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FDA Briefing Document

NDA: 205422 S-012

Drug name: brexpiprazole

Applicant: Otsuka Pharmaceutical Company, Ltd.

Psychopharmacologic Drugs Advisory Committee Meeting

07/18/2025

Division of Psychiatry/Office of Neuroscience

DISCLAIMER STATEMENT

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Glossary

AC	Advisory Committee
AE	adverse event
B-IPF	Brief Inventory of Psychosocial Function
CAPS	Clinician Administered PTSD Scale
CAPS-5	Clinician-Administered PTSD Scale for DSM-5
CI	confidence interval
CGI-S	Clinical Global Impression - Severity
CPK	creatine phosphokinase
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	electrocardiogram
EOP	end-of-phase 2
FAS	full analysis set
FDA	Food and Drug Administration
IMP	investigational medicinal product
ITT	intent-to-treat
MAR	missing at random
MDD	major depressive disorder
MINI	Mini International Neuropsychiatric Interview
MMRM	mixed model for repeated measures
NDA	new drug application
OC	observed cases
PTSD	post-traumatic stress disorder
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The Applicant has proposed the use of brexpiprazole, in combination with sertraline, as a treatment for post-traumatic stress disorder (PTSD). The FDA is convening this Advisory Committee (AC) meeting to discuss the clinical benefit of brexpiprazole in the Applicant's proposed therapeutic context.

1.2 Context for Issues to Be Discussed at the AC

PTSD is a disabling psychiatric condition characterized by intrusive memories, hyperarousal, and avoidant behavior following exposure to actual or threatened death, serious injury, or sexual violence. Patients with PTSD are at high risk for developing other comorbidities, particularly mood and substance use disorders. PTSD is associated with a high risk for suicidal ideation and behavior. Patients with PTSD experience impairments in social and occupational functioning that result in high healthcare utilization and diminished quality of life.

The disorder affects approximately 3.6% of U.S. adults annually, with a higher prevalence in women, and is associated with various comorbidities, suicide risk, and impaired functioning.

Current PTSD treatments include psychotherapy options and pharmacotherapy, with selective serotonin reuptake inhibitors (SSRIs) (sertraline and paroxetine) being FDA-approved and recommended as first-line medications by many treatment guidelines. However, these treatments have limitations, including various side effects and a response rate of only 37 to 62% for SSRIs. Off-label treatments are also used, but data on their efficacy is limited. There remains an unmet need for additional safe and effective PTSD treatments.

The Applicant is proposing the combination of brexpiprazole and sertraline initiated concurrently as a potential alternative to available monotherapy, aiming to address the limitations of existing treatments and provide a more effective option for PTSD management.

1.3 Brief Description of Issues for Discussion at the AC

In the current application, the Applicant provided data from three clinical trials in which the combination of brexpiprazole and sertraline initiated concurrently was compared to sertraline monotherapy in patients with PTSD, with no requirement of prior inadequate response to sertraline or SSRI monotherapy.

As the Agency's typically requires two adequate and well-controlled studies to meet the evidentiary standard for substantial evidence of effectiveness, the Applicant conducted two phase 3, multicenter, randomized, double-blind, controlled, 12-week studies—Studies 331-201-00071 (hereafter, Study 00071) and Study 331-201-00072 (hereafter, Study 00072) in an adult population with PTSD.

In contrast to what is typical of an "adjunctive treatment" model in which participants with a partial response to one treatment would receive a second treatment only after several weeks of the first treatment, in each of these studies, the brexpiprazole and sertraline were initiated concurrently, and this combination treatment was compared to sertraline plus placebo. These studies enrolled participants willing to discontinue antidepressants, excluded participants receiving adequate doses of sertraline, and did not require evidence of inadequate response to sertraline monotherapy. The overall

development goal was discussed during the investigational new drug phase, and it was agreed that the combination treatment needed to consistently outperform sertraline monotherapy to show convincing evidence of efficacy. It was also agreed that, although adjunctive treatments are typically studied in patients who have not experienced adequate benefit from a labelled monotherapy, this was not considered a requirement.

In Study 00071, subjects were randomized to flexibly dosed brexpiprazole (2 to 3 mg) in combination with a fixed-dose of sertraline (150 mg) or to fixed-dose sertraline plus placebo. Study 00072 participants were randomized to one of three fixed-dose groups: brexpiprazole 2 mg plus sertraline 150 mg, brexpiprazole 3 mg plus sertraline 150 mg, or sertraline 150 mg plus placebo. Study 00071 was a positive study; however, in Study 00072, neither active treatment group was superior to sertraline plus placebo. Despite extensive exploratory analyses, the Agency is unable to identify a reason for these discordant results.

