Sert = sertraline.
[a] Brex 2mg + Sert n=132; Brex 3mg + Sert n=124; Sert + Placebo n=129
[b] Brex 2mg + Sert n=125; Brex 3mg + Sert n=118; Sert + Placebo n=124
[c] Brex 2mg + Sert n=121; Brex 3mg + Sert n=118; Sert + Placebo n=122
[d] Brex 2mg + Sert n=121; Brex 3mg + Sert n=116; Sert + Placebo n=119

6.3.2.3 CAPS-5 Performance During Placebo Run-in Period

During the placebo run-in period, mean (SD) CAPS-5 Total Score change from Day 0 to randomization (Week 1) was −8.8 (9.6) points, and −5.1 (6.3) in patients who met the enrichment criteria.

6.3.3 Trial 072: Efficacy Results

6.3.3.1 Primary Endpoint

6.3.3.1.1 Change in CAPS-5 Total Score from Baseline to Week 10

The average effect of the brexpiprazole doses (2 mg/day or 3 mg/day) assessed as part of combination treatment did not demonstrate statistical significance versus sertraline plus placebo on the primary endpoint nor the secondary endpoint (Table 30; Figure 26).

While Trial 072 did not meet its primary endpoint, absolute reductions in primary and key secondary endpoints in the brexpiprazole plus sertraline group were similar to those observed in Trials 061 and 071. The only substantive difference in efficacy outcomes for the 3 trials was that the sertraline plus placebo group in Trial 072 showed a larger response in CAPS-5 (and secondary) outcomes than in Trials 061 and 071, thereby negating any observed treatment effect.

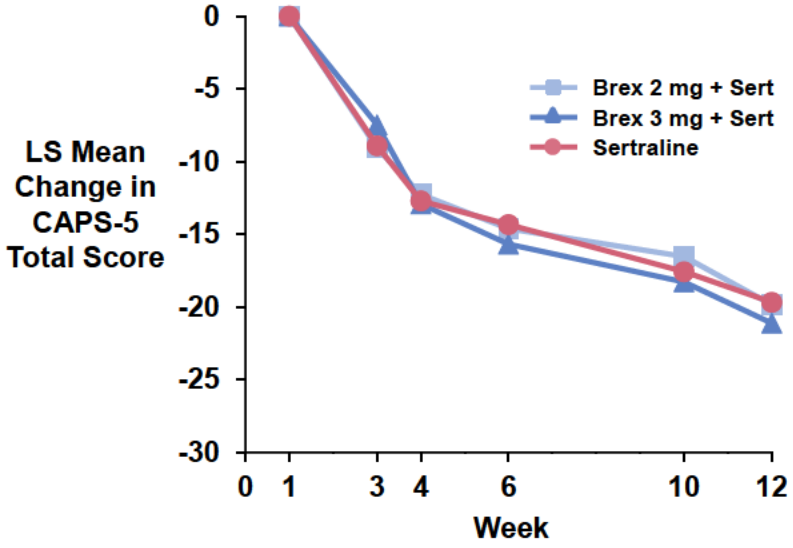
In an effort to identify an explanation for the observed results, the Sponsor investigated a number of items, including trial methodology, site characteristics, patient demographics, psychiatric history, substance use, and PTSD attributes. No definitive trial-related elements have been identified that might explain the lack of separation on the primary endpoint in Trial 072 in contrast to Trials 061 and 071. Except for the dosing regimens, the 3 trials were identical in design, with the same primary endpoint and duration. In Trials 061 and 071 patients received flexible-dose treatments, while in Trial 072, patients received fixed-dose treatments. Fixed versus flexible-dosing did not appear to impact the absolute change from Baseline in CAPS-5 Total Score for the brexpiprazole plus sertraline groups. In the sertraline plus placebo group, the change from Baseline to Week 10 in CAPS-5 Total Score was numerically larger in Trial 072 (−17.6) compared with Trial 061 (−11.4) and Trial 071 (−13.6).

Table 30: Trial 072 Primary Endpoint: Summary of Mean Change in CAPS-5 Total Score from Baseline to Week 10 (Efficacy Sample)

Variable	Brex 2 mg + Sert N = 132	Brex 3 mg + Sert N = 124	Sert + Placebo N = 130
CAPS-5 Total Score, MMRM			
Mean Baseline (SD)	38.80 (8.26)	37.88 (7.38)	39.30 (7.75)
LS Mean Change at Week 10 (SE)	−16.53 (1.19)	−18.28 (1.23)	−17.57 (1.19)
Treatment Difference (95% CI)[a]	1.03 (−2.09, 4.16)	−0.71 (−3.88, 2.46)	
P-Value (vs Sertraline + Placebo)[a]	0.5165	0.6593	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders; LS = least squares; MMRM = mixed-effect model repeated measures; PTSD = post-traumatic stress disorder; SD = standard deviation; SE = standard error; Sert = sertraline.
[a] MMRM analysis for CAPS-5 total. Treatment difference = difference in LS mean changes for MMRM.
Efficacy Sample comprises 388 patients, 386 were included in the primary efficacy analysis since 2 patients who discontinued did not have a CAPS-5 value within the permitted visit window.

Figure 26: Trial 072 LS Mean Change in CAPS-5 Total Score Over Time (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.
The Efficacy Sample comprises 388 patients, 386 were included in the primary efficacy analysis since 2 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.
Baseline CAPS-5 Total Score: Brex 2 mg + Sert = 38.80, n = 132; Brex 3 mg + Sert = 37.88, n = 124; sertraline = 39.30, n = 130.

6.3.3.2 *Key Secondary Efficacy Endpoint Results (CGI-S, B-IPF)*

Neither the 2 mg/day nor the 3 mg/day doses of brexpiprazole plus sertraline showed a difference versus sertraline plus placebo on the CGI-S (Table 31).

On the patient-reported B-IPF, greater improvements were observed in the brexpiprazole plus sertraline 3 mg/day group compared to the sertraline plus placebo (−8.83, 95% CI: −15.82, −1.85, nominal p = 0.0134; Figure 27).

Similar to with the primary endpoint, the changes from Baseline observed in the secondary endpoints in the sertraline plus placebo group were larger in Trial 072 than in Trials 071 and 061.

Table 31: Trial 072 Key Secondary Endpoints: Summary of Mean Change from Baseline to Week 10/Week 12 (Efficacy Sample)

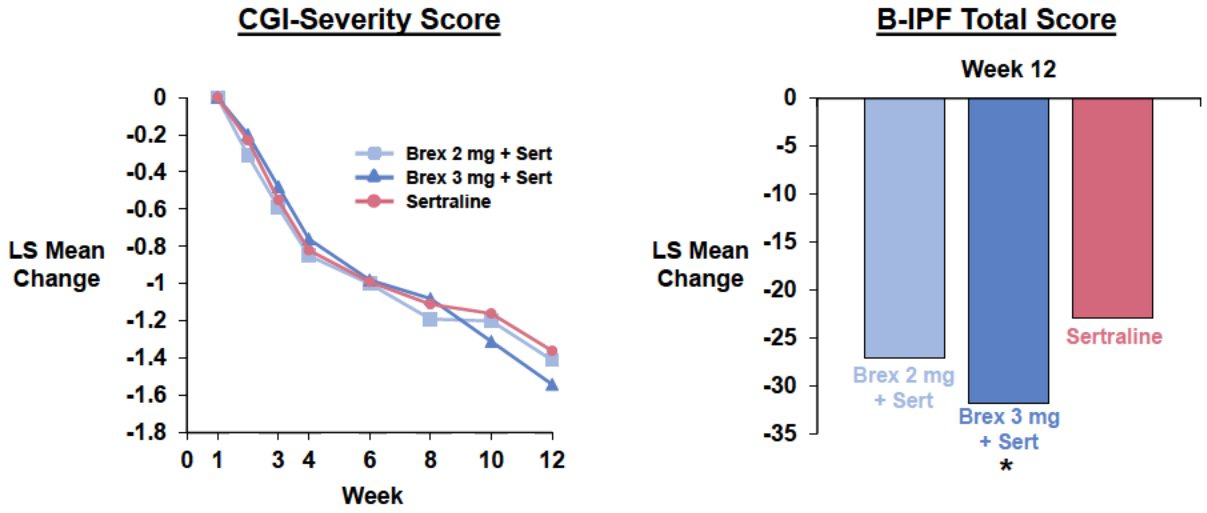
Treatment Group	Brex 2 mg + Sert	Brex 3 mg + Sert	Sert + Placebo
Change from Baseline to Week 10 in CGI-Severity Score			
N	132	124	129
LS Mean[a] (SE[a])	−1.26 (0.10)	−1.31 (0.11)	−1.29 (0.10)
Diff[b] (95% CI)	0.03 (−0.25, 0.31)	−0.03 (−0.31, 0.26)	
p-value[b]	0.8215	0.8584	
Change from Baseline (Day 0) to Week 12 in B-IPF Total Score			
N	98	94	96
LS Mean[a] (SE[a])	−27.12 (2.67)	−31.79 (2.86)	−22.96 (2.71)
Diff[b] (95% CI)	−4.16 (−11.00, 2.69)	−8.83 (−15.82, −1.85)	
p-value[b]	0.2331	0.0134	

Brex = Brexpiprazole; B-IPF = Brief Inventory of Psychosocial Function; CGI = Clinical Global Impression; CI = confidence interval; LS = least squares; PTSD = post-traumatic stress disorder; SD = standard deviation; SE = standard error; Sert = sertraline.

[a] Mixed model repeated measures method with model terms: treatment, (pooled) trial center, previous pharmacological treatment intervention for PTSD (yes/no), visit, treatment by visit and Baseline by visit interaction.

[b.] Difference between Brexpiprazole + Sertraline and Sertraline + Placebo along with corresponding 95% CI and p-value.

Figure 27: Trial 072 Key Secondary Endpoints Over Time (Efficacy Sample)



B-IPF = Brief Inventory of Psychosocial Function; Brex = brexpiprazole; CGI = Clinical Global Impression; LS = least squares; Sert = sertraline.
*p-value <0.05.
Efficacy Sample comprises 388 patients, 385 were included in the CGI-S efficacy analysis since 3 patients who discontinued did not have a post-Baseline CGI-S value within the permitted visit window.
Baseline CGI-S score: Brex 2 mg + Sert = 4.58, n = 132; Brex 3 mg + Sert = 4.55, n = 124; sertraline = 4.65, n = 129.
Efficacy Sample comprises 388 patients, 288 were included in the B-IPF efficacy analysis since 100 patients who discontinued did not have a post-Baseline B-IPF value within the permitted visit window.
Baseline B-IPF score: Brex 2 mg + Sert = 62.18, n = 98; Brex 3 mg + Sert = 63.09, n = 94; sertraline = 59.69, n = 96.

6.3.4 Trial 072: Efficacy Conclusions

This trial did not meet its primary endpoint. Treatment with fixed-dose 2 and 3 mg/day brexpiprazole plus sertraline showed improvement for the primary efficacy endpoint, change from Baseline to the Week 10 Visit in the CAPS-5 Total Score consistent with the effect shown in Trials 061 and 071. Of note, the sertraline plus placebo group also showed similar improvement that was not consistent with the other 2 trials.

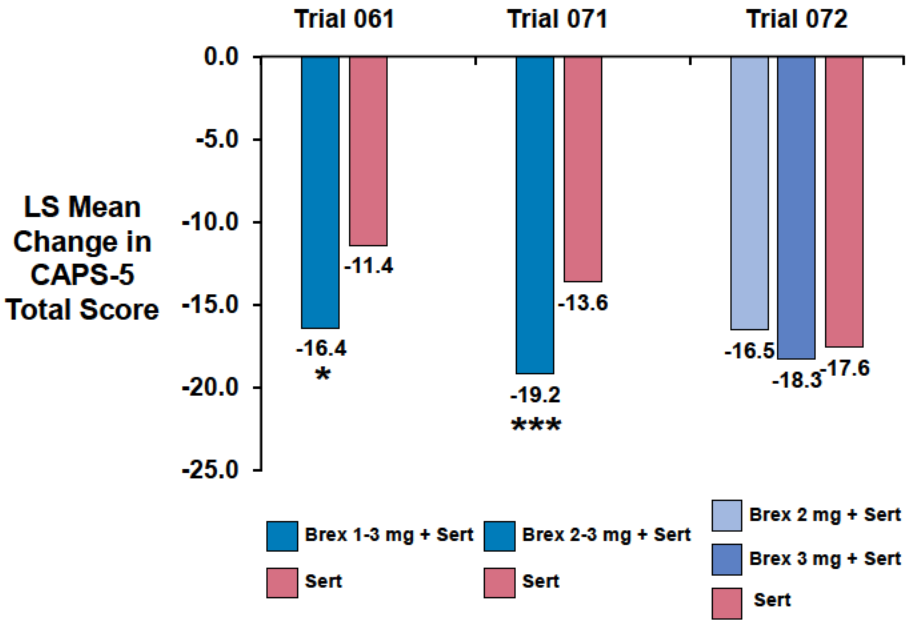
6.4 Comparison of Efficacy Results Across Trials

6.4.1.1 Primary Efficacy Endpoint: Change from Baseline in Clinician-Administered PTSD Scale for DSM-5 Total Score

The therapeutic benefit of combination treatment of brexpiprazole plus sertraline over sertraline alone has been observed within the 2 flexible-dose trials (Trial 061 and Trial 071) with similar treatment effect (LSMD −5.08 and −5.59, respectively) Figure 28 (Figure 28). Trial 072 did not meet its primary endpoint. Despite a lack of separation from sertraline plus placebo in Trial 072, mean reductions in CAPS-5 Total

Score for brexpiprazole plus sertraline were similar across the 3 trials (LS mean change from randomization [Week 1] to Week 10: Trial 061: −16.4; Trial 071: −19.2; Trial 072: −16.5 and −18.3 for brexpiprazole plus sertraline, respectively). As such, data from the clinical program suggests that brexpiprazole in combination with sertraline has a consistent effect on PTSD symptoms.

Figure 28: Primary Endpoint Results Across Trials: CAPS-5 Total Score Change from Baseline to Week 10 (Efficacy Sample)



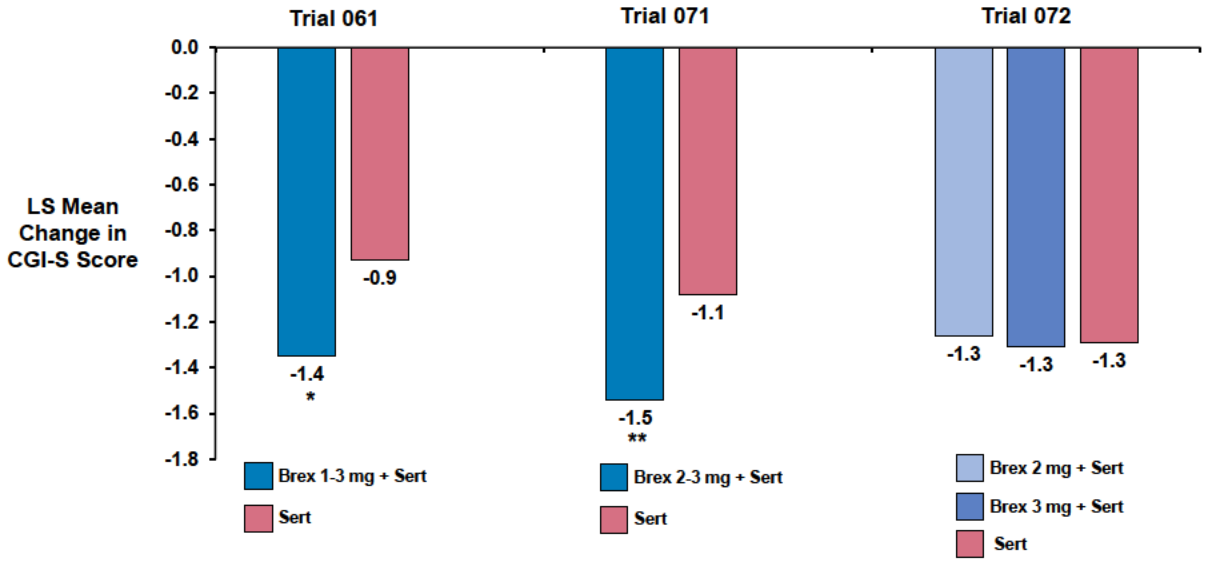
Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.
*nominal p <0.05, ***p <0.001.

Pooled data are presented in Appendix Section 10.5.5 showing that the statistical significance of the difference between the brexpiprazole plus sertraline and sertraline plus placebo treatments, observed in Trial 071, is maintained when both Phase 3 trials were pooled.

6.4.1.2 Secondary Efficacy Endpoint: Change from Baseline in Clinical Global Impression-Severity Score

A summary of the results for the secondary efficacy endpoint, CGI-S based on the Efficacy Sample is shown in Figure 29. In the 2 flexible-dose trials, treatment with the combination of brexpiprazole plus sertraline showed mean improvement of > 1 category of symptom severity (LS mean changes of −1.4 and −1.5) in Trials 061 and 071, respectively. In Trial 072, similar improvements on the CGI-S scale were observed for each of the 3 treatment arms.

Figure 29: Secondary Efficacy Measure Across Trials: CGI-Severity Score Change from Baseline to Week 10 (Efficacy Sample)



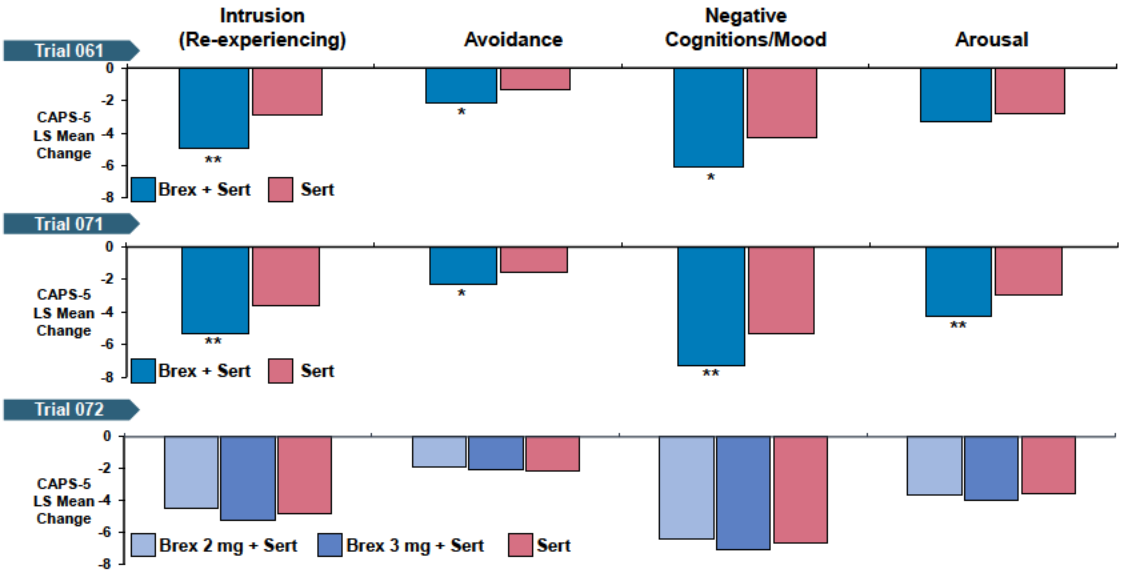
Brex = brexpiprazole; CGI-S = Clinical Global Impression – Severity; LS = least squares; Sert = sertraline.
*p-value <0.05, ** p-value <0.01

6.4.1.3 Other Efficacy Endpoints

6.4.1.3.1 CAPS-5 Symptom Clusters: Intrusion, Avoidance, Negative Cognitions and Mood, and Arousal and Reactivity

In the 2 flexible-dose trials, brexpiprazole plus sertraline demonstrated broad symptom improvements across the 4 clinician-reported CAPS-5 symptom clusters: intrusion (re-experiencing); avoidance; negative cognitions, and mood; arousal, and reactivity symptoms (Figure 30). Again, in Trial 072, patients randomized to brexpiprazole plus sertraline had similar improvements as in Trials 061 and 071. However, patients in this arm did not achieve a statistically significant improvement versus sertraline alone.

Figure 30: CAPS-5 Symptom Clusters Change from Baseline to Week 10 (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline. Nominal *p <0.05, ** p <0.01.

6.4.1.3.2 CAPS-5 Response Rate

For the prespecified response definition of ≥ 30% decrease in CAPS-5 Total Score from Baseline to Week 10, in the 2 flexible-dose trials, brexpiprazole plus sertraline showed a higher response rate than treatment with sertraline plus placebo (see Table 34). A high response rate was also observed in Trial 072 without differences between the treatment arms.

6.4.1.3.3 PTSD Checklist for CAPS-5, Hospital Anxiety and Depression Scale - Patient-Reported Endpoints

Compared with sertraline plus placebo, the brexpiprazole plus sertraline groups demonstrated improvement in the mean change in patient-reported outcome of PCL-5, HADS-A and HADS-D scores from Baseline to Week 10 in the 2 flexible-dose Trials 061 and 071 (Table 32). In the fixed-dose Trial 072 the improvements observed for these outcomes did not differentiate between the treatment arms.

Table 32: Summary of Mean Change from Baseline to Week 10 in Patient-Reported Endpoints for PCL-5 Total Score, Hospital Anxiety and Depression Subscale Scores in 12-Week Controlled Trials in PTSD (Efficacy Sample)

	Trial 061			Trial 071	Trial 072	
Efficacy Variables	**Brex 1-3 mg + Sert**	**Brex 1-3 mg + Placebo**	**Sert + Placebo**	**Brex 2-3 mg + Sert**	**Brex 2 mg + Sert**	**Brex 3 mg + Sert**
PCL-5 Total Score	N = 77	N = 69	N = 75	N = 133	N = 117	N = 113
Treatment Difference vs control[a] (p-value)	−6.01 (0.0143)	−1.18 (0.6433)	−1.08 (0.6586)	−7.28 (0.0008)	0.25 (0.8970)	−2.48 (0.2005)
Treatment difference vs Brex 1-3 mg+Placebo[b] (p-value)	−4.84 (0.0607)					
Treatment difference vs Sert+Placebo[b] (p-value)	−4.93 (0.0487)					
HADS-A Subscale Score	N = 77	N = 68	N = 75	N = 133	N = 118	N = 115
Treatment difference vs control[a] (p-value)	−1.20 (0.0793)	1.20 (0.0930)	0.34 (0.6172)	−1.56 (0.0083)	0.24 (0.6087)	−0.59 (0.2197)
Treatment difference vs Brex1-3 mg+Placebo[b] (p-value)	−2.41 (0.0010)					
LSMD vs Sert+Placebo[b] (P-value)	−1.55 (0.0274)					
HADS-D Subscale Score	N = 77	N = 68	N = 75	N = 133	N = 118	N = 115
Treatment difference vs control[a] (p-value)	−1.45 (0.0249)	0.46 (0.4939)	0.49 (0.4476)	−1.34 (0.0223)	0.02 (0.9697)	−0.72 (0.1870)
Treatment difference vs Brex 1-3 mg+Placebo[b] (p-value)	−1.91 (0.0053)					
Treatment differnce vs Sert+Placebo[b] (p-value)	−1.94 (0.0033)					

Brex = brexpiprazole; HADS-A = Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale - Depression subscale; LSMD = least squares mean difference; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; Sert = sertraline.

[a] Difference between active and placebo along with corresponding nominal p-value in Trial 061. Difference between Brex + Sert and Sert + placebo along with corresponding p-value in Trial 071. Difference between Brex 2 mg or Brex 3 mg and Sert + placebo along with corresponding p-value in Trial 072.

[b] Difference between Brex +Sert and Sert/Brex along with corresponding p-value.

6.4.1.4 Comparison of Results in Subpopulations

The benefit of treatment with brexpiprazole plus sertraline was generally observed across all prespecified subgroups in the 12-week trials. The results from the subgroup analyses were generally consistent with the overall population for age, and previous psychotherapy treatment in the individual trials (see Appendix Section 10.5.4).

Consistent results were observed in pooled subgroups (Appendix Figure 40 and Figure 41).

6.5 Clinical Meaningfulness

The clinical meaningfulness of the primary endpoint results was evaluated by looking at individual-level meaningful score differences. The individual-level meaningful change thresholds were derived from Phase 2 data (Trial 061) using an anchor-based approach (see Section 4.2.3). Thresholds of −8 and −15 points, anchored to a 1- to 2-point improvement on the CGI-S, were identified as an appropriate meaningful score difference on the CAPS-5.

Using 8- and 15- point improvements to represent responders, brexpiprazole plus sertraline group compared to sertraline alone group had an odds ratio (OR) of 1.6 and 1.4, respectively, in Trial 061 and 2.4 and 2.7, respectively, in Trial 071 (Table 33). While the proportion of responders was high and consistent in the brexpiprazole plus sertraline groups across trials, the difference between the groups in Trial 072 was inconsistent with Trial 071 due to the higher responses in the sertraline group (Figure 31).

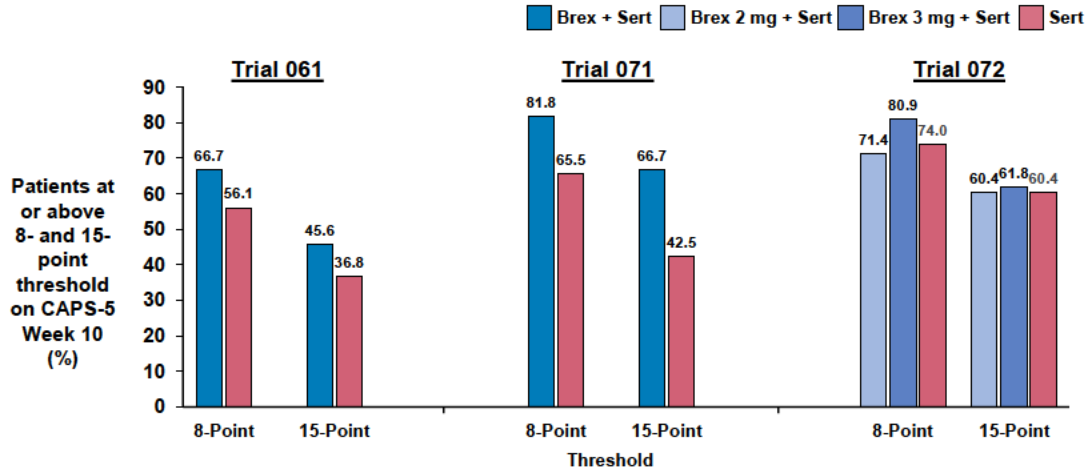
Overall, these results support the interpretability of the score changes on the CAPS-5 in a manner that is consistent with the FDA's Patient-Focused Drug Development Guidance (FDA 2023).

Table 33: Proportion of Patients with a CAPS-5 Response at Week 10 in the Controlled Trials in PTSD

	Trial 061		Trial 071		Trial 072		
Variable	**Brex 1-3 mg + Sert**	**Sert + Placebo**	**Brex 2-3 mg + Sert**	**Sert + Placebo**	**Brex 2 mg + Sert**	**Brex 3 mg + Sert**	**Sert +Placebo**
CAPS-5 Response Rate (8-point Threshold)							
Responders at Week 10, n (%)	38 (66.7)	32 (56.1)	81 (81.8)	57 (65.5)	65 (71.4)	72 (80.9)	71 (74.0)
OR (95% CI)	1.6 (0.7, 3.3)		2.4 (1.2, 4.7)		0.9 (0.5, 1.7)	1.5 (0.7, 3.0)	
p-value (vs Sert + placebo)	0.2495		0.0124		0.6979	0.2618	
CAPS-5 Response Rate (15-point Threshold)							
Responders at Week 10, n (%)	26 (45.6)	21 (36.8)	66 (66.7)	37 (42.5)	55 (60.4)	55 (61.8)	58 (60.4)
OR (95% CI)	1.4 (0.7, 3.0)		2.7 (1.5, 4.9)		1.0 (0.6, 1.8)	1.1 (0.6, 1.9)	
p-value (vs Sert + placebo)	0.3422		0.0011		0.9974	0.8474	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM 5th Edition; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders; OR = odds ratio; PTSD = post-traumatic stress disorder; Sert = sertraline.

Figure 31: Trials 061, 071, and 072 Proportion of Patients with a CAPS-5 Threshold Response at Week 10



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM 5th Edition; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders; PTSD = post-traumatic stress disorder; Sert = sertraline.

The empirically derived responder analyses were supported by the prespecified responder analysis of ≥ 30% change in CAPS-5. In Trials 061 and 071, higher proportions of patients in the brexpiprazole plus sertraline groups had a response ≥ 30% in CAPS-5 compared to the sertraline plus placebo groups, demonstrating the benefits of the combination treatment in patients with PTSD (Table 34).

Table 34: Proportion of Patients with a CAPS-5 Response at Week 10 – (Efficacy Sample)

	Trial 061		Trial 071		Trial 072		
Variable	Brex 1-3 mg + Sert	Sert + Placebo	Brex 2-3 mg + Sert	Sert + Placebo	Brex 2 mg + Sert	Brex 3 mg + Sert	Sert + Placebo
CAPS-5 Response Rate (≥ 30%)							
Proportion of responders at Week 10, n (%)	45 (57.7)	36 (46.8)	102 (68.5)	66 (48.2)	83 (62.9)	87 (69.1)	78 (60.0)
RR (95% CI)[a]	1.31 (0.96, 1.80)		1.40 (1.14, 1.72)		1.07 (0.87, 1.30)	1.21 (1.00, 1.46)	
P-Value (vs Sert + Placebo)	0.0863		0.0009		0.5239	0.0430	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM 5th Edition; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders; RR = response ratio; PTSD = post-traumatic stress disorder; Sert = sertraline.

[a] RR = ratio of response rate, which is the difference in the prespecified response (ie, defined as a decrease of ≥ 30% in CAPS-5 Total Score at Week 10).

6.6 Overall Efficacy Conclusions

Trial 071 provides statistically significant and clinically meaningful evidence that the combination of brexpiprazole 2 to 3 mg/day plus sertraline is superior to sertraline plus placebo in the treatment of PTSD. Benefits were observed on the primary endpoint as well as all secondary endpoints.

Trial 072 did not meet its primary endpoint. Absolute reductions in primary and key secondary endpoints in the brexpiprazole plus sertraline group were similar to those observed in Trials 061 and 071. Post hoc analyses did not reveal a cause for the diverging results.

Trial 061 provides strong supportive evidence that brexpiprazole plus sertraline is superior to sertraline plus placebo in the treatment of PTSD. The analysis of both the primary endpoint as well as multiple clinician- and patient-reported other efficacy endpoints showed a nominally significant and clinically meaningful advantage of brexpiprazole plus sertraline compared to all 3 treatment arms, placebo, sertraline plus placebo, and brexpiprazole plus placebo. Although the trial did not include a prespecified method of controlling for type 1 error, results were determined to be robust when multiple multiplicity adjustments were performed.

In the responder analysis and analyses of clinically meaningful thresholds in CAPS-5, greater proportions of patients in brexpiprazole plus sertraline met the meaningful change of −15 points on the CAPS-5 Response at Week 10 in Trial 071 and Trial 061 compared to the sertraline plus placebo group. The prespecified response rate

(defined as ≥ 30% change from Baseline to Week 10 on the CAPS-5 Total Scores) is consistent with and further supports these results.

The pooled data of both Phase 3 trials show a statistically significant effect that provides further evidence and confidence that brexpiprazole in combination with sertraline is superior to sertraline in the treatment of PTSD.

Brexpiprazole plus sertraline demonstrated broad symptom improvements across the 4 clinician-reported CAPS-5 symptom clusters in Trials 061 and 071.

The data from the brexpiprazole PTSD clinical development program supports the benefit of combination treatment with brexpiprazole plus sertraline for the treatment of adults with PTSD, addressing a critical unmet need for these patients.

7 CLINICAL SAFETY

Summary

- Brexpiprazole in combination with sertraline was well tolerated and is consistent with the well-established safety profile of brexpiprazole from clinical trials and extensive real-world usage in a variety of psychiatric indications. In the 12-week PTSD trials, a similar incidence of AEs was observed with the brexpiprazole plus sertraline group and the sertraline plus placebo group (55.5% vs 56.2%, respectively); AEs were mostly mild to moderate in severity.
- There were no dose-dependent patterns in safety data observed between the brexpiprazole 2 mg and 3 mg dose groups.
- Lower discontinuation rates due to AEs were observed with brexpiprazole plus sertraline than with sertraline plus placebo (4.0% vs 6.9%, respectively).
- There was a lower incidence of SAEs in the brexpiprazole plus sertraline group than in the sertraline plus placebo group (0.8% vs 1.6%).
- Two deaths occurred in the Phase 3 12-week PTSD trials: 1 occurred in the brexpiprazole plus sertraline group and 1 occurred the sertraline plus placebo group. Neither death was considered related to trial drug.
- Consistent with the well-established safety profile of brexpiprazole, the safety topics of interest were reported with a similar frequency in the combination group compared to sertraline alone, except for weight gain.

7.1 Safety Populations

The primary brexpiprazole PTSD safety database consists of the 3 completed 12-week, multicenter, randomized, double-blind trials to assess the efficacy and safety of brexpiprazole plus sertraline (Trials 061, 071, and 072). The core data sets for the safety analysis include all patients who received at least 1 dose of brexpiprazole plus sertraline or sertraline plus placebo in these trials (Table 35). Pooled safety data are presented by treatment group. Safety data for each of the trials are summarized in Appendix Section 10.6. Results from the individual trials are consistent with the pooled data presented throughout this section.

Table 35: Source of Safety Data for Each Treatment Group in the 12-Week Controlled Trials in PTSD

	Number of Patients					
Trial	Brex 2 mg + Sert	Brex 3 mg + Sert	Brex 1- 3 mg + Sert	All Brex + Sert	Sert + Placebo	Total
061	-	-	80	80	79	159
071	-	-	205*	205	196	401
072	185	180	-	365	172	537
Total	**185**	**180**	**285**	**650**	**447**	**1097**

Brex = brexpiprazole; PTSD = post-traumatic stress disorder; Sert = sertraline.
*Trial 071 only included 2-3 mg flexible dose.

Review of the safety data from the PTSD program demonstrated characteristics of events consistent with known safety profile of brexpiprazole based on the extensive post-marketing experience (estimated total cumulative post-market exposure of brexpiprazole through 30 Jun 2023 is 1,689,049 patient-years). A comprehensive and detailed review of all the safety data from all available sources such as nonclinical, literature, clinical, and post-marketing experience did not reveal a change to the well-established and favorable benefit-risk profile of brexpiprazole for approved indications.

7.2 Treatment Exposure

In the PTSD 12-week controlled trials, 650 patients were exposed to ≥ 1 dose of brexpiprazole plus sertraline and 447 patients were exposed to ≥ 1 dose of sertraline plus placebo. Mean treatment duration was similar between the treatment groups (Table 36). Approximately 80% of patients in each of the brexpiprazole plus sertraline dose groups completed at least 6 weeks of treatment. Slightly more than half of all patients (52.0%) in the brexpiprazole plus sertraline group and in each of the brexpiprazole plus sertraline dose groups completed at least 11 weeks (≥ 77 days) of treatment compared with 46.3% of patients in the sertraline plus placebo group.

Across all Phase 2/3 brexpiprazole trials (all indications), 12,550 unique patients have been exposed to at least 1 dose of brexpiprazole, and 8,512 patients (67.8%) completed at least 8 weeks of treatment with brexpiprazole in all indications combined, of which 1,910 patients have been exposed to brexpiprazole for more than 52 weeks of treatment in the previously completed open-label trials for the approved indications of schizophrenia and MDD.

Table 36: Treatment Duration and Overall Exposure in the 12-Week Controlled Trials in PTSD (Safety Sample)

	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1- 3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
Patient days of drug exposure	11,571	10,984	17,885	40,440	26,900	67,340
Treatment duration (days)						
Mean (SD)	63.7 (23.1)	62.6 (24.9)	64.1 (22.4)	63.6 (23.3)	61.3 (24.8)	62.6 (24)
Min, Max	1, 85	2, 85	4, 88	1, 88	2, 105	1, 105
Treatment duration, n (%)						
≥ 1 week	183 (98.9)	173 (96.1)	283 (99.3)	639 (98.3)	433 (96.9)	1072 (97.7)
≥ 3 weeks	167 (90.3)	159 (88.3)	259 (90.9)	585 (90.0)	395 (88.4)	980 (89.3)
≥ 6 weeks	148 (80.0)	142 (78.9)	229 (80.4)	519 (79.8)	332 (74.3)	851 (77.6)
≥ 9 weeks	134 (72.4)	123 (68.3)	205 (71.9)	462 (71.1)	308 (68.9)	770 (70.2)
≥ 10 weeks	128 (69.2)	122 (67.8)	196 (68.8)	446 (68.6)	290 (64.9)	736 (67.1)
≥ 11 weeks	95 (51.4)	97 (53.9)	146 (51.2)	338 (52.0)	207 (46.3)	545 (49.7)
≥ 12 weeks	5 (2.7)	3 (1.7)	6 (2.1)	14 (2.2)	6 (1.3)	20 (1.8)

Brex = brexpiprazole; PTSD = post-traumatic stress disorder; SD = standard deviation; Sert = sertraline.
Note: Duration of exposure = (last trial drug date – first trial drug date) + 1.

7.3 Overview of Adverse Events

In the 12-week controlled trials, incidences of AEs were generally similar between the brexpiprazole plus sertraline group and sertraline plus placebo groups (Table 37). Few patients in each treatment group experienced SAEs, and discontinuations due to AEs were generally low overall with a lower incidence in the brexpiprazole plus sertraline group than the sertraline plus placebo group.

Two deaths occurred during the Phase 3, 12-week controlled trials, 1 in the brexpiprazole plus sertraline group and 1 in the sertraline plus placebo group. Both deaths were assessed as not related to trial drug. One additional death occurred in the placebo group of Trial 061.

Table 37: Adverse Events (All Causalities) in the 12-Week Controlled Trials in PTSD (Safety Sample)

Category, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
Patients with AEs	95 (51.4)	87 (48.3)	179 (62.8)	**361 (55.5)**	**251 (56.2)**	612 (55.8)
Patients with severe AEs	1 (0.5)	2 (1.1)	12 (4.2)	**15 (2.3)**	**13 (2.9)**	28 (2.6)
Patients with SAEs	1 (0.5)	1 (0.6)	3 (1.1)	**5 (0.8)**	**7 (1.6)**	12 (1.1)
Patients discontinued trial drug due to AE	5 (2.7)	8 (4.4)	13 (4.6)	**26 (4.0)**	**31 (6.9)**	57 (5.2)
Deaths*	1 (0.5)	0 (0.0)	0 (0.0)	**1 (0.2)**	**1 (0.2)**	2 (0.2)

AE = adverse event; Brex = brexpiprazole; PTSD = post-traumatic stress disorder; SAE = serious adverse event; Sert = sertraline.
Note: All AEs presented started after start of trial treatment; or if the event was continuous from Baseline and was serious, trial treatment-related, or resulted in death, discontinuation, interruption, or reduction of trial drug.
*One additional death occurred in the placebo group of Trial 061.

7.4 Common Adverse Events

The commonly reported AEs occurring in at least 2% of patients in the all brexpiprazole plus sertraline group or the sertraline plus placebo group were generally consistent across treatment groups (Table 38). The AEs reported in at least 2% of patients in the brexpiprazole plus sertraline group with an incidence greater than in the sertraline plus placebo group were weight increased, somnolence, akathisia, fatigue, dyspepsia, anxiety, and libido decreased.

The most commonly reported AE in at least 5% of patients in the brexpiprazole plus sertraline group and greater than in the sertraline plus placebo group was weight increased. The most commonly reported AEs that occurred in at least 5% of patients in the sertraline plus placebo group and greater than the brexpiprazole plus sertraline group included nausea, headache, and diarrhea.

No dose-dependent patterns in incidence of AEs were noted.