Studies 00071 and 00072 were designed with the intent to serve as two adequate and well-controlled studies that would form the evidentiary basis for a finding of substantial evidence of effectiveness. Study 0071 was a robustly positive study; however, Study 00072 was a clearly and convincingly negative study that did not demonstrate statistical significance on its primary or secondary endpoints. Given the conflicting results of these two studies, the Applicant also submitted phase 2 Study 331-201-00061 (hereafter Study 00061), a randomized, double-blind, placebo- and active-controlled, four-arm, flexible-dose, 12-week trial to provide additional evidence to support the efficacy of combination brexpiprazole plus sertraline for the treatment of PTSD.

Study 00061 was initially designed as an exploratory phase 2 study with enrollment criteria similar to Studies 00071 and 00072. The objectives of the study were to generate hypotheses for the design of phase 3 studies, and specifically to investigate the contribution of the single components (brexpiprazole monotherapy or sertraline monotherapy) to the treatment effect of the brexpiprazole plus sertraline combination therapy compared to placebo. This study included multiple treatment arms: brexpiprazole (1 to 3 mg) monotherapy, sertraline (100 to 200 mg) monotherapy, brexpiprazole (1 to 3 mg) plus sertraline (100 to 200 mg) combination, and placebo. Initially, a hierarchical testing procedure was proposed in the protocol, but the statistical analysis plan (SAP) later abandoned multiplicity control methods due to the study's exploratory nature. Instead, five treatment group comparisons were analyzed without a hierarchical procedure (Table 3).

The Applicant applied post hoc multiplicity control methods and retrospectively selected three comparisons of interests. Brexpiprazole plus sertraline showed statistical superiority versus sertraline plus placebo using the retrospectively selected multiplicity control methods; however, using the originally prespecified hierarchical testing procedure, statistical significance cannot be claimed.

It is important to note that the retrospectively selected three comparisons of interests do not align with the study's primary objectives. The comparison between the brexpiprazole plus sertraline and sertraline plus placebo was retrospectively selected as primary in the hierarchy, but, in the original protocol submission, it was the third to be tested. The retrospective selection of hypotheses and use of post hoc multiple testing procedures raises concerns about inflation of the overall Type I error rate, which is crucial for demonstrating efficacy.

The AC will be asked to consider the evidence of effectiveness provided by these studies. The AC should consider the single positive adequate and well-controlled study (Study 00071), the discordant results

from the second adequate and well-controlled study (Study 00072), and whether the exploratory phase 2 study (Study 00061), which has statistical and methodological concerns, is adequate to overcome the negative results of Study 00072 to establish the effectiveness of brexpiprazole when co-initiated with sertraline for the treatment of PTSD. Although no new safety signals were identified in the development program, the risks of brexpiprazole in combination with sertraline align with the known risks of each drug. The committee will be asked to opine on not just whether the development program has demonstrated the benefits of co-initiation of brexpiprazole and sertraline for the treatment of PTSD, but also to consider the evidence of benefit in the context of the known risks of these two drugs.

1.4 Draft Points for Consideration

- Studies 00071 and 00072 were designed as two adequate and well-controlled phase 3 trials that could provide substantial evidence of effectiveness for brexpiprazole in combination with sertraline for the treatment of PTSD. Study 0071 was a positive study; however, Study 00072 did not demonstrate statistical significance on its primary or secondary endpoints.
- Study 00061, originally a phase 2 exploratory study, was retrospectively analyzed with post hoc multiplicity control methods to provide additional efficacy evidence, raising concerns about Type I error inflation.
- The AC is tasked with evaluating the overall efficacy evidence, considering the single positive phase 3 study, the discordant results from the second phase 3 study, and the phase 2 exploratory study which has statistical and methodological concerns. Any potential benefits should be considered in the context of the known risks of both brexpiprazole and sertraline, as well as the proposal to initiate both drugs concurrently.

The committee will be asked to discuss the evidence of effectiveness for brexpiprazole in combination with sertraline, initiated concurrently, for the treatment of PTSD. Consider the following:

- The strength of evidence provided by the two phase 3 studies 00071 and 00072. In particular, discuss the impact of the discordant results on your overall assessment of efficacy.
- Whether the data from Study 00061 can overcome the negative results from Study 00072 and provide independent substantiation of the results from Study 00071.
- How the known risks of brexpiprazole and sertraline impact your assessment of the benefit risk balance in the context of concurrent initiation of the therapies.

Does the available data presented establish the efficacy of brexpiprazole, when initiated concurrently with sertraline, for the treatment of PTSD?

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

The Applicant has proposed the use of brexpiprazole concurrently initiated with sertraline as a treatment for PTSD.

PTSD is a psychiatric disorder that may occur following exposure to actual or threatened death, serious injury, or sexual violence. It is characterized by:

- Intrusion symptoms (i.e., recurrent dreams or intrusive memories about the event, dissociative reactions in which the individual feels or acts as if the traumatic event were recurring, intense

physiological reactions or psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event).