Table 38: Incidence of Adverse Events Reported by ≥ 2% of Patients in the All Brexpiprazole Plus Sertraline Group or Sertraline Plus Placebo in the 12-Week Controlled Trials in PTSD (Safety Sample)

Preferred Term, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
Nausea	9 (4.9)	15 (8.3)	28 (9.8)	**52 (8.0)**	**50 (11.2)**	102 (9.3)
Headache	13 (7.0)	10 (5.6)	13 (4.6)	**36 (5.5)**	**34 (7.6)**	70 (6.4)
Weight increased	7 (3.8)	6 (3.3)	21 (7.4)	**34 (5.2)**	**6 (1.3)**	40 (3.6)
Diarrhoea	7 (3.8)	11 (6.1)	13 (4.6)	**31 (4.8)**	**27 (6.0)**	58 (5.3)
Somnolence	4 (2.2)	4 (2.2)	17 (6.0)	**25 (3.8)**	**11 (2.5)**	36 (3.3)
Akathisia	7 (3.8)	6 (3.3)	10 (3.5)	**23 (3.5)**	**14 (3.1)**	37 (3.4)
Fatigue	4 (2.2)	3 (1.7)	16 (5.6)	**23 (3.5)**	**15 (3.4)**	38 (3.5)
Insomnia	7 (3.8)	7 (3.9)	9 (3.2)	**23 (3.5)**	**21 (4.7)**	44 (4.0)
Tremor	4 (2.2)	4 (2.2)	10 (3.5)	**18 (2.8)**	**13 (2.9)**	31 (2.8)
Dizziness	5 (2.7)	4 (2.2)	7 (2.5)	**16 (2.5)**	**19 (4.3)**	35 (3.2)
Dyspepsia	3 (1.6)	4 (2.2)	9 (3.2)	**16 (2.5)**	**9 (2.0)**	25 (2.3)
Anxiety	2 (1.1)	6 (3.3)	7 (2.5)	**15 (2.3)**	**10 (2.2)**	25 (2.3)
Dry mouth	2 (1.1)	3 (1.7)	10 (3.5)	**15 (2.3)**	**12 (2.7)**	27 (2.5)
Libido decreased	3 (1.6)	4 (2.2)	6 (2.1)	**13 (2.0)**	**7 (1.6)**	20 (1.8)
Vomiting	5 (2.7)	3 (1.7)	5 (1.8)	**13 (2.0)**	**12 (2.7)**	25 (2.3)
Upper respiratory tract	0	1 (0.6)	5 (1.8)	**6 (0.9)**	**12 (2.1)**	18 (1.6)

Brex = brexpiprazole; PTSD = post-traumatic stress disorder; Sert = sertraline.
Note: All adverse events which started after start of trial treatment; or if the event was continuous from Baseline and were serious, trial drug-related, or resulted in death, discontinuation, interruption, or reduction of trial drug.

7.5 Adverse Events Resulting in Discontinuation

The number of patients who discontinued treatment due to AEs in all brexpiprazole plus sertraline group was lower compared to the sertraline plus placebo group (Table 39). Akathisia was the most frequently reported event leading to treatment discontinuation in the all brexpiprazole plus sertraline group and the sertraline plus placebo group. Notably, the incidence was less than 1% for all preferred terms.

Table 39: Incidence of Adverse Events Resulting in Discontinuation of Trial Drug Occurring in > 1 Patient in the All Brexpiprazole Plus Sertraline or Sertraline Plus Placebo Treatment Group in the 12-Week Controlled Trials in PTSD (Safety Sample)

Preferred Term, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
At least 1 AE	5 (2.7)	8 (4.4)	13 (4.6)	**26 (4.0)**	**31 (6.9)**	57 (5.2)
Akathisia	1 (0.5)	2 (1.1)	1 (0.4)	**4 (0.6)**	**3 (0.7)**	7 (0.6)
Fatigue	0	0	3 (1.1)	**3 (0.5)**	**2 (0.4)**	5 (0.5)
Diarrhoea	0	2 (1.1)	0	**2 (0.3)**	**1 (0.2)**	3 (0.3)
Libido decreased	0	1 (0.6)	1 (0.4)	**2 (0.3)**	**0**	2 (0.2)
Dizziness	0	0	0	**0**	**2 (0.4)**	2 (0.2)
Irritability	0	0	0	**0**	**2 (0.4)**	2 (0.2)
Tremor	0	0	0	**0**	**2 (0.4)**	2 (0.2)

AE = adverse event; Brex = brexpiprazole; Sert = sertraline
Note: All AEs presented started after start of trial treatment; or if the event was continuous from Baseline and was serious, trial drug-related, or resulted in death, discontinuation, interruption, or reduction of trial drug.

7.6 Serious Adverse Events

The incidence of SAEs was lower in all brexpiprazole plus sertraline group than in the sertraline plus placebo group (Table 40). No individual SAEs were reported in more than 1 patient in the all brexpiprazole plus sertraline group or sertraline plus placebo group, and all SAEs were assessed as not related to trial drug by the investigators.

Table 40: Incidence of Serious Adverse Events by Preferred Term in the 12-Week Controlled Trials in PTSD (Safety Sample)

Preferred Term, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
At least 1 AE	1 (0.5)	1 (0.6)	3 (1.1)	**5 (0.8)**	**7 (1.6)**	12 (1.1)
Back pain	0	0	1 (0.4)	**1 (0.2)**	**0**	1 (0.1)
Cyst rupture	0	1 (0.6)	0	**1 (0.2)**	**0**	1 (0.1)
Drowning	1 (0.5)	0	0	**1 (0.2)**	**0**	1 (0.1)
Gastroenteritis	0	0	1 (0.4)	**1 (0.2)**	**0**	1 (0.1)
Suicide attempt	0	0	1 (0.4)	**1 (0.2)**	**0**	1 (0.1)
Cerebrovascular accident	0	0	0	**0**	**1 (0.2)**	1 (0.1)
Diverticulitis	0	0	0	**0**	**1 (0.2)**	1 (0.1)
Hepatic enzyme increased	0	0	0	**0**	**1 (0.2)**	1 (0.1)
Hypertension	0	0	0	**0**	**1 (0.2)**	1 (0.1)
Mania	0	0	0	**0**	**1 (0.2)**	1 (0.1)
Suicidal ideation	0	0	0	**0**	**1 (0.2)**	1 (0.1)
Toxicity to various agents	0	0	0	**0**	**1 (0.2)**	1 (0.1)

AE = adverse event; Brex = brexpiprazole; PTSD = post-traumatic stress disorder; Sert = sertraline.
Note: All AEs presented started after start of trial treatment; or if the event was continuous from Baseline and was serious, trial drug-related, or resulted in death, discontinuation, interruption, or reduction of trial drug.

7.7 Deaths

Two deaths occurred in the Phase 3 completed 12-week controlled trials in PTSD. One death in the brexpiprazole 2 mg/day plus sertraline group and 1 death in the sertraline plus placebo group:

- In Trial 071, 1 patient in the sertraline plus placebo group died due to an SAE of toxic effects of cocaine. The investigator considered the event of toxicity to various agents and cocaine to be not related to trial drug.
- In Trial 072, 1 patient in the brexpiprazole plus sertraline group died due to drowning. The investigator considered the event of accidental drowning to be not related to trial drug.

One additional death occurred in the placebo group of Trial 061. The patient discontinued from the trial due to an SAE of bile duct stone and subsequently died from complications of a corrective procedure.

Patient narratives are provided in Appendix Section 10.7.

7.8 Safety Topics of Interest

Based on the known pharmacology of the drug class effects, as well as safety areas of interest for approved atypical antipsychotic agents, the focused safety topics of interest were identified for additional detailed analyses of brexpiprazole plus sertraline in patients with PTSD. With the exception of effect on weight, the incidence of all safety topics of interest, including EPS and suicidality, was generally similar between the treatment groups (Table 41).

Table 41: Overview of Safety Topics of Interest in the 12-Week Controlled Trials in PTSD (Safety Sample)

Safety Topic, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
Effect on glucose	0	1 (0.6)	2 (0.7)	**3 (0.5)**	**1 (0.2)**	4 (0.4)
Effect on lipids	0	1 (0.6)	1 (0.4)	**2 (0.3)**	**1 (0.2)**	3 (0.3)
Effects on weight	9 (4.9)	7 (3.9)	27 (9.5)	**43 (6.6)**	**10 (2.2)**	53 (4.8)
EPS-related AEs	17 (9.2)	12 (6.7)	31 (10.9)	**60 (9.2)**	**39 (8.7)**	99 (9.0)
Hepatic impairment	1 (0.5)	3 (1.7)	1 (0.4)	**5 (0.8)**	**2 (0.4)**	7 (0.6)
Hypersensitivity	1 (0.5)	1 (0.6)	8 (2.8)	**10 (1.5)**	**4 (0.9)**	14 (1.3)
Orthostatic hypotension, dizziness, and syncope	7 (3.8)	4 (2.2)	10 (3.5)	**21 (3.2)**	**22 (4.9)**	43 (3.9)
Rhabdomyolysis and CPK elevation	1 (0.5)	1 (0.6)	4 (1.4)	**6 (0.9)**	**4 (0.9)**	10 (0.9)
Somnolence	4 (2.2)	5 (2.8)	25 (8.8)	**34 (5.2)**	**20 (4.5)**	54 (4.9)
Suicidality	2 (1.1)	0	2 (0.7)	**4 (0.6)**	**5 (1.1)**	9 (0.8)

AE = adverse event; Brex = brexpiprazole; CPK = Creatine phosphokinase; EPS = Extrapyramidal symptoms; PTSD = post-traumatic stress disorder; Sert = sertraline; VTE = venous thrombotic event.
No events occurred for the following safety topics: Hematopoietic/ leukopenia events, Neuroleptic malignant syndrome, Overdose, Effect on prolactin, QT prolongation, Seizures, VTE (thrombotic and embolic events).

Although there was a higher incidence of weight increased reported in the all brexpiprazole plus sertraline group than in the sertraline plus placebo group, the mean change from Baseline to last visit in body weight was small and not considered clinically meaningful (+1.0 kg with brexpiprazole plus sertraline, and −0.2 kg with sertraline plus placebo).

The mean changes from Baseline in metabolic parameters (fasting serum glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides) were small and similar between the brexpiprazole plus sertraline group and the sertraline plus placebo group (see Appendix Table 65). No

differences were observed between treatment groups in the incidence of significant shifts from Baseline for any of the metabolic parameters at any visit. The differences in the incidence of potentially clinically relevant changes were minimal between the treatment groups and were not clinically meaningful for any of these metabolic parameters (see Appendix Table 66).

Overall, EPS-related TEAEs were reported in 9.0% of patients with a similar incidence observed between the brexpiprazole plus sertraline group and the sertraline plus placebo group (Table 42).

Table 42: Incidence of EPS-Related Treatment-Emergent Adverse Events by EPS Category in the 12-Week Controlled Trials in PTSD (Safety Sample)

Event, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
Patients with any TEAE[a]	17 (9.2)	12 (6.7)	31 (10.9)	**60 (9.2)**	**39 (8.7)**	99 (9.0)
EPS - Akathisia Events	10 (5.4)	6 (3.3)	14 (4.9)	**30 (4.6)**	**15 (3.4)**	45 (4.1)
EPS - Dyskinetic Events	1 (0.5)	0	2 (0.7)	**3 (0.5)**	**0**	3 (0.3)
EPS - Dystonic Events	4 (2.2)	3 (1.7)	11 (3.9)	**18 (2.8)**	**13 (2.9)**	31 (2.8)
EPS - Parkinsonian Events	4 (2.2)	5 (2.8)	10 (3.5)	**19 (2.9)**	**15 (3.4)**	34 (3.1)
EPS - Residual Events	0	0	1 (0.4)	**1 (0.2)**	**1 (0.2)**	2 (0.2)

AE = adverse event; Brex = brexpiprazole; EPS = Extrapyramidal symptoms; MedDRA = Medical Dictionary for Adverse Events; PTSD = post-traumatic stress disorder; Sert = sertraline; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: All AEs which started after start of trial treatment; or if the event was continuous from Baseline and was serious, drug-related, or resulted in death, discontinuation, interruption, or reduction of trial drug. Patients are counted once per term for the most severe of multiple occurrences of a specific MedDRA preferred term.
[a.] Patients with AEs in multiple SOCs were counted only once towards the total.

7.9 Clinical Laboratory, Vital Signs, ECG, and C-SSRS Evaluation

Important laboratory parameters were reviewed to evaluate the safety topics of interest as listed in the Section 7.8 (effect on glucose, lipids, metabolic changes, hepatic impairment, and creatine kinase). There were no clinically relevant differences between the brexpiprazole plus sertraline group and the sertraline plus placebo group in any other laboratory test values.

Additional review of the vital sign and ECG parameters did not identify any clinically meaningful changes (see Appendix Table 62 for vital signs and Table 63 for categorical changes in ECG).

C-SSRS evaluation during the treatment period reported low and similar rate of suicidal behavior and suicidal ideation between the combination and sertraline alone treatment groups (see Appendix Table 64).

7.10 Long-Term Safety

A total of 12,550 unique patients have been exposed to at least 1 dose of brexpiprazole in the clinical development program including 6,631 in the MDD trials (adjunctive with antidepressants including sertraline), 1,074 in the agitation associated with dementia due to Alzheimer's disease trials, 3,170 in the schizophrenia trials, 155 in the attention deficit hyperactivity disorder trial, 748 in the PTSD trials, 504 in the bipolar mania trials, and 268 in the Borderline Personality Disorder trials.

In the long-term open-label MDD trials (up to 52 weeks), 1,189 patients received treatment with adjunctive brexpiprazole and antidepressant treatment for more than 52 weeks treatment duration. A total of 339 patients received at least 1 dose of adjunctive brexpiprazole with sertraline treatment in the long-term open-label US Investigational New Drug trials for MDD. The reported TEAEs in the long-term trials were consistent with the known safety profile of brexpiprazole. The majority of these TEAEs were mild or moderate in severity. Upon comparison with the safety profile observed for the MDD short-term, placebo-controlled trials, no additional safety findings were observed with brexpiprazole plus antidepressant treatment in the long-term trials.

In the long-term open-label schizophrenia trials, a total of 721 patients received treatment with brexpiprazole for more than 52 weeks treatment duration.

No new safety issues were identified associated with long-term (up to 52 weeks) use of brexpiprazole in the previously completed long-term trials in approved indications.

7.11 Overall Safety Conclusions

Overall, brexpiprazole in combination with sertraline demonstrated a favorable tolerability and safety profile consistent with those of sertraline alone. No new risks were identified in the PTSD population treated with brexpiprazole (2 to 3 mg/day) plus sertraline (100 to 200 mg/day), and the findings from the 12-week controlled trials confirm that brexpiprazole is safe and well tolerated in combination with sertraline in the treatment of PTSD. The incidence of TEAEs was similar across both treatment groups with low frequency of SAEs. The safety topics of special interest demonstrated that the known safety profile of brexpiprazole was not changed when used in combination with sertraline.

8 BENEFITS AND RISK CONCLUSIONS

PTSD is a serious, long-term, psychiatric disorder with a significant unmet need for safe and effective, evidence-based treatment. With only 2 FDA-approved treatments, both with moderate response rates and inconsistent efficacy across symptom clusters, many people with PTSD continue suffering from its severe consequences and need options that better address their burdensome, heterogeneous, and complex symptoms.

Brexpiprazole in combination with sertraline treatment provides consistent and predictable therapeutic outcomes in the treatment of PTSD and was generally well tolerated with no added risk. In this largest clinical development program in PTSD to date, combination treatment with brexpiprazole plus sertraline was more effective in relieving symptoms of PTSD and demonstrated larger response rates than sertraline alone in 2 of 3 studies.

Furthermore, brexpiprazole plus sertraline demonstrated broad and consistent symptom improvements across the 4 PTSD symptom clusters, addressing limitations of approved treatments, which have shown moderate and inconsistent efficacy across symptom clusters. The combination treatment was well tolerated and is consistent with the well-established safety profile of brexpiprazole from clinical trials and extensive real-world usage across several indications.

The evidence supports a positive benefit-risk profile for brexpiprazole in combination with sertraline for the treatment of PTSD in adults.

9 REFERENCES

Al Jowf GI, Ahmed ZT, An N, Reijnders RA, Ambrosino E, Rutten BPF, et al. A Public Health Perspective of Post-Traumatic Stress Disorder. Int J Environ Res Public Health. 2022;19(11).

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Text Revision. 2022.

American Psychological Association. Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults. Guideline Development Panel for the Treatment of PTSD in Adults 2025.

Arnsten AF. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci. 2015;18(10):1376-1385.

Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-676.

Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiatry. 1990;51(6):236-238.

Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ. 2002;21(2):271-292.

Carey P, Suliman S, Ganesan K, Seedat S, Stein DJ. Olanzapine monotherapy in posttraumatic stress disorder: efficacy in a randomized, double-blind, placebo-controlled study. Hum Psychopharmacol. 2012;27(4):386-391.

Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Ann Pharmacother. 2004;38(9):1395-1399.

Cohen H, Zohar J, Kaplan Z, Arnt J. Adjunctive treatment with brexpiprazole and escitalopram reduces behavioral stress responses and increase hypothalamic NPY immunoreactivity in a rat model of PTSD-like symptoms. Eur Neuropsychopharmacol. 2018;28(1):63-74.

Cook JM, Zeber JE, Simiola V, Rossom R, Scherrer JF, Owen-Smith AA, et al. Comparisons Between Patients Diagnosed with PTSD in Primary Care Versus Mental Health Care in Five Large Civilian Health Care Systems. J Clin Psychol Med Settings. 2021;28(2):221-228.

Coon CD, Cappelleri JC. Interpreting Change in Scores on Patient-Reported Outcome Instruments. Ther Innov Regul Sci. 2016;50(1):22-29.

Davis LL, Annette U, Patrick G-S, Jessica M, Jerome B, Remi B, et al. Patient journey of civilian adults diagnosed with posttraumatic stress disorder—A chart review study. Current Medical Research and Opinion. 2024;40(3):505-516.

Davis LL, Schein J, Cloutier M, Gagnon-Sanschagrin P, Maitland J, Urganus A, et al.

The Economic Burden of Posttraumatic Stress Disorder in the United States From a Societal Perspective. J Clin Psychiatry. 2022;83(3).

de Paula BB, Leite-Panissi CR. Distinct effect of 5-HT1A and 5-HT2A receptors in the medial nucleus of the amygdala on tonic immobility behavior. Brain Res. 2016;1643:152-158.

Dell'Aquila A, Berle D. Predictors of alcohol and substance use among people with post-traumatic stress disorder (PTSD): findings from the NESARC-III study. Soc Psychiatry Psychiatr Epidemiol. 2023;58(10):1509-1522.

Dowd SM, Zalta AK, Burgess HJ, Adkins EC, Valdespino-Hayden Z, Pollack MH. Double-blind randomized controlled study of the efficacy, safety and tolerability of eszopiclone vs placebo for the treatment of patients with post-traumatic stress disorder and insomnia. World J Psychiatry. 2020;10(3):21-28.

Dunn OJ. Multiple Comparisons Among Means. Journal of the American Statistical Association. 1961;56(293):52-64.

FDA. Draft Guidance: Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making. 2023.

Ferry B, Roozendaal B, McGaugh JL. Involvement of alpha1-adrenoceptors in the basolateral amygdala in modulation of memory storage. Eur J Pharmacol. 1999;372(1):9-16.

Germain A, Richardson R, Moul DE, Mammen O, Haas G, Forman SD, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. J Psychosom Res. 2012;72(2):89-96.

Goldstein RB, Smith SM, Chou SP, Saha TD, Jung J, Zhang H, et al. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. Soc Psychiatry Psychiatr Epidemiol. 2016;51(8):1137-1148.

Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication (ADM) 76-338. . Rockville, MD: National Institute of Mental Health; 1976.

Halvorsen J. Defining clinically significant change. Br J Psychiatry. 2016;209(1):85.

Hochberg Y. A Sharper Bonferroni Procedure for Multiple Tests of Significance. Biometrika. 1988;75(4):800-802.

Holder N, Woods A, Neylan TC, Maguen S, Seal KH, Bernardy N, et al. Trends in Medication Prescribing in Patients With PTSD From 2009 to 2018: A National Veterans Administration Study. J Clin Psychiatry. 2021;82(3).

Holm S. A Simple Sequentially Rejective Multiple Test Procedure. Scandinavian Journal of Statistics. 1979;6(2):65-70.

Hunt JC, Chesney SA, Jorgensen TD, Schumann NR, deRoon-Cassini TA. Exploring the gold-standard: Evidence for a two-factor model of the Clinician Administered PTSD Scale for the DSM-5. Psychol Trauma. 2018;10(5):551-558.

Jain R, Chepke C, Davis LL, McIntyre RS, Raskind MA. Dysregulation of Noradrenergic Activity: Its Role in Conceptualizing and Treating Major Depressive Disorder, Schizophrenia, Agitation in Alzheimer's Disease, and Posttraumatic Stress Disorder. J Clin Psychiatry. 2024;85(4).

Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, et al. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatol. 2017;8(sup5):1353383.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617-627.

Kleiman SE, Bovin MJ, Black SK, Rodriguez P, Brown LG, Brown ME, et al. Psychometric properties of a brief measure of posttraumatic stress disorder-related impairment: The Brief Inventory of Psychosocial Functioning. Psychol Serv. 2020;17(2):187-194.

Koenen KC, Sumner JA, Gilsanz P, Glymour MM, Ratanatharathorn A, Rimm EB, et al. Post-traumatic stress disorder and cardiometabolic disease: improving causal inference to inform practice. Psychol Med. 2017;47(2):209-225.

Krystal JH, Davis LL, Neylan TC, M AR, Schnurr PP, Stein MB, et al. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry. 2017;82(7):e51-e59.

Krystal JH, Neumeister A. Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. Brain Res. 2009;1293:13-23.

Krystal JH, Rosenheck RA, Cramer JA, Vessicchio JC, Jones KM, Vertrees JE, et al. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. Jama. 2011;306(5):493-502.

Leeies M, Pagura J, Sareen J, Bolton JM. The use of alcohol and drugs to self-medicate symptoms of posttraumatic stress disorder. Depress Anxiety. 2010;27(8):731-736.

Li X, Inoue T, Abekawa T, Weng S, Nakagawa S, Izumi T, et al. 5-HT1A receptor agonist affects fear conditioning through stimulations of the postsynaptic 5-HT1A receptors in the hippocampus and amygdala. Eur J Pharmacol. 2006;532(1-2):74-80.

MacQueen G, Born L, Steiner M. The selective serotonin reuptake inhibitor sertraline: its profile and use in psychiatric disorders. CNS Drug Rev. 2001;7(1):1-24.

Maeda K, Sugino H, Akazawa H, Amada N, Shimada J, Futamura T, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350(3):589-604.

National Center for PTSD. How Common Is PTSD in Adults? 2025 [Available from: https://www.ptsd.va.gov/understand/common/common_adults.asp.]

Padala PR, Madison J, Monnahan M, Marcil W, Price P, Ramaswamy S, et al. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol. 2006;21(5):275-280.

Parrott S. PTSD in the News: Media Framing, Stigma, and Myths About Mental Illness. Electronic News. 2023;17(3):181-197.

Pietrzak RH, Goldstein RB, Southwick SM, Grant BF. Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: results from Wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions. J Anxiety Disord. 2011;25(3):456-465.

Pollack MH, Hoge EA, Worthington JJ, Moshier SJ, Wechsler RS, Brandes M, et al. Eszopiclone for the treatment of posttraumatic stress disorder and associated insomnia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry. 2011;72(7):892-897.

Posner K, Brent DA, Lucas C, Gould MS, Stanley BH. , al. e. Columbia-Suicide Severity Rating Scale (C-SSRS). New York, NY2008.

Raskind MA, Peskind ER, Chow B, Harris C, Davis-Karim A, Holmes HA, et al. Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans. N Engl J Med. 2018;378(6):507-517.

Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007;61(8):928-934.

Rodriguez P, Holowka DW, Marx BP. Assessment of posttraumatic stress disorder-related functional impairment: a review. J Rehabil Res Dev. 2012;49(5):649-665.

Sherin JE, Nemeroff CB. Post-traumatic stress disorder: the neurobiological impact of psychological trauma. Dialogues Clin Neurosci. 2011;13(3):263-278.

Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-19.

Stefanovics EA, Rosenheck RA, Jones KM, Huang G, Krystal JH. Minimal Clinically Important Differences (MCID) in Assessing Outcomes of Post-Traumatic Stress Disorder. Psychiatr Q. 2018;89(1):141-155.

Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry.

2002;159(10):1777-1779.

Strawn JR, Geracioti TD, Jr. Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. Depress Anxiety. 2008;25(3):260-271.

Sumner JA, Cleveland S, Chen T, Gradus JL. Psychological and biological mechanisms linking trauma with cardiovascular disease risk. Transl Psychiatry. 2023;13(1):25.

Torrisi SA, Leggio GM, Drago F, Salomone S. Therapeutic Challenges of Post-traumatic Stress Disorder: Focus on the Dopaminergic System. Front Pharmacol. 2019;10:404.

US Department of Veterans Affairs. VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Version 4.0. 2023.

Varker T, Kartal D, Watson L, Freijah I, O'Donnell M, Forbes D, Phelps, A, Hopwood, M., McFarlane, A., Cooper, J., Wade, D., Bryant, R., & Hinton, M. Defining response and nonresponse to posttraumatic stress disorder treatments: A systematic review. Clinical Psychology: Science and Practice,. 2020;27(4):Article e12355.

Ware JE, Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000;25(24):3130-3139.

Weathers F, Blake D, Schnurr P, Kaloupek D, Marx B, Keane T. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). [Assessment]. 2013a [Available from: www.ptsd.va.gov.]

Weathers F, Blake D, Schnurr P, Kaloupek D, Marx B, Keane T. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) - Past week version. White River Junction, VT: National Center for PTSD; 2015.

Weathers F, Blake D, Schnurr P, Kaloupek D, Marx B, Keane T. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) - Past week version. White River Junction, VT: National Center for PTSD; 2018a.

Weathers F, Litz B, Keane T, Palmieri P, Marx B, Schnurr P. PTSD Checklist for DSM-5 (PCL-5) – Standard [Measurement instrument]. Version Date 29 August 2023. 2013b [Available from: https://www.ptsd.va.gov/.]

Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. Psychol Assess. 2018b;30(3):383-395.

Williams T, Phillips NJ, Stein DJ, Ipser JC. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev. 2022;3(3):Cd002795.

Yehuda R, Hoge CW, McFarlane AC, Vermetten E, Lanius RA, Nievergelt CM, et al. Post-traumatic stress disorder. Nat Rev Dis Primers. 2015;1:15057.

Young EA, Breslau N. Cortisol and catecholamines in posttraumatic stress disorder: an epidemiologic community study. Arch Gen Psychiatry. 2004;61(4):394-401.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370.

10 APPENDICES

10.1 Complete Enrollment Criteria by Trial

10.1.1 Inclusion Criteria for Trials 061, 071, and 072

1. Patients who are able to complete the consent process and/or consent obtained from a legally acceptable representative (as required by institutional review board/independent ethics committee) prior to the initiation of any protocol-required procedures.
2. Ability, in the opinion of the principal investigator, to understand the nature of the trial and follow protocol requirements, including the prescribed dosage regimens, tablet/capsule ingestion, and discontinuation of prohibited concomitant medication; to read and understand the written word in order to complete patient-reported outcomes measures; and to be reliably rated on assessment scales.
3. Male and female outpatients 18 to 65 years of age, inclusive, at the time of informed consent.
4. Patients who have PTSD, diagnosed according to DSM-5, and confirmed by the MINI.
5. The patient has a CAPS-5 Total Score ≥ 33 at Screening and Day 0 Visits.
6. Onset of symptoms meeting the DSM-5 criteria for PTSD symptoms for a minimum of 6 months prior to Screening.
7. Patients willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.

10.1.2 Exclusion Criteria for Trial 061

Sex and Reproductive Status

1. Sexually active males or women of childbearing potential who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of trial drug. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. Males who do not agree to abstain from sperm donation during the trial and for 30 days after the last dose of trial drug.
2. Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving trial drug.

Target Disease

3. Patients who are receiving disability payments because of PTSD or any other

psychiatric disorder; unless the disability payments will not be impacted by potential improvements demonstrated in the trial, OR the patient is engaged in compensation litigation or other processes whereby personal gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorder.

4. The index traumatic event that led to development of PTSD took place > 15 years before Screening.
5. The index traumatic event occurred before age 16.
6. Patients with PTSD who, in the investigator's opinion, are considered resistant/refractory to psychotropic treatment by history.
7. Patients who are currently receiving Zoloft (sertraline) with adequate dose and duration (> 50 mg/day for a minimum of 8 weeks).
8. Patients who have had initiation of, or a change in, psychotherapy, eye movement desensitization and reprocessing (EMDR) therapy or any other intervention for the treatment of PTSD symptoms within 28 days prior to the Screening Visit or it is anticipated that the patient will have a change in psychotherapy, EMDR therapy, or in any other intervention during the trial.
9. Patients who meet the DSM-5 criteria for a current major depressive episode (ie, currently symptomatic).
10. Patients who have current or recent history (within 6 months prior to the Screening Visit) of an anxiety disorder that has been the primary focus of psychiatric treatment including: generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive, and other related disorders.
11. Patients who have a DSM-5 diagnosis of delirium, major neurocognitive, or other cognitive disorder; schizophrenia, schizoaffective disorder, or other psychotic disorder; bipolar I or II disorder, or bipolar disorder not otherwise specified; eating disorder (including anorexia nervosa or bulimia); or borderline or antisocial personality disorders, or intellectual disability.
12. Patients who have a current diagnosis or history of substance or alcohol use disorder (excluding nicotine) (DSM-5 criteria) 120 days prior to the Screening Visit.
13. Patients who have a positive urine drug screen that, in the judgment of the investigator with concurrence of the medical monitor, could compromise the patient’s safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results.
14. Patients who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method or other neurological disorders or systemic medical diseases where the traumatic brain

injury or neurological/systemic disorder is likely to affect assessment of efficacy or safety or directly impact patient safety, in the investigator's opinion.

15. Patients who have experienced a traumatic event within 3 months of Screening.

Medical History and Concurrent Diseases

16. Patients with a significant risk of committing suicide based on history, mental status examination, investigator's judgment, or C-SSRS answer of "yes" to question 4 or 5 (current or within the last 90 days).
17. Patients with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days prior to the Day 0 Visit).
18. Patients who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, cardiovascular, pulmonary, or gastrointestinal disorders such as ischemic heart disease, myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and aspartate transaminase [AST] or alanine aminotransferase (ALT) elevated to > 2 × upper limit of normal [ULN]), or bariatric surgeries that may cause malabsorption.

    Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the patient to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation. Patients who are severely obese, as confirmed by a corresponding high BMI (BMI ≥ 40 kg/m^2), need to be reviewed and discussed with the medical monitor.
19. Patients with insulin-dependent diabetes mellitus (IDDM) (ie, any patient using insulin) are excluded. Patients with non-IDDM may be eligible for the trial if their condition is stable as determined by satisfying ALL of the following criteria:

    - Glycosylated hemoglobin (HbA1c) < 7.0%, AND
    - Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (non-fasting). If the non-fasting Screening glucose is ≥ 200 mg/dL, patients must be retested in a fasted state and the retest value must be ≤ 125 mg/dL, AND
    - Patient has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to Screening or diabetes has been well-controlled by diet for at least 28 days prior to Screening, AND

- Patient has not had any hospitalizations within the 12 months prior to Screening due to diabetes or complications related to diabetes, AND
- Patient's diabetes is not newly diagnosed during Screening for the trial.

20. Patients with uncontrolled hypertension (diastolic blood pressure [DBP] > 95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in systolic blood pressure (SBP) and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms.

    NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a patient based on the criteria noted above.

21. Patients with epilepsy or a history of seizures, except for a single seizure episode; for instance childhood febrile seizure, post-traumatic, or alcohol withdrawal.

Physical and Laboratory Results

22. Patients with abnormal laboratory tests results, vital signs results, or ECG findings, unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the patient or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed.

    In addition, patients with the following laboratory test and ECG results at Screening must be excluded from the trial:

    - Platelets ≤ 75000/mm^3
    - Hemoglobin ≤ 9 g/dL
    - Neutrophils, absolute ≤ 1000/mm^3
    - AST > 2 × ULN
    - ALT > 2 × ULN
    - Creatine phosphokinase (CPK) > 3 × ULN, unless discussed with and approved by the medical monitor
    - Creatinine ≥ 2 mg/dL
    - QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing

    Tests with exclusionary results should be repeated to ensure reproducibility of the abnormality before excluding a patient based on the criteria noted

above. For ECG, perform 3 consecutive recordings. If 2 of the 3 remain exclusionary then the patient must be excluded.

Disallowed Recent and Concomitant Medication

23. Patients who would be likely to require prohibited concomitant therapy during the trial.
24. Patients who received brexpiprazole in any prior clinical trial or currently taking commercially available brexpiprazole (Rexulti®).

Allergies and Adverse Drug Reactions

25. Patients with a history of neuroleptic malignant syndrome or serotonin syndrome.
26. Patients with a history of true allergic response (ie, not intolerance) to more than 1 class of medications.

Other

27. Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
28. Patients who participated in a clinical trial within the last 60 days or who participated in more than 2 clinical trials within the past year.
29. Any patient who, in the opinion of the Sponsor, investigator, or medical monitor, should not participate in the trial.

10.1.3 Exclusion Criteria for Trials 071 and 072

1. Sexually active males or women of childbearing potential who do not agree to practice 2 different methods of birth control or remain abstinent during the trial and for 30 days after the last dose of trial drug. If employing birth control, 2 of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, birth control depot injection, condom with spermicide, or sponge with spermicide. Males who do not agree to abstain from sperm donation during the trial and for 30 days after the last dose of trial drug.
2. Females who are breast-feeding and/or who have a positive pregnancy test result prior to receiving trial drug.
3. Patients who are receiving disability payments because of PTSD or any other psychiatric disorder; unless the disability payments will not be impacted by potential improvements demonstrated in the trial, OR the patient is engaged in compensation litigation or other processes whereby personal gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorder.

4. The index traumatic event that led to development of PTSD took place > 9 years before Screening.
5. The index traumatic event occurred before age 16.
6. Patients who are currently experiencing trauma, have ongoing contact with their assailant/abuser, or have ongoing legal matters related to their assault/abuse.
7. Patients with PTSD who, in the investigator's opinion, are considered resistant/refractory to psychotropic treatment by history.
8. Patients who are currently receiving sertraline with adequate dose and duration (> 50 mg/day for a minimum of 8 weeks).
9. Patients who have had initiation of, or a change in, psychotherapy or any other intervention for the treatment of PTSD within 28 days prior to the Screening Visit or it is anticipated that the patient will have a change in psychotherapy or in any other intervention for PTSD (eg, equine therapy, yoga, mindfulness, etc) during the trial.
10. Patients who meet the DSM-5 criteria for a current major depressive episode (ie, currently symptomatic).
11. Patients who have current or recent history (within 6 months prior to the Screening Visit) of an anxiety disorder that has been the primary focus of psychiatric treatment including generalized anxiety disorder, social anxiety disorder, panic disorder, obsessive-compulsive, and other related disorders.
12. Patients who have a DSM-5 diagnosis of delirium, major neurocognitive, or other cognitive disorder; schizophrenia, schizoaffective disorder, or other psychotic disorder; bipolar I or II disorder, or bipolar disorder not otherwise specified; eating disorder (including anorexia nervosa or bulimia); or borderline or antisocial personality disorders, or intellectual disability.
13. Patients who have a current diagnosis or history of substance or alcohol use disorder (excluding nicotine) (DSM-5 criteria) 120 days prior to the Screening Visit.
14. Patients who have a positive urine drug screen that, in the judgment of the investigator with concurrence of the medical monitor, indicates substance abuse that could compromise the patient's safety or ability to comply with the trial procedures that could interfere with the interpretation of trial results.
15. Patients who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method or other neurological disorders or systemic medical diseases where the traumatic brain injury or neurological/systemic disorder is likely to affect assessment of efficacy or safety or directly impact patient safety, in the investigator's opinion.

16. Patients who have experienced a traumatic event within 3 months of Screening.
17. Patients with a significant risk of committing suicide based on history, mental status examination, investigator's judgment, or C-SSRS answer of "yes" to question 4 or 5 (current or within the last 90 days) or patients with any suicidal behavior during the last year prior to the Screening Visit.
18. Patients with hypothyroidism or hyperthyroidism (unless condition has been stabilized with medications for at least the past 90 days prior to the Day 0 Visit).
19. Patients who currently have clinically significant neurological, hepatic, renal, metabolic, hematological, immunological, gastrointestinal, pulmonary, or cardiovascular disorders such as ischemic heart disease, myocardial infarction, congestive heart failure (whether controlled or uncontrolled), angioplasty, stenting, or coronary artery bypass surgery, HIV seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C (defined as positive serology and AST or ALT elevated to > 2 × ULN), or bariatric surgeries that may cause malabsorption. Medical conditions that are minor or well-controlled may be considered acceptable if the condition does not expose the patient to an undue risk of a significant AE or interfere with assessments of safety or efficacy during the course of the trial. The medical monitor should be contacted in any instance where the investigator is uncertain regarding the stability of a patient's medical condition(s) and the potential impact of the condition(s) on trial participation. Patients who are severely obese, as confirmed by a corresponding high body mass index (BMI; ≥ 40 kg/m^2), need to be reviewed and discussed with the medical monitor.
20. Patients with diabetes mellitus (both insulin-dependent and non-insulin-dependent) may be eligible for the trial if their condition is stable and well-controlled as determined by satisfying ALL of the following criteria:

    a) Glycosylated hemoglobin (HbA1c) < 8.0%, AND

    b) Screening glucose must be ≤ 125 mg/dL (fasting) or < 200 mg/dL (non-fasting). If the non-fasting Screening glucose is ≥ 200 mg/dL, patients must be retested in a fasted state and the retest value must be ≤ 125 mg/dL,

    AND

    c) Patient has not had any hospitalizations within the 12 months prior to Screening due to diabetes or complications related to diabetes. Patients with non-IDDM (ie, any patients not using insulin) must also satisfy the below criterion:

    a) Patient has been maintained on a stable regimen of oral antidiabetic medication(s) for at least 28 days prior to Screening or diabetes has been well-controlled by diet for at least 28 days prior to Screening.

Patients with newly diagnosed diabetes during Screening are excluded.

21. Patients with uncontrolled hypertension (DBP > 95 mmHg in any position) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in SBP and/or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes standing compared to the previous supine blood pressure, OR development of symptoms.

    NOTE: Blood pressure measurements may be repeated once to ensure reproducibility of the exclusionary result(s) before excluding a patient based on the criteria noted above.

22. Patients with epilepsy or a history of seizures, except for a single seizure episode; for instance, childhood febrile seizure, a post-traumatic seizure episode, or an alcohol withdrawal seizure.

23. Patients with abnormal laboratory tests results, vital signs results, or ECG findings, unless, based on the investigator's judgment, the findings are not medically significant and would not impact the safety of the patient or the interpretation of the trial results. The medical monitor should be contacted to discuss individual cases, as needed. In addition, patients with any of the following laboratory test and ECG results at Screening must be excluded from the trial:

    a) Platelets ≤ 75000/mm^3

    b) Hemoglobin ≤ 9 g/dL

    c) Neutrophils, absolute ≤ 1000/mm^3

    d) AST > 2 × ULN

    e) ALT > 2 × ULN

    f) CPK > 3 × ULN, unless discussed with and approved by the medical monitor

    g) Creatinine ≥ 2 mg/dL

    h) QTcF ≥ 450 msec in men and ≥ 470 msec in women, unless due to ventricular pacing

    Tests with exclusionary results should be repeated once to ensure reproducibility of the abnormality before excluding a patient based on the criteria noted above. For ECG, perform 3 consecutive recordings. If 2 of the 3 remain exclusionary then the patient must be excluded.

24. Patients who would be likely to require prohibited concomitant therapy during the trial.

25. Patients who received brexpiprazole in any prior clinical trial or patients who have taken or are currently taking commercially available brexpiprazole (Rexulti®).

26. Patients with a history of neuroleptic malignant syndrome or serotonin syndrome.
27. Patients with a history of true allergic response (ie, not intolerance) to more than 1 class of medications.
28. Prisoners or patients who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled into this trial.
29. Patients who participated in a clinical trial within the last 60 days or who participated in more than 2 clinical trials within the past year.
30. Any patient who, in the opinion of the Sponsor, investigator, or medical monitor, should not participate in the trial.

10.2 Trial Schedule of Events

Table 43: Trial 061 Schedule of Efficacy Assessments

Assessment	Screening[a] (Day −14 to Day −3)	Week 1 Visit Day 0	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 2 days)	Week 8 Visit (± 2 days)	Week 10 Visit (± 2 days)	Week 12/ ET[b] Visit (± 2 days)	Post-treatment Follow-up[c] (+ 2 days)
CAPS-5[d]	X	X	X		X		X		X	X	
SOTS		X				X				X	
CGI-S		X	X	X	X	X	X	X	X	X	
PCL-5		X	X		X		X		X	X	
HADS		X	X		X		X		X	X	
Wearable device[e]		X	X	X	X	X	X	X	X	X	

CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression – Severity; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; ET = end of treatment; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; SOTS = Symptoms of Trauma Scale;

[a] Screening begins upon completion of the consent process. Although the screening period takes place between Day −14 and Day −3 prior to enrollment, patients will participate in Screening activities for a minimum of 3 days. It is requested to complete Screening as quickly as possible. In the event that a patient cannot be randomized prior to expiration of the 14-day screening period, additional 14-day extension(s) of Screening may be requested from the medical monitor. Any extension should be requested prior to the expiration of the previous extension or screening period, as applicable.

[b] If a patient discontinues early, every effort should be made to complete the "End of Week 12/ET" evaluations as soon as possible and whenever possible prior to starting any new medication or treatment.

[c] Telephone contact or clinic visit (investigator's discretion) for evaluation of safety.

[d] The CAPS-5 Past Month version will be completed for all patients at Screening to determine eligibility and the CAPS-5 Past Week version will be completed at the Baseline (Day 0) Visit to assure that the patient continues to qualify for the trial. The CAPS-5 Past Week version will also be completed at all visits after the Baseline (Day 0) Visit when the assessment is scheduled for collection.

[e] The wearable device will be put on the patient's nondominant wrist, whenever possible, at the Baseline (Day 0) Visit and worn daily until Week12/ET. The trial site will download Actigraphy data during each patient visit.

Table 44: Trials 071 and 072 Schedule of Efficacy Assessments

Assessment	Screening (Day −14 to Day −1)[a]	Day 0	Week 1 Visit (± 2 days)	Week 2 Visit (± 2 days)	Week 3 Visit (± 2 days)	Week 4 Visit (± 2 days)	Week 6 Visit (± 3 days)	Week 8 Visit (± 3 days)	Week 10 Visit (± 3 days)	Week 12/ ET Visit (± 3 days)	Post-treatment Follow-up (21 [+ 2] days)
CAPS-5	X	X	X		X	X	X		X	X	
CGI-S		X	X	X	X	X	X	X	X	X	
PCL-5[b]		X	X		X		X		X	X	
HADS[b]		X	X		X		X		X	X	
SF-36v2[b]		X						X		X	
B-IPF[b]		X						X		X	

B-IFP = Brief Inventory of Psychosocial Function; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI-S = Clinical Global Impression – Severity; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PCL-5 = PTSD Checklist for DSM-5; SF-36v2 = 36-item Short-Form Health Survey Version 2.

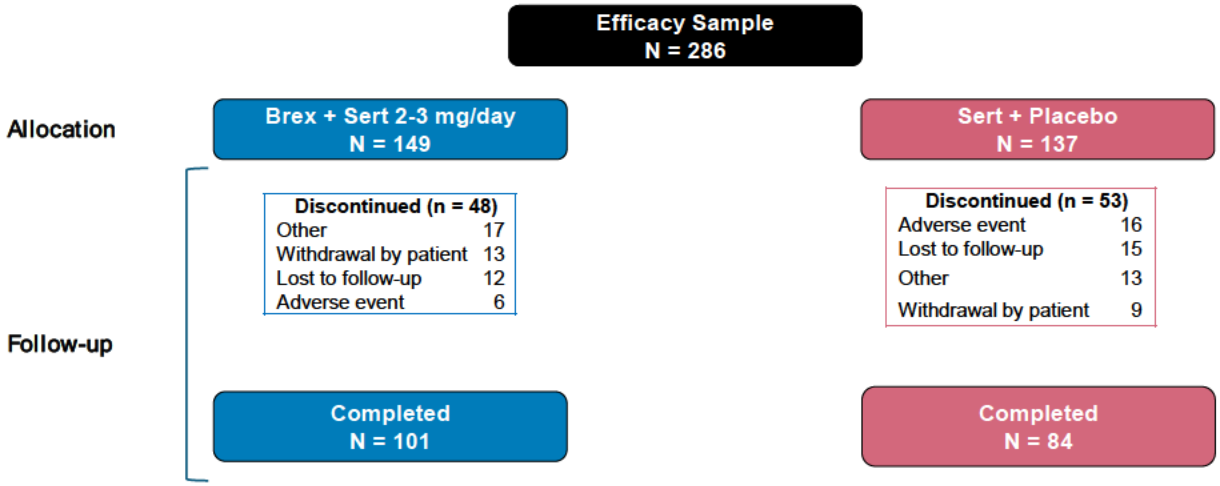
[a] Screening assessments may be completed over more than 1 day. In the event that a patient cannot be enrolled prior to expiration of the 14-day screening period, an additional 14-day extension of Screening may be requested from the medical monitor.

[b] Assessment completed directly by the patient using the 'patient-facing Engage app'.

10.3 Trial 071 Disposition and Patient Characteristics

10.3.1 Efficacy Sample Patient Disposition

Figure 32: Trial 071 Efficacy Sample Patient Disposition



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder; Sert = sertraline.
Note: "Other" in discontinuation box includes "other" plus all remaining discontinuation reasons not listed.
Prespecified Efficacy Sample: all randomized patients who took at least 1 dose of double-blind trial drug and have a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score PLUS: CAPS-5 Total Score of ≥ 27 at the randomization visit (Week 1), and an improvement in terms of reduction in CAPS-5 Total Score of less than 50% at end of the placebo run-in period (Phase A) to exclude patients who responded to placebo during the placebo run-in phase.

10.3.2 Efficacy Sample Patient Demographic Characteristics and Disease History

Table 45: Trial 071 Key Demographic Characteristics (Efficacy Sample)

Parameter	Brex 2-3 mg + Sert N = 149	Sert + Placebo N = 137
Age (years)		
Mean (SD)	38.7 (11.9)	37.4 (12.7)
Median (min, max)	37.0 (19, 65)	35.0 (18, 65)
Age Group, n (%)		
< 55	132 (88.6)	119 (86.9)
≥ 55	17 (11.4)	18 (13.1)
Sex, n (%)		
Male	38 (25.5)	26 (19.0)
Female	111 (74.5)	111 (81.0)
Race, n (%)		
White	108 (72.5)	97 (70.8)
Black or African American	30 (20.1)	24 (17.5)
American Indian or Alaska Native	6 (4.0)	2 (1.5)
Asian	3 (2.0)	7 (5.1)
Native Hawaiian or Other Pacific Islander	1 (0.7)	0 (0.0)
Other	1 (0.7)	7 (5.1)
Ethnicity, n (%)		
Not Hispanic or Latino	130 (87.2)	115 (83.9)
Hispanic or Latino	17 (11.4)	20 (14.6)
Unknown	0 (0.0)	1 (0.7)
Other	2 (1.3)	1 (0.7)
BMI (kg/m^2)		
Mean (SD)	30.5 (6.7)	29.7 (7.0)
Median (min, max)	30.1 (18.2, 48.9)	28.9 (18.3, 50.2)

BMI = body mass index; Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

Table 46: Trial 071 Post-Traumatic Stress Disorder Disease History (Efficacy Sample)

Parameter	Brex 2-3 mg + Sert N = 149	Sert + Placebo N = 137
Years Since Trauma		
Mean (SD)	4.3 (2.5)	4.0 (2.4)
Median (min, max)	4.1 (0.5, 9.5)	3.8 (0.5, 9.0)
Age at Index Trauma, years		
Mean (SD)	34.5 (12.2)	33.5 (12.6)
Median (min, max)	33.0 (15, 59)	31.0 (16, 62)
No Previous Medication Treatment, n (%)	103 (69.1)	102 (74.5)
No Previous Psychotherapy, n (%)	90 (60.4)	97 (70.8)
Trauma Type, n (%)		
Assault (With or Without Weapon)	49 (32.9)	60 (43.8)
Captivity	0 (0.0)	1 (0.7)
Combat or Exposure to War-Zone	4 (2.7)	3 (2.2)
Exposure To Sudden Death	19 (12.8)	10 (7.3)
Life-Threatening Illness or Injury	7 (4.7)	4 (2.9)
Motor Vehicle or Other Transportation Accident	13 (8.7)	17 (12.4)
Natural Disaster, Fire, or Explosion	4 (2.7)	4 (2.9)
Serious Harm or Death for Which You Are Responsible	1 (0.7)	0 (0.0)
Serious Non-Transportation Accident	1 (0.7)	1 (0.7)
Sexual Trauma	40 (26.8)	29 (21.2)
Other	11 (7.4)	8 (5.8)

Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

10.3.3 Full Analysis Set Baseline Efficacy Scale Scores

Table 47: Trial 071 Summary of Baseline Efficacy Scale Scores (Full Analysis Set)

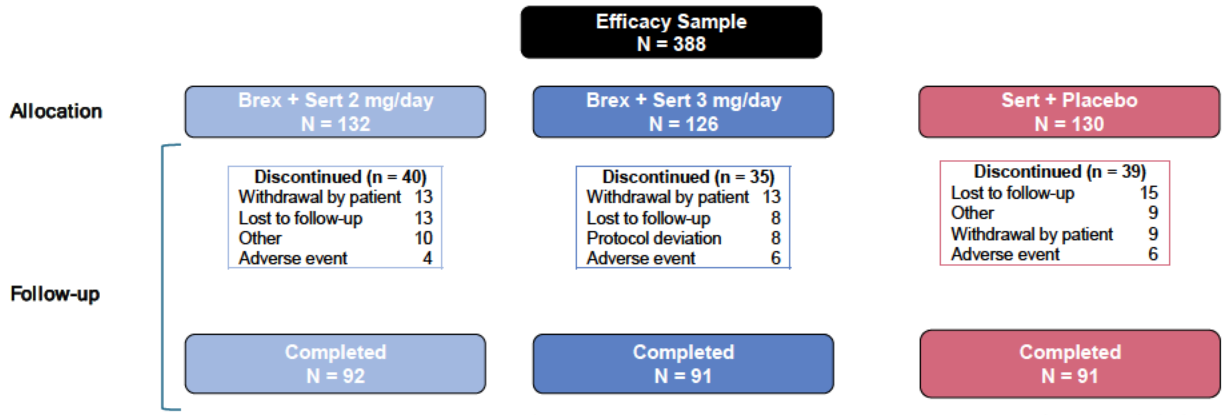
Scale	Brex 2-3 mg + Sert N = 196	Sert + Placebo N = 184
CAPS-5 Total Severity Score		
Mean (SD)	33.8 (10.6)	33.8 (11.4)
Min, Max	6, 61	5, 65
CAPS-5 Subscale Intrusion Score		
Mean (SD)	8.1 (3.7)	8.1 (3.8)
Min, Max	0, 17	0, 19.0
CAPS-5 Subscale Avoidance Score		
Mean (SD)	4.1 (1.8)	4.2 (1.9)
Min, Max	0, 7	0, 8
CAPS-5 Subscale Cognitions and Mood Score		
Mean (SD)	12.5 (5.1)	12.7 (5.3)
Min, Max	0, 26	0, 26
CAPS-5 Subscale Arousal and Reactivity Score		
Mean (SD)	9.1 (3.4)	8.8 (3.5)
Min, Max	2, 18	0, 16
CGI-Severity of Illness Score		
Mean (SD)	4.3 (0.8)	4.4 (0.8)
Min, Max	2, 6	2, 6
HADS-Anxiety Score		
Mean (SD)	13.2 (3.9)	13.3 (3.5)
Min, Max	3, 21	3, 21
HADS-Depression Score		
Mean (SD)	10.1 (4.0)	9.9 (4.2)
Min, Max	0, 20	0, 21
PCL-5 Total Score		
Mean (SD)	42.8 (14.9)	43.2 (15.7)
Min, Max	6, 74	8, 76

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CGI = clinical global impressions; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; Flex = flexible; HADS = Hospital Anxiety and Depression Scale; PCL-5 = PTSD Checklist for DSM-5; SD = standard deviation; PTSD = post-traumatic stress disorder; Sert = sertraline.

10.4 Trial 072 Disposition and Patient Characteristics Efficacy Sample

10.4.1 Efficacy Sample Patient Disposition

Figure 33: Trial 072 Efficacy Sample Patient Disposition



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; PTSD = post-traumatic stress disorder; Sert = sertraline.
Note: "Other" in discontinuation box includes "other" and all remaining discontinuation reasons.
Prespecified Efficacy Sample: all randomized patients who took at least 1 dose of double-blind trial drug and have a Baseline value and at least 1 post-Baseline evaluation for the CAPS-5 Total Score PLUS: CAPS-5 Total Score of ≥ 27 at the randomization visit (Week 1), and an improvement in terms of reduction in CAPS-5 Total Score of less than 50% at end of the placebo run-in period (Phase A) to exclude patients who responded to placebo during the placebo run-in phase.

10.4.2 Efficacy Sample Patient Demographic Characteristics and Disease History

Table 48: Trial 072 Key Demographic Characteristics (Efficacy Sample)

Parameter	Brex 2 mg + Sert N = 132	Brex 3 mg + Sert N = 126	Sert + Placebo N = 130
Age (years)			
Mean (SD)	37.7 (12.4)	35.8 (11.6)	37.9 (12.9)
Median (min, max)	36.5 (18, 65)	32.5 (18, 61)	35.5 (18, 65)
Age Group, n (%)			
< 55	117 (88.6)	115 (91.3)	111 (85.4)
≥ 55	15 (11.4)	11 (8.7)	19 (14.6)
Sex, n (%)			
Female	99 (75.0)	97 (77.0)	94 (72.3)
Male	33 (25.0)	29 (23.0)	36 (27.7)
Race, n (%)			
White	96 (72.7)	84 (66.7)	95 (73.1)
Black or African American	25 (18.9)	29 (23.0)	28 (21.5)
Asian	5 (3.8)	6 (4.8)	4 (3.1)
American Indian or Alaska Native	1 (0.8)	1 (0.8)	1 (0.8)
Native Hawaiian or Other Pacific Islander	2 (1.5)	1 (0.8)	0 (0.0)
Other	3 (2.3)	5 (4.0)	2 (1.5)
Ethnicity, n (%)			
Not Hispanic or Latino	97 (73.5)	95 (75.4)	102 (78.5)
Hispanic or Latino	35 (26.5)	29 (23.0)	28 (21.5)
Unknown	0 (0.0)	1 (0.8)	0 (0.0)
Other	0 (0.0)	1 (0.8)	0 (0.0)
BMI (kg/m^2)			
Mean (SD)	29.0 (6.6)	29.3 (6.8)	28.8 (6.2)
Median (min, max)	27.9 (17.4, 53.1)	28.5 (16.3, 48.1)	27.9 (18.2, 46.8)

BMI = body mass index; Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

Table 49: Trial 072 Post-Traumatic Stress Disorder Disease History (Efficacy Sample)

Parameter	Brex 2 mg + Sert N = 132	Brex 3 mg + Sert N = 126	Sert + Placebo N = 130
Years Since Trauma			
Mean (SD)	4.1 (2.6)	4.0 (2.4)	3.9 (2.2)
Median (min, max)	3.8 (0.5, 9.0)	3.5 (0.5, 9.0)	3.7 (0.6, 8.9)
Age at Index Trauma, years			
Mean (SD)	33.6 (12.4)	31.8 (11.6)	34.1 (12.6)
Median (min, max)	33.0 (16, 64)	29.0 (17, 59)	31.5 (16, 64)
No Previous Medication Treatment, n (%)	104 (78.8)	103 (81.7)	104 (80.0)
No Previous Psychotherapy, n (%)	94 (71.2)	86 (68.3)	92 (70.8)
Trauma Type			
Assault (With or Without Weapon)	46 (34.8)	42 (33.3)	53 (40.8)
Captivity	4 (3.0)	0 (0.0)	1 (0.8)
Combat or Exposure to War-Zone	2 (1.5)	1 (0.8)	1 (0.8)
Exposure to Sudden Death	22 (16.7)	28 (22.2)	17 (13.1)
Exposure to Toxic Substance	0 (0.0)	0 (0.0)	1 (0.8)
Life-Threatening Illness or Injury	8 (6.1)	3 (2.4)	6 (4.6)
Motor Vehicle or Other Transportation Accident	17 (12.9)	12 (9.5)	14 (10.8)
Natural Disaster, Fire, or Explosion	1 (0.8)	1 (0.8)	5 (3.8)
Serious Non-Transportation Accident	2 (1.5)	1 (0.8)	0 (0.0)
Sexual Trauma	24 (18.2)	29 (23.0)	24 (18.5)
Other	6 (4.5)	9 (7.1)	8 (6.2)

Brex = brexpiprazole; SD = standard deviation; Sert = sertraline.

10.5 Additional Efficacy Results

10.5.1 Prespecified Sensitivity Analyses

10.5.1.1 Sensitivity Analysis Methodology Across Trials

In addition to the Delta Adjustment analyses described in Section 6, Table 50 summarizes the prespecified sensitivity analyses planned for each of the 12-week trials to evaluate the robustness to missing data handling for the primary endpoint of

CAPS-5 Total Score change from Baseline at Week 10. However, given the result of Trial 072, the sensitivity analyses are not provided.

Table 50: Prespecified Sensitivity Analyses Across Trials

Methods	Description
Delta Adjustment Analysis (Tipping Point)	Multiple imputation based on MAR is applied to all missing values first. Then penalty is systematically added to the imputed values of the combination treatment group after patients discontinue, due to reasons listed below, to determine the point at which the treatment no longer shows a significant treatment difference ($p > 0.05$). • due to AE or Lack of Efficacy • due to AE or Lack of Efficacy or withdrew consent • due to Any reasons
Control-based (Sertraline) Imputation	Imputation of missing data in the treatment group is based on the control group's distribution. Two imputation methods were used: • Monotone multiple imputation: Imputes variables sequentially, from the variable with the least missing data to the most. • Markov Chain Monte Carlo: Imputes all missing data of a given patient simultaneously.
Model-Based Approach	The Model-based approach using the below methods were conducted: • Shared Parameter (Wu-Bailey): Jointly models the longitudinal outcome and dropout process, assuming they share common random effects. • Pattern Mixture Model: Stratifies data based on missing data patterns and estimates separate models for each pattern. • Random Coefficient Model: Uses individual-specific regression coefficients to model longitudinal data, allowing for heterogeneity in trajectories across patients.

AE = adverse event; MAR = missing at random.

10.5.1.2 Trial 061 Sensitivity Analysis Results

The sensitivity analysis results for Trial 61 generally demonstrated consistency with the primary efficacy results of brexpiprazole plus sertraline versus sertraline plus placebo across various missingness assumptions (Table 51).

Table 51: Trial 061 Additional Prespecified Sensitivity Analyses Results for CAPS-5 Total Score

Analysis		LSMD Brex + Sert vs Sert + Placebo (95% CI) p-value
Control-based (sertraline) Imputation	MCMC imputation	−4.36 (−8.10, −0.62) p = 0.0223
	Monotone based imputation	−4.59 (−8.40, −0.778) p = 0.0183
Model-Based Imputation	Shared Parameter Model	−2.09 (−4.15, −0.03) p = 0.0465
	Pattern Mixture Model	−2.30 (−4.84, 0.23) p = 0.0747
	Random Coefficient Model	−1.89 (−4.10, 0.32) p = 0.0939

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LSMD = least squares mean difference; PTSD = post-traumatic stress disorder; Sert = sertraline.

10.5.1.3 Trial 071 Sensitivity Analysis Results

The sensitivity analysis results for Trial 071 demonstrated the robustness of the primary efficacy results of brexpiprazole plus sertraline versus sertraline plus placebo across various missingness assumptions (Table 52).

Table 52: Trial 071 Additional Prespecified Sensitivity Analyses Results for CAPS-5 Total Score

Analysis		LSMD Brex + Sert vs Sert + Placebo (95% CI) p-value
Control-based (sertraline) Imputation	MCMC imputation	−4.32 (−7.36, −1.28) p = 0.0053
	Monotone based imputation	−4.47 (−7.72, −1.22) p = 0.0071
Model-Based Imputation	Shared Parameter Model	−4.23 (−6.87, −1.59) p = 0.0017
	Pattern Mixture Model	−4.98 (−7.84, −2.13) p = 0.0006
	Random Coefficient Model	−4.32 (−6.87, −1.78) p = 0.0009

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LSMD = least squares mean difference; MCMC = Markov chain Monte Carlo; PTSD = post-traumatic stress disorder; Sert = sertraline.