- Persistent avoidance of memories, thoughts, feelings, or external reminders associated with the traumatic event.
- Negative alterations in mood and cognition associated with the traumatic event (i.e., inability to experience positive emotions, inability to remember an important aspect of the traumatic event, distorted cognition or guilt about the cause or consequences of the traumatic event).
- Marked alterations in arousal and reactivity (i.e., hypervigilance, exaggerated startle response, angry outbursts with little or no provocation, poor concentration, insomnia).

Patients with PTSD are at high risk for developing other comorbidities, particularly mood and substance use disorders. PTSD is associated with a high risk for suicidal ideation and behavior. Patients with PTSD experience impairments in social and occupational functioning that result in high healthcare utilization and diminished quality of life. Per the National Institute of Mental Health, an estimated 3.6% of U.S. adults had PTSD in the past year, with higher past-year prevalence in women (5.2%) than men (1.8%).

Current treatment options for PTSD include psychotherapy (cognitive processing therapy, eye movement desensitization and reprocessing, and prolonged exposure) and pharmacotherapy. The selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are the recommended first-line medications in most treatment guidelines and are the only medications approved by the Food and Drug Administration (FDA) for PTSD (Forbes et al. 2010). Although both drugs have shown better results than placebo (Watts et al. 2013; Hoskins et al. 2015), they only produce a response rate of 37 to 62% in patients with PTSD (Brady et al. 2000; Davidson et al. 2001; Marshall et al. 2001; Stein et al. 2003). In these studies, treatment response was defined as a >30% reduction from baseline on the Clinician Administered PTSD Scale (CAPS) score and a rating of "much" or "very much" improvement on the Clinical Global Impressions Improvement scale. Adverse reactions associated with SSRIs, including sertraline and paroxetine, usually include diarrhea, dizziness, fatigue, headache, nausea, sexual dysfunction, sweating, tremor, and weight gain. Compared to other antidepressants, paroxetine has anticholinergic effects, due to blockade of acetylcholine receptors. Adverse reactions related to its anticholinergic effects, such as dry mouth and constipation, and urinary difficulties, can be expected with its use (Nevels et al. 2016). Sertraline was approved for PTSD in 1999, paroxetine in 2001. No new medications have been approved for PTSD since then.

Off-label treatments for PTSD include atypical antipsychotics, clonidine, prazosin, bupropion, buspirone, monoamine oxidase (MAO) inhibitors, mirtazapine, gabapentin, lamotrigine, trazodone, and propranolol. Efficacy data on off-label options are typically limited to case reports, making it difficult to assess the balance between benefits for this patient population and known risks of these drugs. The large number of off-label treatments that have been tried may reflect limited efficacy of the approved treatments for many patients. There is an unmet need for additional safe and effective treatment options for PTSD.

2.2 Pertinent Drug Development and Regulatory History

Brexpiprazole is an atypical antipsychotic thought to exert its pharmacological effect through partial agonism of serotonin subtype-1a (5-HT1A) and dopamine-2 (D2) receptors, and antagonism of serotonin subtype-2a (5-HT2A) receptors. It is currently FDA-approved for treatment of schizophrenia in adults and

adolescents, adjunctive treatment of major depressive disorder (MDD) in adults, and for the treatment of agitation associated with dementia due to Alzheimer's disease.

On April 8, 2024, the Applicant submitted the present efficacy supplement for brexpiprazole in combination with sertraline for the treatment of adults with PTSD.

Highlights of Regulatory History

Brexpiprazole for treatment of PTSD was developed under an investigational new drug (IND) application opened in 2013. In that year, during a Pre-IND meeting, the Applicant sought advice on a proposed IND-opening study (Study 14865A) to investigate brexpiprazole as adjunctive therapy to paroxetine or sertraline in adult patients suffering from PTSD with an incomplete response to treatment with either sertraline or paroxetine. The Agency agreed on the proposed clinical trial population. On September 1, 2015, the Applicant notified the Agency of their decision to terminate Study 14865A for insufficient enrollment due to difficulties in identifying participants suitable for randomization to receive brexpiprazole.

On October 10, 2016, the Applicant submitted a new protocol for the proposed PTSD indication, Study 00061. The study was a phase 2 trial in subjects with PTSD with no prior requirement of inadequate response to sertraline or SSRIs. The objectives of the study were to generate hypotheses for the design of phase 3 studies, and specifically to investigate the contribution of the single components (brexpiprazole monotherapy or sertraline monotherapy) to the treatment effect of the brexpiprazole plus sertraline combination therapy compared to placebo. At that time, the Applicant did not submit the SAP for the Agency's review. The SAP, submitted later within the briefing document for an End-of-Phase 2 (EOP2) meeting with the Agency, stated that "*The hierarchical testing procedure that was planned in the protocol would not be performed due to the exploratory nature of the PoC (Proof of Concept) study.*" As a result, no multiple comparison procedure was implemented to control the overall Type I error among the treatment arms in Study 00061.