10.5.2 Trial 061 Retrospective Multiplicity Adjustment

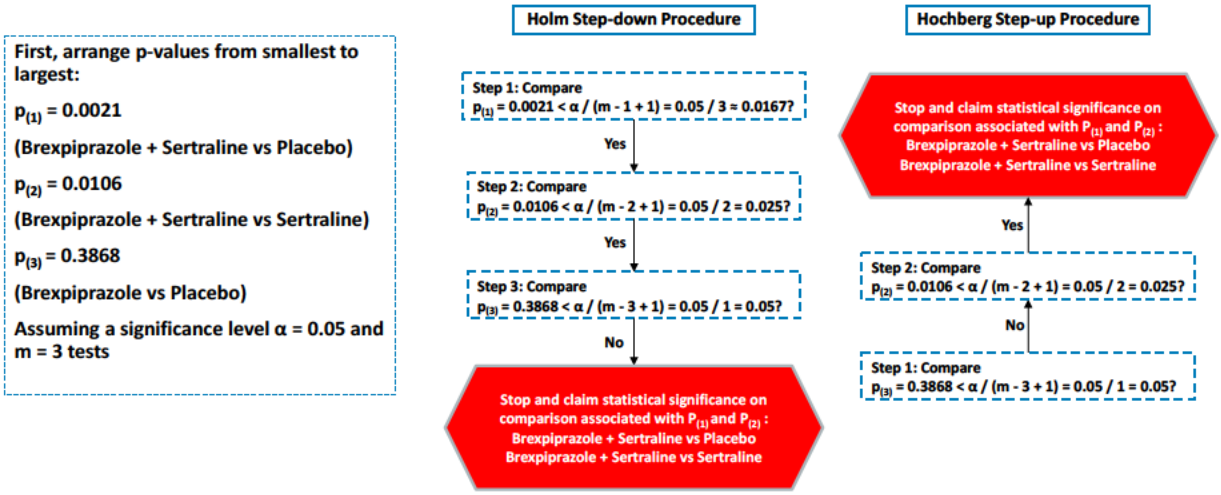
Three methods (Bonferroni adjustment, Holm step-down, and Hochberg step-up procedures) were applied retrospectively to evaluate the robustness of the statistical significance of the pairwise comparisons associated with the primary objective when controlling for study-wise type 1 error. The 3 pairwise comparisons related to the primary objective of evaluating the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adults with PTSD are as follows:

- Brexpiprazole plus sertraline versus placebo
- Brexpiprazole plus sertraline versus sertraline
- Brexpiprazole versus placebo (as monotherapy treatment)

The Bonferroni adjustment compared each comparison with 2-sided alpha of 0.0167, given the alpha value of 0.05 and there are 3 comparisons (0.05/3 = 0.0167).

Figure 34 shows details of the Holm step-down and Hochberg step-up procedures and that the alpha=0.025 is the resulting threshold used in both methods for the 2 pairwise comparisons involving the brexpiprazole plus sertraline treatment group.

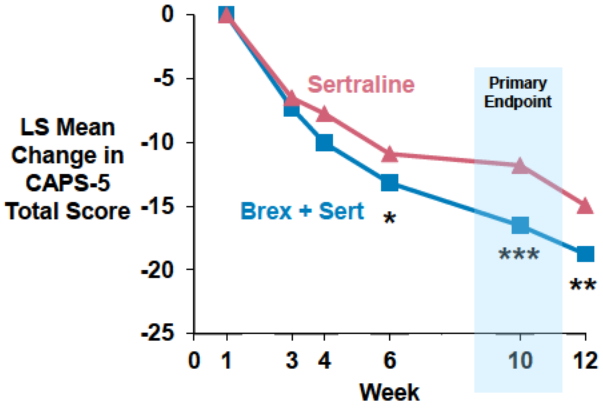
Figure 34: Trial 061 Flowchart for Holm and Hochberg Procedures



Source: (Hochberg 1988; Holm 1979)

10.5.3 Trials 071 and 072 Primary Efficacy Endpoint Results in Full Analysis Set

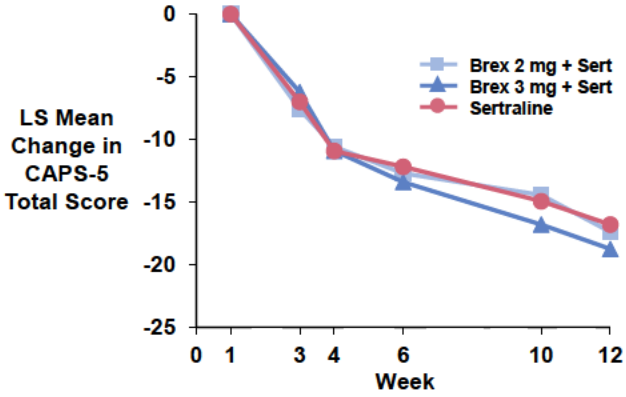
Figure 35: Trial 071 Change from Baseline in CAPS-5 by Visit (FAS)



	Brexpiprazole + Sertraline	Sertraline
CAPS-5 Total score at Week 1, Mean (SD)	**33.81** (10.59)	**33.59** (11.31)
Mean Change in CAPS-5 Total score at Week 10, LS Mean (SE)	**-16.52** (0.98)	**-11.80** (1.03)
Treatment Difference at Week 10 (95% CI)	**-4.72 (-7.39, -2.05)**	
p-value	**0.0006**	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; FAS = full analysis set; LS = least squares; SD = standard deviation; SE = standard error; Sert = sertraline.
*Nominal p <0.05, ** Nominal p <0.01, ***p <0.001.
Baseline CAPS-5 Brex + Sert = 33.8, n = 195; Sertraline = 33.6, n = 181.
The FAS comprises 380 patients, 376 were included in the efficacy analysis since 4 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.

Figure 36: Trial 072 Change from Baseline in CAPS-5 by Visit (FAS)

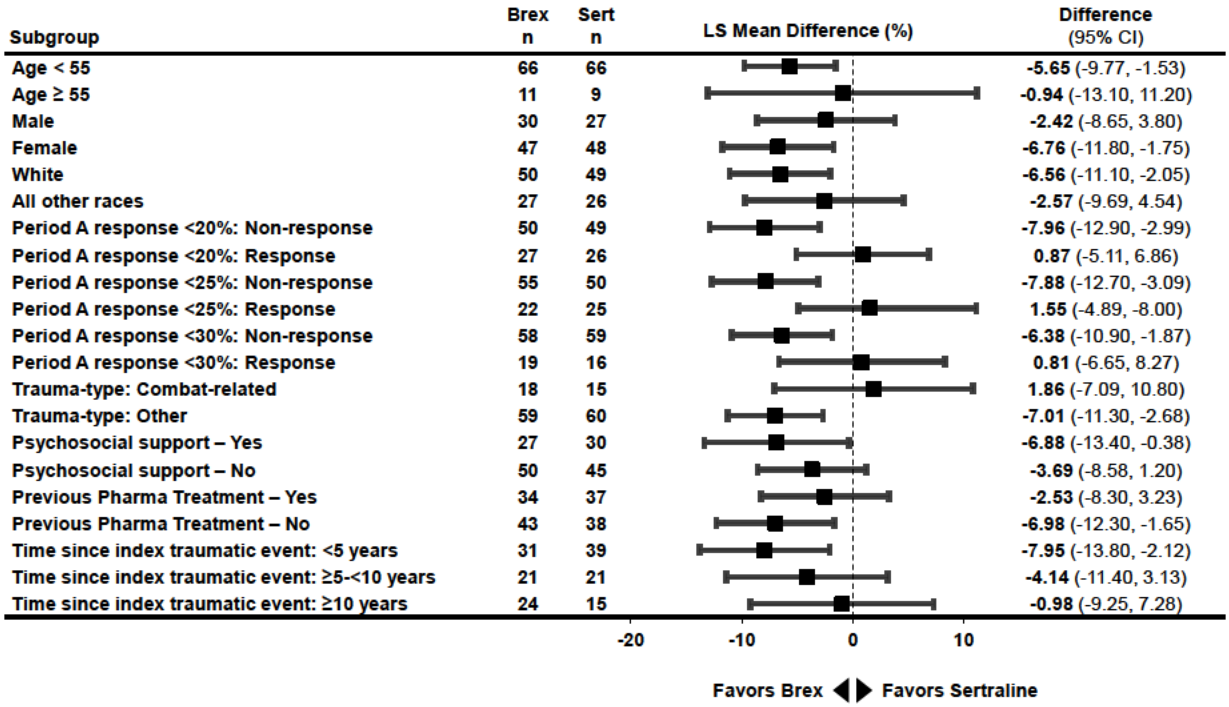


	Brex 2 mg + Sert	Brex 3 mg + Sert	Sertraline
CAPS-5 Total Score at Week 1, Mean (SD)	**33.32** (12.36)	**33.20** (10.82)	**34.93** (11.27)
Mean Change in CAPS-5 Total Score at Week 10, LS Mean (SE)	**-14.44** (1.00)	**-16.79** (1.03)	**-14.93** (1.03)
Treatment Difference at Week 10 (95% CI)	**0.49 (-2.16, 3.15) p = 0.7150**	**-1.85 (-4.55, 0.84) p = 0.1768**	

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; FAS = Full Analysis Set; LS = least squares; PTSD = post-traumatic stress disorder; SD =standard deviation; SE = standard error; Sert = sertraline.
Baseline CAPS-5 Brex 2 mg + Sert = 33.3, n = 177; Brex 3 mg + Sert = 33.2, n = 164 Sertraline = 34.9, n = 165.
The Full Analysis Set comprises 509 patients, 506 were included in the efficacy analysis since 3 patients who discontinued did not have a post-Baseline CAPS-5 value within the permitted visit window.

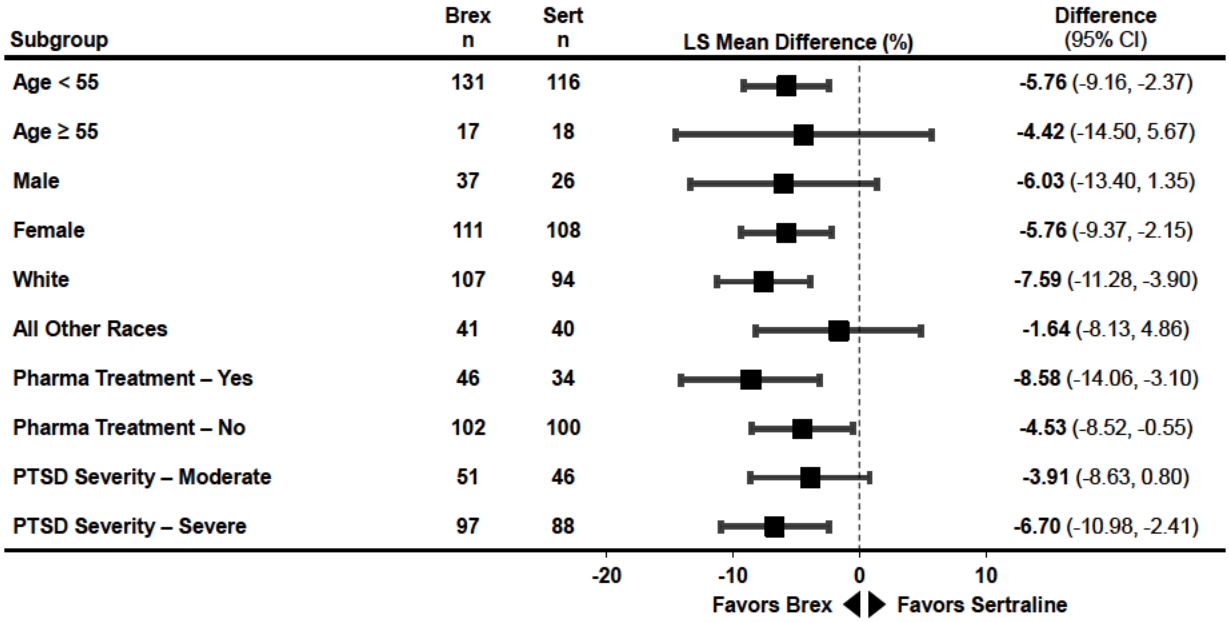
10.5.4 CAPS-5 Subgroup Analysis Results by Individual Trial

Figure 37: Trial 061 Change in CAPS-5 Total Score from Baseline to Week 10 by Subgroup for Brexpiprazole Plus Sertraline vs Sertraline Plus Placebo (Efficacy Sample)



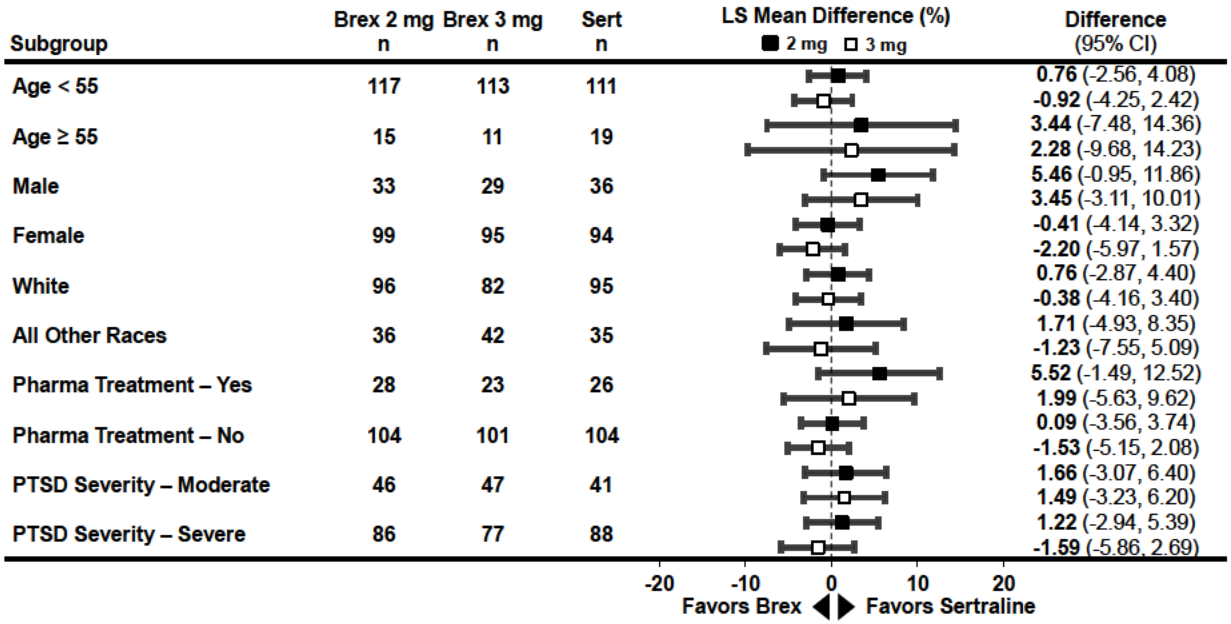
Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.

Figure 38: Trial 071 Forest Plot: Mean Change from Baseline to Week 10 in CAPS-5 Total Score for All Subgroup Analyses (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.

Figure 39: Trial 072 Forest Plot: Mean Change from Baseline to Week 10 in CAPS-5 Total Score for All Subgroup Analyses (Efficacy Sample)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.

10.5.5 Pooled Efficacy Analyses

Trials were pooled to assess the overall treatment effect in larger populations as the trials had similar designs, endpoints, dosing and patient populations. Results for the pooled analyses on the change from Baseline in CAPS-5 are presented below.

When combining the two Phase 3 trials (071 and 072), treatment with brexpiprazole plus sertraline showed a reduction of −18.30-point in the clinician-administered CAPS-5 Total Score from Baseline to Week 10. Brexpiprazole plus sertraline still separated on the mean change CAPS-5 Total Score (LS mean difference = −2.73 [95% CI: −4.81, −0.65]; p = 0.0101) from sertraline plus placebo, when the data from the negative Trial 072 were pooled with the positive Trial 071.

When pooling the data across the 3 trials 061, 071 and 072, brexpiprazole in combination with sertraline demonstrated greater improvement from Baseline to Week 10 (LS mean difference = −3.49 [95% CI: −5.43, −1.55]; p = 0.0004) versus sertraline on the primary endpoint. The result of this pooled analysis shows that the treatment effect of brexpiprazole plus sertraline from Baseline to Week 10 compared to sertraline plus placebo was robust.

The therapeutic benefit of combination treatment over sertraline plus placebo was demonstrated in the pooled Phase 3 (Trials 071 and 072) and when all 3 trials were pooled (Trials 061, 071, and 072).

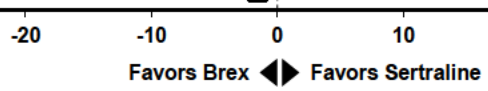
Table 53: Primary Efficacy Measure: Mean Change from Baseline to Week 10 in Clinician-Administered PTSD Scale for CAPS-5 (DSM-5) Total Score - Efficacy Sample in Individual and Pooled Trials

		Baseline	Change from Baseline	Treatment Difference Versus Placebo	
Pool Treatment Group	N	Mean (SD)	LS Mean (SE)	LSMD[a] (95% CI[a])	p-value[a]
Pooled Phase 3 (071+072)					
Brex+Sert	404	38.35 (7.60)	−18.30 (0.73)	−2.73 (−4.81, −0.65)	0.0101
Sert+Placebo	264	38.98 (7.74)	−15.57 (0.86)	-	-
Pooled All (071+061+072)					
Brex+Sert	481	37.93 (8.39)	−17.82 (0.68)	−3.49 (−5.43, −1.55)	0.0004
Sert+Placebo	339	38.44 (8.40)	−14.33 (0.75)	-	-

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; CI = confidence interval; Flex = flexible-dose (brexpiprazole 1-3 mg/day); MMRM = Mixed Model Repeated Measurements; PTSD = post-traumatic stress disorder; LS = least squares; LSMD = least squares mean difference; SD = standard deviation; SE = standard error; Sert = sertraline.
Note: Covariate is trauma type for Trial 061. Covariate is previous PTSD medication (yes/no) for Trials 071, 072, and the Pooled Phase 3. For Pooled Flex and all, covariate is not used in model. Also, 3-way interaction trial by visit by treatment is added to all pooled models.
[a] MMRM method with treatment as a model terms: treatment visit, treatment by visit, covariate, trial site and Baseline by visit interaction.
[b] Difference between active and sertraline plus placebo along with corresponding 95% CI and p-value.
[c] Difference between Brex+Sert and Sert/Brex along with corresponding 95% CI and p-value.

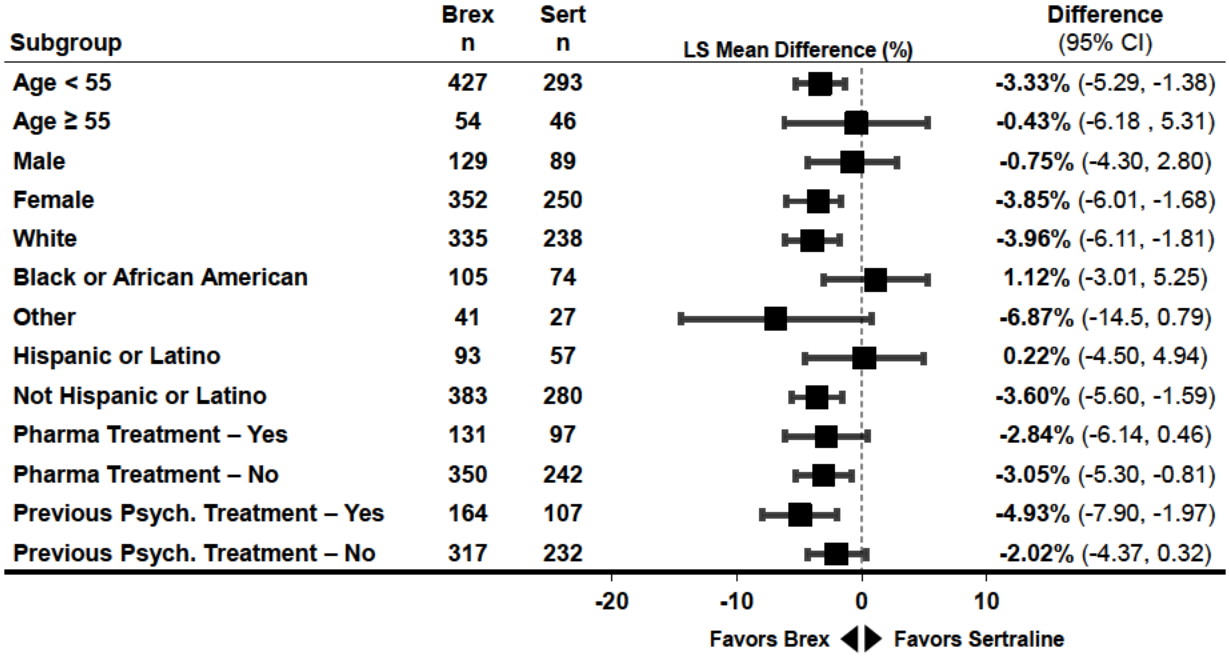
Figure 40: Forest Plot: Mean Change from Baseline to Week 10 in CAPS-5 Total Score for All Subgroup Analyses - Efficacy Sample for Pooled Phase 3 Trials

Subgroup	Brex n	Sert n	Difference (95% CI)
Age < 55	361	227	**-2.66%** (-4.86, -0.47)
Age ≥ 55	43	37	**-0.54%** (-7.32, 6.24)
Male	99	62	**0.05%** (-4.29, 4.40)
Female	305	202	**-3.31%** (-5.70, -0.91)
White	285	189	**-3.25%** (-5.68, -0.83)
Black or African American	84	52	**0.86%** (-3.95, 5.66)
Other	35	23	**-4.34%** (-13.0, 4.30)
Hispanic or Latino	80	48	**2.00%** (-3.15, 7.16)
Not Hispanic or Latino	320	214	**-3.36%** (-5.65, -1.07)
Pharma Treatment – Yes	97	60	**-2.89%** (-7.08, 1.30)
Pharma Treatment – No	307	204	**-2.31%** (-4.75, 0.13)
Previous Psych. Treatment – Yes	137	77	**-4.16%** (-7.55, -0.76)
Previous Psych. Treatment – No	267	187	**-1.57%** (-4.22, 1.07)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.