During the EOP2 meeting held on May 2, 2019, the Agency provided guidance on the phase 3 development program. The Applicant emphasized the change in the development goal from "adjunctive" to "combination," implying that evidence of an inadequate response to sertraline was not required for enrollment in the phase 3 studies. The Agency agreed that, although adjunctive treatments are typically studied in patients who have not experienced adequate benefit from a labelled monotherapy, this was not considered a requirement.

Additionally, the Agency agreed that a brexpiprazole monotherapy arm was not needed in the phase 3 studies given its lack of effectiveness compared to placebo in Study 00061. The Agency also suggested omitting a placebo arm, as the key question is whether brexpiprazole plus sertraline is more effective than sertraline alone. At the EOP2 meeting, the Applicant presented a revised study plan in response to the Agency's recommendations. Instead of the originally planned two identical flexible-dose studies, the new plan included one fixed-dose trial and one flexible-dose trial. Both trials would compare the combination therapy (either fixed or flexible dose, depending on the study) to fixed-dose sertraline.

The Applicant asked if the combination treatment needed to consistently outperform sertraline monotherapy for convincing evidence of efficacy. The Agency clarified that the combination treatment should show superiority to approved sertraline monotherapy and meet the statutory standard for substantial evidence of effectiveness.

In responses for a Pre-supplemental NDA (sNDA) meeting in October 2023, the Agency agreed that the proposed data package, consisting of Studies 00071, 00072, and 00061, appeared sufficient to file an sNDA. The Agency clarified that, in consideration of the lack of a demonstrated contribution of components (sertraline or brexpiprazole) and lack of control for Type I error over multiple comparisons, whether Study 00061 could contribute to a finding of substantial evidence of effectiveness would be a matter of review. The Agency also informed the Applicant that Study 00071 alone would unlikely be able to support effectiveness.

3 Summary of Issues for the AC

3.1 Efficacy Issues

There are two efficacy issues:

1. Interpretability of Phase 3 studies:

   Studies 00071 and 00072 were designed as adequate and well-controlled phase 3 studies for brexpiprazole plus sertraline in PTSD. However, their results were conflicting: Study 00071 was positive, while Study 00072 did not demonstrate statistical significance on its primary or secondary endpoints. Despite extensive exploratory analyses, the Agency is unable to identify a reason for these discordant results. This discordance complicates the interpretation of the overall efficacy evidence from these pivotal trials.

2. Ability of Study 00061 to contribute to substantial evidence of effectiveness:

   Study 00061, originally designed as an exploratory phase 2 study, was retrospectively analyzed to provide additional efficacy evidence. However, several factors limit its ability to contribute substantially to the evidence:

   - Post hoc application of multiplicity control methods.
   - Retrospective selection of comparisons of interest.
   - Deviation from originally prespecified hierarchical testing procedure.
   - Concerns about inflation of Type I error rate due to these retrospective changes.

3.1.1 Sources of Data for Efficacy

The Applicant has submitted data from one phase 2, 12-week study (Study 00061) and two 12-week phase 3 studies (Studies 00071 and 00072) involving subjects with PTSD (Table 1).

Table 1. Studies Submitted for Efficacy

Trial No. (Trial Phase)	Description (Treatment Duration)	Dose/Schedule	Primary Endpoint	No. of Subjects Randomized	Study Population
331-201-00061 (Study 00061) (Phase 2)	Multicenter, randomized, double-blind, placebo- and active-controlled monotherapy or combination therapy (12-week double-blind treatment)	Flexible dose Brex (1-3 mg/day) + Sert (100-200 mg/day) Brex (1-3 mg/day) + placebo Sert (100-200 mg/day) + placebo Placebo + placebo	Change from baseline (Week 1) to Week 10 in CAPS-5 total score	N=321 Brex 1-3 mg/day + Sert (n=82) Brex 1-3 mg/day + placebo (n=75) Sert 100-200 mg/day + placebo (n=81) Placebo + placebo (n=83)	Adults aged 18-65 years with PTSD
331-201-00071 (Study 00071) (Phase 3)	Multicenter, randomized, double-blind, combination therapy (12-week double-blind treatment)	Flexible dose Brex (2-3 mg/day) + Sert (150 mg/day) Sert (150 mg/day) + Placebo	Change from baseline (Week 1) to Week 10 in CAPS-5 total score	N=416 Brex 2–3 mg/day + Sert (n=214) Sert + Placebo (n=202)	Adults aged 18-65 years with PTSD
331-201-00072 (Study 00072) (Phase 3)	Multicenter, randomized, double-blind, fixed-dose, combination therapy (12-week double-blind treatment)	Fixed dose Brex (2 mg/day) +Sert (150 mg/day) Brex (3 mg/day) + Sert (150 mg/day) Sert (150 mg/day) + placebo	Change from baseline (Week 1) to Week 10 in CAPS-5 total score	N=553 Brex 2 mg/day + Sert (n=191) Brex 3 mg/day + Sert (n=185) Sert 150 mg/day + Placebo (n=177)	Adults aged 18-65 years with PTSD

Source: Modified by Applicant's Clinical Overview, Table 2.5.4.1.1-1.

Abbreviations: Brex, brexpiprazole; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PTSD, post-traumatic stress disorder; Sert, sertraline

3.1.1.1 Study Description – Study 00061

Study 00061 was a randomized, double-blind, multisite, placebo- and active-controlled, four-arm trial. The objectives of the study were to evaluate the efficacy, safety, and tolerability of brexpiprazole as monotherapy or as combination treatment with sertraline in adult subjects with PTSD.

3.1.1.1.1 Design Study 00061

Study 00061 consisted of three periods: a 14-day screening period during which subjects were washed out of all prohibited medications, a 12-week double-blind treatment period, and a 14-day follow-up period (Figure 1). The 12-week double-blind period started with a 1-week double-blind placebo run-in (Blinded Phase A), during which all subjects meeting entry criteria received double-blind placebo for 7 days, as in Studies 00071 and 00072. The placebo run-in period was intended to identify placebo responders. All subjects were randomized regardless of their response during the placebo run-in period to maintain the blinding, and placebo responders were included in the primary efficacy analysis, in

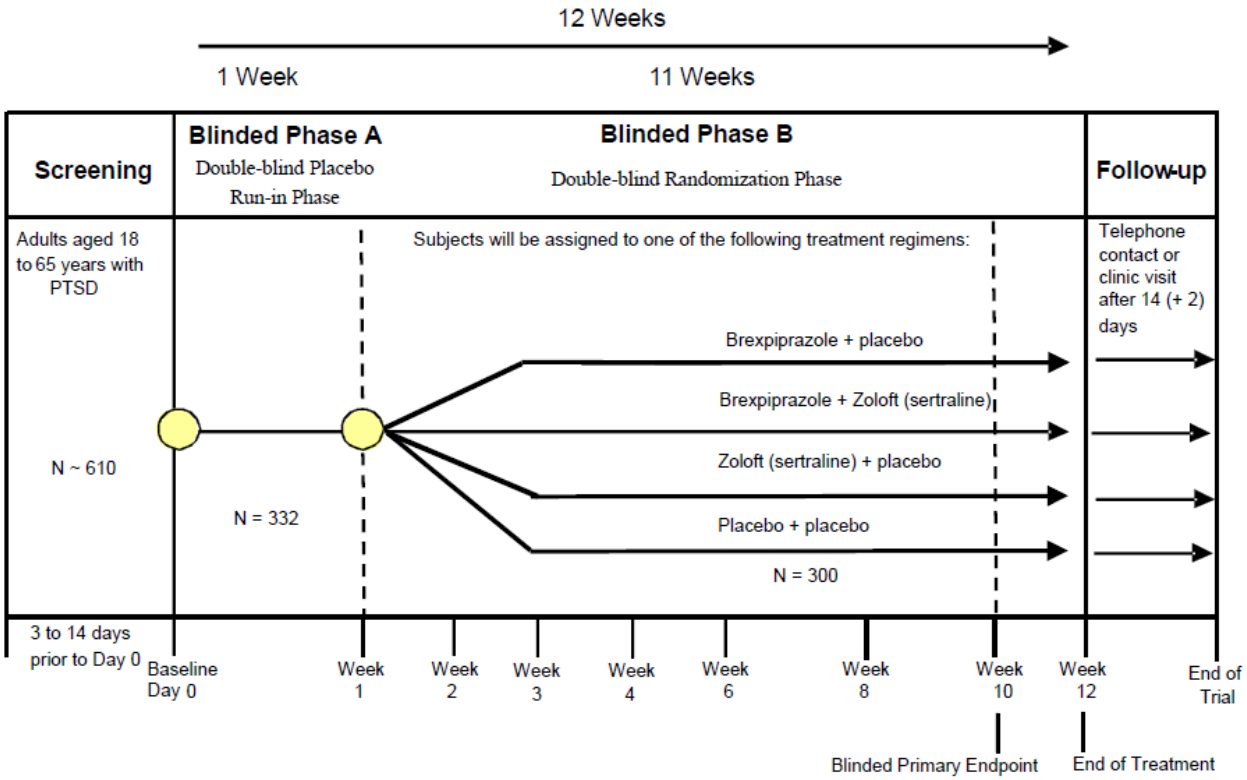
contrast to Studies 00071 and 00072. The blinded Phase A was followed by a blinded Phase B (Weeks 1 to 12) during which subjects were randomized 1:1:1:1 to one of the following four arms:

- Brexpiprazole plus placebo
- Brexpiprazole plus sertraline
- Sertraline plus placebo
- Placebo plus placebo

This was followed by a follow-up visit after 14 days of the last dose of the investigational medicinal product (IMP).