Figure 41: Forest Plot: Mean Change from Baseline to Week 10 in CAPS-5 Total Score for All Subgroup Analyses (Efficacy Sample for All Pooled Trials)



Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; CI = confidence interval; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; PTSD = post-traumatic stress disorder; Sert = sertraline.

10.5.6 Exploratory Endpoints

10.5.6.1 Exploratory Endpoint Definitions

Symptoms of Trauma Scale

The SOTS is a 12-item 7-point symptom severity rating scale designed to measure change. Ratings for each of the 12 symptoms can range from 1 = Absent to 7 = Extreme. Because the SOTS provides a means of rating of symptoms at 7 levels of severity (absent, minimal, mild, moderate, moderate severe, severe, and extreme), it can assess changes in trauma symptoms, which will become increasingly important as new interventions, both psychosocial and pharmacological, emerge. Ratings are based upon information obtained from a structured clinical interview, using both behavior observed during the 20 to 30 minute interview as well as the patient's report regarding functioning for the past week.

36-item Short-Form Health Survey Version 2

The SF-36v2 is a patient-reported questionnaire with a standard recall period of 4 weeks which measures generic health-related quality of life on 2 broad domains, physical and mental composites, across 8 health domain scales: physical functioning,

pain, role physical, general health, vitality/fatigue, social functioning, role emotional, and mental health. The SF-36v2 uses norm-based scoring established in 2009 to generate scores on a scale of 0 to 100 where lower scores on the physical component summary and mental component summary represent a lower health-related quality of life and a score of 50 references the normal US population. In addition to the composite scores and the individual health domain scores, the SF-36v2 provides a risk for depression score and the SF-36v2 health utility index on a scale from 0.0 (worst measured health state) to 1.0 (best measured health state).

10.5.6.2 Trial 061 Symptoms of Trauma Scale Total

Table 54: Trial 061 Other Efficacy Endpoints: Summary of SOTS Total Score Mean Change from Baseline (Day 0) to Week 12 (Efficacy Sample)

	Change from Baseline (Day 0)						
Treatment Group	N	LS Mean[a] (SE[a])	Mean (SD)	Min	Max	Difference[a] (95% CI)	p-value[a]
Brex + Sert[b]	57	−15.2 (1.22)	−15.3 (12.23)	−47.0	26.00	−2.36 (−5.56, 0.84)	0.1481
Brex + Sert vs Sert[c]	-	-	-	-	-	−1.15 (−4.42, 2.11)	0.4872
Brex + Sert vs Brex[c]	-	-	-	-	-	−2.46 (−5.86, 0.94)	0.1561
Brex[b]	47	−12.7 (1.36)	−12.8 (10.34)	−42.0	9.00	0.10 (−3.26, 3.46)	0.9554
Sertraline[b]	56	−14.0 (1.25)	−14.4 (10.54)	−37.0	5.00	−1.21 (−4.44, 2.02)	0.4624
Placebo	60	−12.8 (1.20)	−12.0 (11.52)	−50.0	17.00	-	-

Brex = brexpiprazole; CI = confidence interval; LS = least squares; SD = standard deviation; SE = standard error; Sert = sertraline; SOTS = Symptoms of Trauma Scale.

[a.] Mixed model repeated measures method with model terms: treatment, (pooled) trial site, type of trauma, visit, and treatment by visit and Baseline by visit interaction.

[b.] Difference between active and placebo along with corresponding 95% CI and p-value for other than Baseline visits.

[c.] Difference between Brex + Sertraline and Sertraline/Brex along with corresponding 95% CI and p-value for other than Baseline visits.

10.5.6.3 Trial 071 Exploratory Endpoints

Table 55: Trial 071 Summary of Patient-Reported Health-Related Quality of Life Exploratory Efficacy Results (Efficacy Sample)

Endpoint	Treatment Group	N	Mean (SD) Score at Baseline (Day 0)	LS Mean (SE) Change from Baseline to Week 12	Treatment Difference at Week 12	
					LS Mean (95% CI)	p-value
SF-36v2 Physical component[a]	Brex + Sert	103	52.8 (11.3)	−2.0 (0.8)	−0.56 (−2.49, 1.38)	0.57
	Sert + Placebo	94	50.3 (11.7)	−1.5 (0.8)		
Physical functioning	Brex + Sert	103	48.1 (10.5)	0.8 (0.7)	0.25 (−1.62, 2.12)	0.79
	Sert + Placebo	94	46.4 (11.2)	0.6 (0.8)		
Role physical	Brex + Sert	103	45.9 (11.2)	1.7 (0.9)	0.27 (−2.10, 2.64)	0.82
	Sert + Placebo	94	44.5 (10.8)	1.4 (1.0)		
Pain	Brex + Sert	103	45.8 (11.3)	2.6 (0.9)	1.68 (−0.76, 4.11)	0.18
	Sert + Placebo	94	41.7 (10.5)	0.9 (1.0)		
General health	Brex + Sert	103	46.0 (10.2)	4.1 (0.9)	2.73 (0.62, 4.84)	0.01
	Sert + Placebo	94	45.2 (10.5)	1.4 (0.9)		
SF-36v2 Mental component[a]	Brex + Sert	103	25.6 (9.9)	15.4 (1.4)	5.33 (1.73, 8.94)	0.004
	Sert + Placebo	94	25.9 (9.7)	10.1 (1.5)		
Vitality/fatigue	Brex + Sert	103	35.2 (8.1)	8.4 (1.2)	2.87 (−0.09, 5.82)	0.06
	Sert + Placebo	94	34.7 (7.9)	5.5 (1.2)		
Social functioning	Brex + Sert	103	30.6 (9.0)	12.2 (1.2)	3.50 (0.46, 6.54)	0.02
	Sert + Placebo	94	30.6 (9.4)	8.7 (1.3)		
Role emotional	Brex + Sert	103	31.8 (10.1)	10.7 (1.2)	4.59 (1.40, 7.78)	0.005
	Sert + Placebo	94	31.1 (9.5)	6.1 (1.3)		
Mental health	Brex + Sert	103	31.1 (9.1)	13.0 (1.3)	4.83 (1.57, 8.10)	0.004
	Sert + Placebo	94	30.6 (8.6)	8.1 (1.4)		
SF-6D health utility index[b]	Brex + Sert	102	0.57 (0.09)	0.09 (0.01)	0.05 (0.01, 0.08)	0.004
	Sert + Placebo	93	0.56 (0.08)	0.04 (0.01)		

Brex = brexpiprazole; SF-36v2 = 36-item Short-Form Health Survey version 2; SF-6D = Short-Form Six-Dimension; Sert = sertraline.

Mixed model for repeated measures; n-values are for patients with measurements at Baseline (Day 0) for SF-36, or randomization (Week 1) otherwise.
a. SF-36v2 uses norm-based scoring that ranges from 0 (worst health state) to 100 (best health state), where 50 references the normal US population (Ware 2000).
b. SF-6D health utility index ranges from 0 (worst health state) to 1 (best health state) (Brazier et al 2002).

Table 56: Trial 071 Summary of Sleep-Specific Exploratory Efficacy Results (Efficacy Sample)

Endpoint	Treatment Group	N	Mean (SD) Score at Baseline	LS mean (SE) change from Baseline to Week 12	Treatment Difference at Week 12		
					LS Mean (95% CI)	p-value	Cohen's d
CAPS-5 item B2 'Distressing dreams severity'[a]	Brex + Sert	148	1.6 (1.4)	−0.7 (0.1)	−0.19 (−0.54, 0.16)	0.29	0.13
	Sert + Placebo	134	1.5 (1.4)	−0.5 (0.1)			
CAPS-5 item E6 'Sleep disturbance severity'[a]	Brex + Sert	148	2.6 (0.9)	−0.9 (0.1)	−0.34 (−0.70, 0.02)	0.06	0.22
	Sert + Placebo	134	2.7 (0.9)	−0.6 (0.1)			
PCL-5 item 2 'Repeated, disturbing dreams of the stressful experience'[b]	Brex + Sert	133	2.0 (1.4)	−1.0 (0.1)	−0.34 (−0.65, −0.03)	0.03	0.27
	Sert + Placebo	124	1.8 (1.5)	−0.7 (0.1)			
PCL-5 item 20 'Trouble falling or staying asleep'[b]	Brex + Sort	133	3.1 (1.1)	−1.1 (0.1)	−0.32 (−0.71, 0.08)	0.12	0.20
	Sert + Placebo	124	3.0 (1.1)	−0.8 (0.2)			

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least square; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; SD = standard deviation; SE = standard error; Sert = sertraline.
Note: Mixed model for repeated measures; n-values are for patients with measurements at randomization (Week 1).
[a.] CAPS-5 item scores range from 0 (absent) to 4 (extreme/incapacitating) (Weathers et al 2015).
[b.] PCL-5 item scores range from 0 (not at all) to 4 (extremely) (Weathers et al 2013b).

10.5.6.4 Trial 072 Exploratory Endpoints

Table 57: Trial 072 Summary of Patient-Reported Health-Related Quality of Life Exploratory Efficacy Results (Efficacy Sample)

Endpoint	Treatment group	N	Mean (SD) score at Baseline (Day 0)	LS mean (SE) change from Baseline (Day 0) to Week 12	Treatment difference from sertraline + placebo at Week 12	
SF-36v2 Physical component[a]	Brex 2 mg + Sert	98	53.8 (10.2)	−1.2 (0.8)	1.44 (−0.63, 3.52)	0.17
	Brex 3 mg + Sert	92	55.6 (10.5)	−1.0 (0.9)	1.61 (−0.53, 3.75)	0.14
	Sert + placebo	95	54.7 (9.3)	−2.6 (0.8)	–	–
Physical functioning	Brex 2 mg + Sert	98	49.4 (9.2)	1.0 (0.7)	0.88 (−0.89, 2.66)	0.33
	Brex 3 mg + Sert	92	49.7 (8.8)	2.5 (0.8)	2.37 (0.55, 4.20)	0.011
	Sert + placebo	95	49.8 (8.3)	0.2 (0.7)	–	–
Role physical	Brex 2 mg + Sert	98	47.1 (9.6)	1.3 (0.9)	1.48 (−0.85, 3.81)	0.21
	Brex 3 mg + Sert	92	48.6 (10.2)	1.7 (1.0)	1.93 (−0.47, 4.34)	0.11
	Sert + placebo	95	47.8 (10.1)	−0.2 (0.9)	–	–
Pain	Brex 2 mg + Sert	98	45.9 (10.0)	4.9 (1.0)	4.18 (1.49, 6.86)	0.002
	Brex 3 mg + Sert	92	48.3 (11.0)	2.8 (1.1)	2.05 (−0.75, 4.84)	0.15
	Sert + placebo	95	46.5 (11.0)	0.7 (1.0)	–	–
General health	Brex 2 mg + Sert	98	46.3 (9.6)	1.6 (0.9)	−0.69 (−2.96, 1.57)	0.55
	Brex 3 mg + Sert	92	49.6 (9.4)	3.0 (0.9)	0.66 (−1.65, 2.97)	0.58
	Sert + placebo	95	48.9 (8.9)	2.3 (0.9)	–	–
SF-36v2 Mental component[a]	Brex 2 mg + Sert	98	25.8 (9.5)	13.1 (1.3)	1.19 (−2.06, 4.45)	0.47
	Brex 3 mg + Sert	92	27.1 (10.7)	13.3 (1.4)	1.44 (−1.90, 4.79)	0.40
	Sert + placebo	95	26.6 (9.7)	11.9 (1.3)		

Endpoint	Treatment group	N	Mean (SD) score at Baseline (Day 0)	LS mean (SE) change from Baseline (Day 0) to Week 12	Treatment difference from sertraline + placebo at Week 12	
Vitality/fatigue	Brex 2 mg + Sert	98	36.6 (9.0)	7.7 (1.1)	1.03 (−1.66, 3.73)	0.45
	Brex 3 mg + Sert	92	38.0 (9.8)	6.1 (1.1)	−0.56 (−3.34, 2.22)	0.69
	Sert + placebo	95	37.6 (9.5)	6.6 (1.1)	-	-
Social functioning	Brex 2 mg + Sert	98	30.3 (8.8)	10.8 (1.2)	1.56 (−1.61, 4.73)	0.33
	Brex 3 mg + Sert	92	31.8 (9.5)	12.4 (1.3)	3.23 (−0.04, 6.50)	0.053
	Sert + placebo	95	30.9 (8.4)	9.2 (1.2)	-	-
Role emotional	Brex 2 mg + Sert	98	31.8 (8.9)	9.2 (1.2)	1.27 (−1.77, 4.30)	0.41
	Brex 3 mg + Sert	92	33.3 (9.9)	9.7 (1.3)	1.70 (−1.43, 4.82)	0.29
	Sert + placebo	95	33.4 (9.1)	8.0 (1.2)	-	-
Mental health	Brex 2 mg + Sert	98	31.8 (8.4)	10.4 (1.1)	1.45 (−1.30, 4.19)	0.30
	Brex 3 mg + Sert	92	32.7 (8.8)	11.2 (1.2)	2.17 (−0.65, 5.00)	0.13
	Sert + placebo	95	31.8 (9.0)	9.0 (1.1)	-	-
SF-6D health utility index[b]	Brex 2 mg + Sert	98	20.3 (7.1)	−7.6 (0.8)	−1.20 (−3.12, 0.73)	0.22
	Brex 3 mg + Sert	92	19.5 (7.3)	−8.0 (0.8)	−1.59 (−3.57, 0.39)	0.12
	Sert + placebo	95	20.3 (7.5)	−6.4 (0.8)	-	-

Brex = brexpiprazole; LS = least squares; MMRM = mixed model for repeated measures; SD = standard deviation; SE = standard error; Sert = sertraline; SF-36v2 = 36-item Short-Form Health Survey version 2; SF- 6D = Short-Form Six-Dimension.
MMRM; n-values are for patients with measurements at Baseline (Day 0) for SF-36, or randomization (Week 1) otherwise.
[a] SF-36v2 uses norm-based scoring that ranges from 0 (worst health state) to 100 (best health state), where 50 references the normal US population (Ware 2000).
[b] SF-6D health utility index ranges from 0 (worst health state) to 1 (best health state) (Brazier et al 2002).

Table 58: Trial 072 Summary of Sleep-Specific Exploratory Efficacy Results (Efficacy Sample)

Endpoint	Treatment group	N	Mean (SD) score at Baseline	LS mean (SE) change from Baseline to Week 12	Treatment difference from sertraline + placebo at Week 12	P-value	Cohen's d
CAPS-5 item B2 'Distressing dreams severity'[a]	Brex 2 mg + Sert	132	1.6 (1.4)	−0.7 (0.1)	−0.13 (−0.46, 0.19)	0.42	0.10
	Brex 3 mg + Sert	124	1.7 (1.4)	−0.9 (0.1)	−0.31 (−0.64, 0.02)	0.062	0.23
	Sert + placebo	130	1.4 (1.4)	−0.6 (0.1)	–	–	–
CAPS-5 item E6 'Sleep disturbance severity'[a]	Brex 2 mg + Sert	132	2.4 (1.1)	−0.8 (0.1)	−0.27 (−0.63, 0.08)	0.13	0.19
	Brex 3 mg + Sert	124	2.5 (1.0)	−1.0 (0.1)	−0.41 (−0.77, −0.05)	0.025	0.28
	Sert + placebo	130	2.7 (0.9)	−0.6 (0.1)	–	–	–
PCL-5 item 2 'Repeated, disturbing dreams of the stressful experience'[b]	Brex 2 mg + Sert	118	1.8 (1.3)	−0.8 (0.1)	−0.28 (−0.60, 0.04)	0.090	0.22
	Brex 3 mg + Sert	114	1.8 (1.3)	−0.8 (0.1)	−0.28 (−0.61, 0.05)	0.093	0.22
	Sert + placebo	118	1.7 (1.4)	−0.5 (0.1)	–	–	–
PCL-5 item 20 'Trouble falling or staying asleep'[b]	Brex 2 mg + Sert	118	2.8 (1.3)	−0.9 (0.1)	−0.20 (−0.57, 0.18)	0.30	0.14
	Brex 3 mg + Sert	114	2.8 (1.2)	−1.1 (0.2)	−0.38 (−0.76, 0.00)	0.050	0.26
	Sert + placebo	118	2.8 (1.1)	−0.7 (0.1)	–	–	–

Brex = brexpiprazole; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; LS = least squares; MMRM = mixed model for repeated measures; PCL-5 = PTSD Checklist for DSM-5; PTSD = post-traumatic stress disorder; SD = standard deviation; SE = standard error; SF-36v2 = 36-item Short-Form Health Survey version 2.
MMRM; n-values are for patients with measurements at Baseline (Day 0) for SF-36, or randomization (Week 1) otherwise.
[a] CAPS-5 item scores range from 0 (absent) to 4 (extreme/incapacitating) (Weathers et al 2015).
[b] PCL-5 item scores range from 0 (not at all) to 4 (extremely) (Weathers et al 2013b).

10.6 Individual Trial Safety Data

10.6.1 Trial 061

10.6.1.1 Summary of Adverse Events

Post-randomization, TEAEs were reported by 72% of patients overall, with similar incidence between treatment groups (Table 59).

Table 59: Trial 061 Summary of Adverse Events (Safety Sample)

Category , n (%)	Brex + Sert N = 80	Brex + Placebo N = 75	Sert + Placebo N = 79	Placebo N = 82
Patient days of drug exposure	5137	4602	5023	5466
Patients with adverse events	61 (76.3)	56 (74.7)	57 (72.2)	69 (84.1)
Patients with TEAEs	58 (72.5)	53 (70.7)	55 (69.6)	64 (78.0)
Patients with serious TEAEs	2 (2.5)	1 (1.3)	0 (0.0)	4 (4.9)
Patients with non-serious TEAEs[a]	58 (72.5)	53 (70.7)	55 (69.6)	63 (76.8)
Patients with severe TEAEs	6 (7.5)	4 (5.3)	3 (3.8)	6 (7.3)
Patients discontinued trial drug due to adverse events	5 (6.3)	6 (8.0)	4 (5.1)	6 (7.3)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)

Brex = brexpiprazole; Sert = sertraline; TEAE = treatment-emergent adverse event.
Note. TEAE is defined as an AE that started after start of trial drug treatment; or if the event was continuous from Baseline and was worsening, serious, trial drug-related, or resulted in death, discontinuation, interruption or reduction of trial drug. Multiple occurrences of TEAEs are counted once, per specific preferred term.
[a.] After database lock, 1 TEAE (serotonin syndrome) was upgraded from non-serious to serious in the safety database.

10.6.2 Trial 071

10.6.2.1 Summary of Adverse Events

Post-randomization, 60.0% of patients in the brexpiprazole plus sertraline group and 58.2% of patients in the sertraline plus placebo group reported ≥ 1 TEAE (Table 60).