Study staff and subjects were blinded to some study design features to reduce potential bias in assessments. Therefore, the study appeared to investigators, raters and subjects as a continuous, double-blind, 12-week treatment period with a 14-day follow-up period. Figure 1 depicts the unblinded design of Study 00061.

Figure 1. Study 00061 Unblinded Schema



Source: Figure 3.1-1 in Applicant's Revised Clinical Protocol Addendum for Study 00061, Version 2.0, dated June 8, 2017.
Abbreviation: PTSD, post-traumatic stress disorder

3.1.1.1.2 Dosages Study 00061

The starting dose, maximum allowable dose, and recommended target dose range for the active treatment arms were as follows:

1. Brexpiprazole plus placebo:
    a. Starting dose: 0.5 mg/day, maximum dose: 3 mg/day, target dose: 1 to 3 mg/day.

2. Brexpiprazole plus sertraline:
    a. Brexpiprazole starting dose: 0.5 mg/day, maximum dose: 3 mg/day, target dose: 1 to 3 mg/day.
    b. Sertraline starting dose: 50 mg/day, maximum dose: 200 mg/day, target dose: 100 to 200 mg/day.
3. Sertraline plus placebo:
    a. Starting dose: 50 mg/day, maximum dose: 200 mg/day, target dose: 100 to 200 mg/day.
4. Placebo plus placebo

During the 3-week titration period, no dose adjustments were allowed. Subjects unable to tolerate the assigned dose during this period were withdrawn from the study. Dose increases could occur only at the Week 4 visit. Dose decreases were permitted between the Week 3 and Week 6 visits. After Week 6, no further dose adjustments were allowed. Subjects unable to maintain their Week 6 dose due to tolerability issues were withdrawn from the study.

Both brexpiprazole and sertraline were titrated to target dose ranges (1 to 3 mg for brexpiprazole and 100 to 200 mg for sertraline). Given the exploratory nature of this investigation, its primary objectives were to examine the individual contributions of each drug, assess the combined effect of the two medications, and inform the optimal dosage of the combination for subsequent research; doses of both drugs were within the approved dose range for other indications for both drugs.

3.1.1.1.3 Population Study 00061

The inclusion/exclusion criteria for the PTSD population in Study 00061 were as follows:

Key inclusion criteria:

- Male and female outpatients 18 to 65 years of age, inclusive, at the time of informed consent; PTSD diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), and confirmed by the Mini International Neuropsychiatric Interview (MINI); Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score ≥33 at screening and baseline Visits (Day 0); Onset of PTSD symptoms for a minimum of 6 months prior to screening; Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the trial period.

Key exclusion criteria:

- Participants currently receiving sertraline with an adequate dose and duration (>50 mg/day for a minimum of 8 weeks); with index traumatic event occurred before age 16 years; who have experienced a traumatic event within 3 months of screening; who meet the DSM-5 criteria for a current major depressive episode (i.e., currently symptomatic) or any other psychiatric disorder; subjects with a significant risk of committing suicide based on history, mental status examination, investigator's judgment, or Columbia-Suicide Severity Rating Scale (C-SSRS) answer of "yes" to question 4 or 5 (current or within the last 90 days) or subjects with any suicidal behavior during the last year prior to the screening visit; participants willing to discontinue antidepressants.
- Index traumatic event leading to PTSD occurred >15 years prior to screening.

Of note, the study enrolled only participants willing to discontinue antidepressants and excluded participants receiving adequate doses of sertraline at time of screening. The Applicant had initially developed brexpiprazole as adjunctive treatment to sertraline for the treatment of PTSD. Because adjunctive treatments are typically studied in patients who have not experienced adequate benefit from a labelled monotherapy, during the development phase the Applicant emphasized the change in the

development goal from “adjunctive” to “combination,” implying that evidence of an inadequate response to sertraline was not required for enrollment in the study (refer to Section 2.2 Pertinent Drug Development and Regulatory History).

Participants with a current major depressive episode were excluded from the studies to prevent confounding the treatment effect with improvements in depressive symptoms. This was an important consideration given that brexpiprazole is already approved as an adjunctive therapy to antidepressants for treating MDD in adults.

3.1.1.1.4 Efficacy Assessment Study 00061

The primary efficacy endpoint was the change in CAPS-5 total score from baseline (Week 1) to Week 10. The protocol blinded the primary endpoint by decoupling the timing of the primary analysis from the duration of the study; indeed, the total study duration was 12 weeks, but site personnel (and participants) were blinded to the timing of the assessment of the primary endpoint, which occurred at Week 10.

The **CAPS-5** is a clinician-rated, structured interview designed to assess PTSD diagnostic status and symptom severity as defined by the DSM-5. The studies used the CAPS-5 past month version at screening and the CAPS-5 past week version at all other assessment timepoints. In Version 5 of the CAPS, clinicians consider both the intensity and frequency of a symptom when assigning a rating on this scale.