Table 60: Trial 071 Summary of Adverse Events (Safety Sample)

Category, n (%)	Brex + Sert N = 205	Sert + Placebo N = 196	Total N = 401
Patient days of drug exposure	12748	11243	23991
Patient with AEs	123 (60.0)	114 (58.2)	237 (59.1)
Patients with TEAEs	123 (60.0)	114 (58.2)	237 (59.1)
Patients with serious TEAEs	1 (0.5)	4 (2.0)	5 (1.2)
Patients with non-serious TEAEs	123 (60.0)	113 (57.7)	236 (58.9)
Patients with severe TEAEs	6 (2.9)	6 (3.1)	12 (3.0)
Patients discontinued trial drug due to TEAEs	8 (3.9)	20 (10.2)	28 (7.0)
Deaths	0	1 (0.5)	1 (0.2)

AE = adverse event; Brex = Brexpiprazole, Sert = Sertraline; TEAE = treatment-emergent adverse events.
Note: Treatment-emergent adverse event is defined as an adverse event that started after trial drug treatment; or if the event was continuous from Baseline and was worsening, serious, trial drug-related, or resulted in death, discontinuation, interruption, or reduction of trial therapy.
Multiple occurrences of treatment-emergent adverse event are counted once per MedDRA preferred term.

10.6.3 Trial 072

10.6.3.1 Summary of Adverse Events

Post-randomization, 51.4% of patients in the brexpiprazole 2 mg plus sertraline group, 48.3% of patients in the brexpiprazole 3 mg plus sertraline group, and 51.2% of patients in the sertraline plus placebo group reported ≥ 1 TEAE (Table 61).

Table 61: Trial 072 Summary of Adverse Events (Safety Sample)

Category, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg+ Sert N = 180	Sert + Placebo N = 172	Total N = 537
Patient days of drug exposure	11571	10984	10634	33189
Patients with AEs	95 (51.4)	87 (48.3)	88 (51.2)	270 (50.3)
Patients with TEAEs	95 (51.4)	87 (48.3)	88 (51.2)	270 (50.3)
Patients with serious TEAEs	1 (0.5)	1 (0.6)	3 (1.7)	5 (0.9)
Patients with non-serious TEAEs	95 (51.4)	87 (48.3)	85 (49.4)	267 (49.7)
Patients with severe TEAEs	1 (0.5)	2 (1.1)	4 (2.3)	7 (1.3)
Patients discontinued trial drug due to TEAEs	5 (2.7)	8 (4.4)	8 (4.7)	21 (3.9)
Deaths	1 (0.5)	0	0	1 (0.2)
Patients with Adverse Events During Period A	43 (23.2)	47 (26.1)	33 (19.2)	123 (22.9)

AE = adverse event; Brex = Brexpiprazole, Sert = Sertraline; TEAE = treatment-emergent adverse events.
Treatment-emergent adverse event is defined as an adverse event that started after trial drug treatment; or if the event was continuous from Baseline and was serious, trial drug-related, or resulted in death, discontinuation, interruption, or reduction of trial therapy.

10.7 Narratives for Patient Deaths

Trial 071

A 45-year-old white male with PTSD died due to the SAE of toxicity to various agents.

The patient consented to participate in the trial and was assigned to the sertraline plus placebo group.

On Day 24, the patient experienced the SAE of toxicity to various agents. On the same day, in the morning, the patient was smoking an unknown substance (likely cocaine) and experienced serious seizures like symptoms such as twitching of the neck, eyes rolled back in the head, foaming at the mouth, and incontinence of urine. The patient was taken to the emergency and was pronounced as deceased. The patient's autopsy was performed, and the cause of death was reported as toxic effects of cocaine.

No concomitant medications were taken within 14 days prior to the onset of the event. No corrective treatments were administered.

Action taken on the treatment with regard to this event is not applicable. The patient died on Day 24 due to unknown cause.

The investigator assessed the event of toxicity to various agents to be not related to trial drug. The Sponsor considered the event to be not related to trial drug.

No relevant vital signs, electrocardiograms, clinical laboratory, or questionnaire test results were reported.

Trial 072

A 30-year-old white female with PTSD died due to the SAE of drowning.

The patient consented to participate in the trial and was assigned to the brexpiprazole 2 mg + sertraline group.

Based on available information, the patient stopped taking the trial medication prior to the event and demonstrated poor compliance overall including trial visits. The patient also continued to use prohibited medications.

On Trial Day 91, 1 day prior to death, the patient was found in the bathtub full of water with head submerged at private residence, later transported to the hospital by her brother. According to the parents, the patient had texted her brother informing she was going to commit suicide, when he called Emergency Medical Services (EMS) and family arrived at her apartment, she was found to be inside bathtub drowned in the water. EMS and family found empty bottles of Klonopin (clonazepam), propranolol, doxycycline and empty wine bottles. Urine toxicology screening was positive for marijuana, benzodiazepines, blood ethanol at 344, sodium at 156, AST was 118 and ALT was 80 (units and reference ranges not provided). On arrival in the intensive care unit, the patient was intubated on invasive mechanical ventilator.

The patient passed away on Trial Day 92.

The investigator reported that the patient was discontinued from the trial because she continued to take prohibited medications (clonazepam, specifically). Per the Council for International Organizations of Medical Sciences report, the patient received last dose of trial drug on Trial Day 53. It was reported that however, trial medications were dispensed at the Week 6 visit on Trial Day 59. The patient also had compliance issues during the trial.

The autopsy concluded that the cause of death was accidental drowning, ruling out suicide and noting the presence of contusion on the right knee. Forensic toxicology results indicated the presence of ethanol, alprazolam, clonazepam, 7-aminoclonazepam, and propranolol in the blood. Per the Medical Examiner drowning was not a suicide act. The passive suicidal ideations, with text messaging to people and no suicide note, in her opinion was not suicide, but an accidental drowning. The patient had therapeutic levels of benzodiazepines in her system. In addition, she had tetrahydrocannabinol and a large amount of alcohol which in the medical examiner’s opinion would not fall under lethal levels. These combined could have possibly contributed to the accidental drowning. The patient had already been given a warning and asked not to take any benzodiazepines per the informed consent agreement. Unfortunately, during the trial, she had a positive drug screening for clonazepam.

Postmortem were reviewed which revealed that she had seen 2 other physicians and was prescribed benzodiazepines which were prohibited in this trial.

Concomitant medications taken up to 14 days before the onset of the events included propranolol. No corrective treatments were administered. Action taken on the treatment regarding this event is not applicable. The patient died on Day 92.

The investigator assessed the event of drowning to be not related, and the Sponsor considered the event to be not related to trial drug. The following relevant Columbia Suicide Severity Rating Scale questionnaire results were reported:

Date (Day)	Suicidal Behavior						
	Attempts	Nonsuicidal Self-Injurious Behavior	Interrupted Attempts	Aborted Attempt	Preparatory Acts or Behavior	Suicidal Behavior	Completed Suicide
(b) (6) (8)	No	No	No	No	No	No	No
(16)	No	No	No	No	No	No	No
(25)	No	No	No	No	No	No	No
(36)	No	No	No	No	No	No	No
(58)	No	No	No	No	No	No	No

Date (Day)	Suicidal Ideation							
	Questions		With Respect to Most Severe Ideation					
	Wish to be Dead	Nonspecific Active Suicidal Thoughts	Most Severe Ideation	Frequency	Duration	Controllability	Deterrents	Reasons for Ideation
(b) (6) (8)	No	No	–	–	–	–	–	–
(16)	One day her friend's birthday was (b) (6)	No	1	Less than once a week	Fleeting - few seconds or minutes	Easily able to control thoughts	Does not apply	Completely to end or stop the pain
(25)	No	No	–	–	–	–	–	–
(36)	No	No	–	–	–	–	–	–
(58)	No	No	–	–	–	–	–	–

The following relevant vital signs measurements were reported:

Date (Day)	Blood Pressure (mmHg)	Heart Rate (BPM)	Oxygen Saturation (%)	Respiratory Rate (breaths per minute)
(b) (6) (Day 92)	156/101	8	100	30

Trial 061

A 55-year-old, white female with PTSD died due to the SAE of bile duct stone.

The patient consented to participate in the trial and was assigned to the placebo treatment group. The patient received the first dose of placebo on Trial Day 1 and the last dose of placebo on Trial Day 46. The patient's last day in the trial was Trial Day 74.

On Trial Day 42 the patient's lab test showed elevated liver function parameters. On the same day, patient's total bilirubin was 0.5 mg/dL (normal range: 0.2 - 1.2 mg/dL), ALT was 91 U/L (6 - 34 U/L), AST was 163 U/L (9 - 34 U/L), gamma-glutamyl transferase (GGT) was 728 U/L (4 - 49 U/L), and alkaline phosphatase was 170 U/L

(35 - 123 U/L). On Trial Day 43, the patient experienced an SAE of bile duct stone. Concomitant medications taken up to 14 days before the onset of the events included lisinopril.

On Trial Day 46, bilirubin was 1.0 mg/dL (0.2 - 1.2 mg/dL), ALT was 220 U/L (6 - 34 U/L), AST was 164 U/L (9 – 34 U/L), GGT was 1439 U/L (4 - 49 U/L) and alkaline phosphatase was 252 U/L (35 - 123 U/L). On the same day the trial drug was withdrawn and the patient was discontinued from the trial due to this event. On Trial Day 56, the patient had mild nausea and the total bilirubin was 1.9 mg/dL (0.2 - 1.2 mg/dL), ALT was 182 U/L (6 - 34 U/L), AST was 121 U/L (9 - 34 U/L), GGT was 1610 U/L (4 - 49 U/L), alkaline phosphatase was 322 U/L (35 - 123 U/L) and blood lactate dehydrogenase was 300 U/L (53 - 234 U/L). On Trial Day 62, abdominal ultrasound showed a fatty liver and diffuse hepatocellular disease. The patient continued to complain of nausea. On Trial Day 74, bilirubin was 4.2 mg/dL (0.2 - 1.2 mg/dL), ALT was 214 U/L (6 - 34 U/L), AST was 147 U/L (9 - 34 U/L), GGT was 1274 U/L (4 - 49 U/L), and blood lactate dehydrogenase was 240 U/L (53 - 234 U/L).

On Trial Day 75, the patient had nausea, vomiting, fatigue, pruritis, dark urine, and discoloration of stool. On Trial Day 80, the patient’s magnetic resonance imaging and magnetic resonance cholangiopancreatography indicated calculus in the distal common bile duct proximal to the ampulla and dilated intra and extra hepatic bile duct. The patient underwent an endoscopic retrograde cholangiopancreatography with sphincterotomy. The patient developed a complication during the procedure and died on Trial Day 99 due to choledocholithiasis.

The event was considered as not related to the trial drug considering the patient’s gallstone history as a strong confounding factor for the event.

10.8 Additional Safety Data

Table 62: Incidence of Clinically Relevant Vital Sign Abnormalities in the 12-Week Controlled Trials in PTSD (Safety Sample)

		Brex 2 mg + Sert N = 185			Brex 3 mg + Sert N = 180			Brex 1-3 mg + Sert N = 285			All Brex + Sert N = 650			Sert + Placebo N = 447			Total N = 1097		
Vital Sign Parameter		**Ne[1]**	**n[2]**	**%**	**Ne[1]**	**n[2]**	**%**	**Ne[1]**	**n[2]**	**%**	**Ne[1]**	**n[2]**	**%**	**Ne[1]**	**n[2]**	**%**	**Ne[1]**	**n[2]**	**%**
Heart rate standing (beats/min)	Low	185	0	(0.0)	176	0	(0.0)	280	2	(0.7)	**641**	**2**	**(0.3)**	**444**	**2**	**(0.5)**	1085	4	(0.4)
	High	185	2	(1.1)	176	0	(0.0)	280	4	(1.4)	**641**	**6**	**(0.9)**	**444**	**1**	**(0.2)**	1085	7	(0.6)
Heart rate supine (beats/min)	Low	185	1	(0.5)	176	1	(0.6)	280	2	(0.7)	**641**	**4**	**(0.6)**	**445**	**4**	**(0.9)**	1086	8	(0.7)
	High	185	1	(0.5)	176	0	(0.0)	280	0	(0.0)	**641**	**1**	**(0.2)**	**445**	**1**	**(0.2)**	1086	2	(0.2)
SBP standing (mmHg)	Low	185	0	(0.0)	176	0	(0.0)	280	1	(0.4)	**641**	**1**	**(0.2)**	**444**	**6**	**(1.4)**	1085	7	(0.6)
	High	185	0	(0.0)	176	1	(0.6)	280	0	(0.0)	**641**	**1**	**(0.2)**	**444**	**0**	**(0.0)**	1085	1	(0.1)
SBP supine (mmHg)	Low	185	1	(0.5)	176	0	(0.0)	280	0	(0.0)	**641**	**1**	**(0.2)**	**445**	**1**	**(0.2)**	1086	2	(0.2)
	High	185	0	(0.0)	176	0	(0.0)	280	0	(0.0)	**641**	**0**	**(0.0)**	**445**	**0**	**(0.0)**	1086	0	(0.0)
DBP standing (mmHg)	Low	185	0	(0.0)	176	0	(0.0)	280	1	(0.4)	**641**	**1**	**(0.2)**	**444**	**1**	**(0.2)**	1085	2	(0.2)
	High	185	0	(0.0)	176	0	(0.0)	280	1	(0.4)	**641**	**1**	**(0.2)**	**444**	**1**	**(0.2)**	1085	2	(0.2)
DBP supine (mmHg)	Low	185	1	(0.5)	176	0	(0.0)	280	0	(0.0)	**641**	**1**	**(0.2)**	**445**	**0**	**(0.0)**	1086	1	(0.1)
	High	185	0	(0.0)	176	2	(1.1)	280	3	(1.1)	**641**	**5**	**(0.8)**	**445**	**1**	**(0.2)**	1086	6	(0.6)
Weight (kg)	Low	185	5	(2.7)	179	9	(5.0)	281	16	(5.7)	**645**	**30**	**(4.7)**	**446**	**29**	**(6.5)**	1091	59	(5.4)
	High	185	20	(10.8)	179	14	(7.8)	281	31	(11.0)	**645**	**65**	**(10.1)**	**446**	**23**	**(5.2)**	1091	88	(8.1)
Orthostatic hypotension	Low	185	0	(0.0)	176	0	(0.0)	280	2	(0.7)	**641**	**2**	**(0.3)**	**444**	**2**	**(0.5)**	1085	4	(0.4)

Brex = brexpiprazole; DBP = diastolic blood pressure; PTSD = post-traumatic stress disorder; SBP = systolic blood pressure; Sert = sertraline.
[1]Ne is the total number of patients with at least 1 post-Baseline numeric result for the given vitals parameter.
[2]n is the number of patients with vital sign of potential clinical relevance.

Table 63: Incidence of Categorical Changes in QTcB or QTcF in the 12-Week Controlled Trials in PTSD (Safety Sample)

	Brex 2 mg + Sert		Brex 3 mg + Sert		Brex1-3 mg + Sert		All Brex		Sert + Placebo		Total	
Classification Category	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
QTcB												
New Onset (> 500 msec)¥	147	0 (0.0)	144	0 (0.0)	160	0 (0.0)	451	0 (0.0)	273	0 (0.0)	724	0 (0.0)
30 - 60 msec	147	10 (6.8)	144	9 (6.3)	160	11 (6.9)	451	30 (6.7)	273	15 (5.5)	724	45 (6.2)
≥ 60 msec	147	3 (2.0)	144	0 (0.0)	160	0 (0.0)	451	3 (0.7)	273	2 (0.7)	724	5 (0.7)
QTcF												
New Onset (> 500 msec)¥	147	0 (0.0)	144	0 (0.0)	160	0 (0.0)	451	0 (0.0)	273	0 (0.0)	724	0 (0.0)
30 - 60 msec	147	9 (6.1)	144	3 (2.1)	160	12 (7.5)	451	24 (5.3)	273	11 (4.0)	724	35 (4.8)
≥ 60 msec	147	1 (0.7)	144	0 (0.0)	160	0 (0.0)	451	1 (0.2)	273	1 (0.4)	724	2 (0.3)

Brex = brexpiprazole, PTSD = post-traumatic stress disorder; QTcB = QT interval corrected for heart rate using Bazett's formula; QTcF = QT interval corrected for heart rate using Fridericia's formula; Sert = sertraline.
Trials 071 and 072.
¥ New onset > 500 msec in QTcB, QTcF means a patient who attains a value > 500 msec during treatment period but not at Baseline visit.

Table 64: Columbia Suicide Severity Rating Scale in the 12-Week Controlled Trials in PTSD (Safety Sample)

Parameter, n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sert + Placebo N = 447	Total N = 1097
Lifetime History						
Suicidal behavior	0	0	0	**0**	**0**	0
Suicidal ideation	0	0	8 (2.8)	**8 (1.2)**	**10 (2.2)**	18 (1.6)
Treatment Phase						
Suicidal Behavior	0	0	2 (0.7)	**2 (0.3)**	**1 (0.2)**	3 (0.3)
Actual attempt	0	0	2 (0.7)	**2 (0.3)**	**0**	2 (0.2)
Interrupted attempt	0	0	0	**0**	**0**	0
Aborted attempt	0	0	0	**0**	**0**	0
Preparatory acts/behavior	0	0	0	**0**	**0**	0
Suicidal behavior	0	0	0	**0**	**1 (0.2)**	1 (0.1)
Treatment Phase						
Suicidal Ideation	15 (8.1)	9 (5.0)	16 (5.6)	**40 (6.2)**	**39 (8.7)**	79 (7.2)
Ideation with plan/intent	0	0	0	**0**	**0**	0
Ideation with intent, no plan	0	0	0	**0**	**2 (0.4)**	2 (0.2)
Suicidal ideation-no intent	1 (0.5)	1 (0.6)	1 (0.4)	**3 (0.5)**	**8 (1.8)**	11 (1.0)
Non-specific suicidal thought	5 (2.7)	3 (1.7)	2 (0.7)	**10 (1.5)**	**11 (2.5)**	21 (1.9)
Wish to be dead	13 (7.0)	9 (5.0)	16 (5.6)	**38 (5.8)**	**39 (8.7)**	77 (7.0)

Brex = brexpiprazole; PTSD = post-traumatic stress disorder; Sert = sertraline.

Table 65: Mean Change from Baseline to Week 12 (End Dose) in Metabolic Parameters in 12-Week Controlled Trials in PTSD (Safety Sample)

Parameter	All Brex + Sert N = 650	Sert + Placebo N = 447
Triglycerides, fasting (mg/dL)		
n[a]	469	306
Mean change at last visit (SD)	4.39 (67.18)	6.91 (67.00)
Total cholesterol, fasting (mg/dL)		
n[a]	470	306
Mean change at last visit (SD)	6.59 (28.60)	4.92 (28.85)
HDL cholesterol, fasting (mg/dL)		
n[a]	438	286
Mean change at last visit (SD)	1.28 (9.08)	-0.82 (8.77)
LDL cholesterol, fasting (mg/dL)		
n[a]	435	284
Mean change at last visit (SD)	4.72 (25.89)	3.55 (25.43)
Glucose, fasting (mg/dL)		
n[a]	474	306
Mean change at last visit (SD)	−0.01 (17.64)	0.88 (14.75)

HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTSD = post-traumatic stress disorder; SD = standard deviation.
[a.] Total number of treated patients with both Baseline and evaluation of the given parameter at the specific visit. Baseline = last predose evaluation; Last visit = last available post-Baseline evaluation including early term.

Table 66: Incidence of Treatment-Emergent Shifts in Metabolic Parameters in 12-Week Controlled Trials in PTSD (Safety Sample)

	All Brex + Sert		Sertraline	
Shifts from Normal to High Except For HDL (Normal to Low for HDL)	Baseline N	Anytime Post-Baseline n (%)	Baseline N	Anytime Post-Baseline n (%)
Triglycerides, fasting (mg/dL)	348	30 (8.6)	236	15 (6.4)
Cholesterol, fasting (mg/dL)	294	13 (4)	218	7 (3)
HDL cholesterol, fasting (mg/dL)	373	30 (8)	244	21 (9)
LDL cholesterol, fasting (mg/dL)	181	2 (1)	117	1 (1)
Glucose, fasting (mg/dL)	368	8 (2)	248	3 (1)

Brex = brexpiprazole; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTSD = post-traumatic stress disorder; Sert = sertraline.