The CAPS-5 is widely used in clinical research to assess PTSD symptoms. Earlier versions of the CAPS supported approval of sertraline and paroxetine for the treatment for PTSD.

A systematic review of the literature on treatment response in PTSD describes a range of potential thresholds of change in the CAPS-5 total score that could be considered to demonstrate a treatment response, which includes a 10-point change as the minimum amount of change (Varker et al. 2020)). The Agency’s review of published literature and review of the scale suggests that a 10-point change in the CAPS-5 total score could be considered clinically meaningful.

Given the exploratory nature of the study, the protocol did not specify secondary endpoints, but generally reported “other efficacy assessments”, including Clinical Global Impression - Severity (CGI-S).

Briefly, the CGI-S is a 7-point categorical scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's experience with patients who have the same diagnosis. The CGI-S is considered an acceptable global measure for use as a secondary endpoint.

Efficacy assessments were performed at the following visits:

- CAPS-5: Weeks 1, 3, 6, 10, 12
- CGI-S: Weeks 1, 2, 3, 4, 6, 8, 10, 12

3.1.1.1.5 Efficacy Results Study 00061

Populations and Baseline Characteristics

In Study 00061, the analysis populations were defined as follows:

- **Enrolled sample**—All subjects enrolled in the placebo lead-in phase.
- **Randomized sample**—All subjects randomized into this trial.
- **Intent-to-treat (ITT) population**—All subjects in the randomized sample who took at least one dose of double-blind IMP and have a baseline and at least one postbaseline evaluation for the CAPS-5 total score. This is the primary efficacy analysis population.

As shown in Table 2, of the 690 subjects screened, 336 were enrolled in the trial and, after the 1-week placebo run-in period (Phase A), a total of 321 subjects were randomized at Week 1 (Phase B) at 48 sites in the United States to one of four treatment arms: brexpiprazole plus sertraline (82 subjects), brexpiprazole plus placebo (75 subjects), sertraline plus placebo (81 subjects), or placebo (83 subjects). The percentages of subjects who discontinued were similar among these four treatment groups (29% in the brexpiprazole plus sertraline group, 33% in the brexpiprazole plus placebo group, 27% in the sertraline plus placebo group, and 23% in the placebo group).

Table 2. Subject Disposition, Study 00061

Variable	Brexpiprazole Plus Sertraline (N=82)	Brexpiprazole Plus Placebo (N=75)	Sertraline Plus Placebo (N=81)	Placebo Plus Placebo (N=83)	Total (N=321)
No. of subjects	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]	n (%)[a]
Screened					690
Enrolled					336
Randomized (phase B)	82 (100)	75 (100)	81 (100)	83 (100)	321 (100)
Completed	58 (71)	50 (67)	59 (73)	64 (77)	231 (72)
Discontinued	24 (29)	25 (33)	22 (27)	19 (23)	90 (28)
Analyzed for efficacy[b]	79 (96)	72 (96)	77 (95)	80 (96)	308 (96)
Analyzed for safety[c]	80 (98)	75 (100)	79 (98)	82 (99)	316 (98)

Source: Modified from the Applicant's Study 00061 CSR Table 10.1-1.

[a] Percentages were based on the number of subjects in the randomized sample.

[b] Randomized and received at least one dose of double-blind trial medication and had a baseline and one postbaseline CAPS-5 total score were analyzed for efficacy.

[c] Randomized subjects who received at least one dose of double-blind IMP were analyzed for safety.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CSR, clinical study report; IMP, investigational medicinal product; PTSD, post-traumatic stress disorder

The most common reason for discontinuation was *Withdrawal by Subject*, followed by *Adverse Event*, which are common in clinical trials. All reasons for discontinuation were balanced between the treatment groups (data not shown).

The four treatment arms were balanced on all characteristics assessed (see Table 14); thus, the results are less likely to be biased by baseline imbalances in demographic or clinical confounders.

Primary Endpoint Analysis and Results

The efficacy analysis was performed on the ITT population, and participants were included in the treatment group as randomized. The ITT population used in this efficacy analysis also included participants who responded to placebo during the placebo run-in period (placebo responders), unlike

the population used for the primary efficacy analysis in Studies 00071 and 00072 (full analysis set [FAS] for enriched subjects).

For analyses of double-blind randomized Phase B data, the baseline was defined as the end of Phase A (Week 1) measurement. If the end of Phase A (Week 1) measurement was not available or not done, then the value from Baseline (Day 0) visit was used as baseline.

Changes from baseline in CAPS-5 total score were analyzed using a mixed model for repeated measures (MMRM) analysis with an unstructured variance covariance matrix. The model included fixed class-effect terms for treatment, pooled trial site, type of trauma (combat-related: *Yes* or *No*), visit week, and an interaction term of treatment by visit week and included the interaction term of baseline values of CAPS-5 total score by visit week as a covariate. All scheduled visits during double-blind treatment were included in the model, but the primary comparison was performed at the Week 10 Visit.

The protocol (addendum, version 1.0, dated September 29, 2016) proposed a hierarchical testing procedure in the order of:

1. Brexpiprazole plus sertraline versus placebo plus placebo.
2. Brexpiprazole plus placebo versus placebo plus placebo.
3. Brexpiprazole plus sertraline versus sertraline plus placebo.

In the addendum amendment #1 (dated June 8, 2017, protocol version 2.0), the Applicant indicated that additional test(s) might be added, and that the order of the tests may change; the final order of the hierarchical statistical testing procedure would be specified in the SAP. However, the SAP dated November 7, 2018, was submitted along with the EOP2 meeting package on March 13, 2019, after the study was completed and, therefore, was not reviewed by the Agency's statistical team. The SAP stated that "the hierarchical testing procedure that was planned in the protocol will not be performed due to the exploratory nature of the PoC (proof of concept) study." Consequently, the results of this study can only be interpreted at the nominal significance level, as no methods to control for multiplicity were ultimately employed.

Per the order proposed in the protocol addendum, the brexpiprazole plus sertraline group showed statistically significant superiority over placebo plus placebo (treatment effect −6.0; 95% confidence interval [CI] −9.79, −2.19). However, the second comparison (brexpiprazole plus placebo versus placebo plus placebo) did not reach statistical significance, thus halting the testing procedure. Had the testing procedure continued, the brexpiprazole plus sertraline group would have shown statistically significant superiority over sertraline plus placebo (treatment effect −5.1; 95% CI −8.96, −1.20).

It is important to note that p-values in Table 3 can only be interpreted at the nominal significance level due to the lack of multiplicity control.

Table 3. LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00061, ITT Population*

CAPS-5 Total Score	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)
n	77	69	75	78
Mean at baseline (SD)	35.7 (11.50)	33.9 (13.31)	36.5 (10.19)	35.1 (10.68)
LS Mean change from baseline at Week 10 (SE)	−16.4 (1.43)	−12.2 (1.57)	−11.4 (1.46)	−10.5 (1.40)
Treatment difference versus **placebo plus placebo** (95% CI)	−6.0 (−9.79, −2.19)	−1.74 (−5.70, 2.22)	−0.9 (−4.74, 2.92)	
Nominal p-value	0.0021	0.3868	0.6399	
Treatment difference brexpiprazole plus sertraline versus **sertraline plus placebo** (95% CI)	−5.1 (−8.96, −1.20)			
Nominal p-value	0.0106			
Treatment difference brexpiprazole plus sertraline versus **brexpiprazole plus placebo** (95% CI)	−4.2 (−8.26, −0.23)			
Nominal p-value	0.0384			

Source: Study 00061 CSR Table 11.4.1.1-1, verified by the statistical reviewer.

* Nine subjects in the ITT population were excluded from analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; CSR, clinical study report; ITT, intent-to-treat; LS, least squares; n, number of subjects included in the primary efficacy analysis in each treatment group; SD, standard deviation; SE, standard error

3.1.1.2 Study Description—Studies 00071 and 00072

The findings from Study 00061 informed the design of the subsequent two phase 3 studies. Based on these results, the Applicant determined that a brexpiprazole plus placebo arm would not be included in the phase 3 studies. Following discussions with the Agency during the EOP2 meeting, the Applicant also decided to omit a placebo arm, as the primary research question was to determine whether the combination of brexpiprazole and sertraline demonstrated greater efficacy than sertraline alone. The population criteria for the phase 3 studies were similar to those of Study 00061, reflecting a shift in the development objective from "adjunctive" to "combination" therapy. This change in terminology implies that evidence of an inadequate response to sertraline was not a prerequisite for study enrollment.

Studies 00071 and 00072 were phase 3, randomized, double-blind, multisite, controlled, 12-week trials, with the primary objective to evaluate efficacy of the combination of brexpiprazole plus sertraline compared to sertraline plus placebo in reducing PTSD symptoms as measured by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Sertraline is an approved treatment for PTSD (Zoloft, NDA 019839/S-026, Viatris Specialty LLC, December 7, 1999) at daily dosages of 50 to 200 mg.

3.1.1.2.1 Design of Studies 00071 and 00072

The two studies were identical except for the dosing design, Study 00071 being a flexible-dose study and Study 00072 a fixed-dose study. Specifically, Study 00071 had two arms: one flexible-dose arm of

brexpiprazole 2 to 3 mg combined with sertraline (fixed dose of 150 mg) and a fixed-dose sertraline arm of 150 mg plus placebo. Study 00072 had three arms: two fixed-dose arms of 2 mg and 3 mg brexpiprazole in combination with sertraline (fixed dose 150 mg) and a fixed-dose sertraline arm of 150 mg plus placebo.

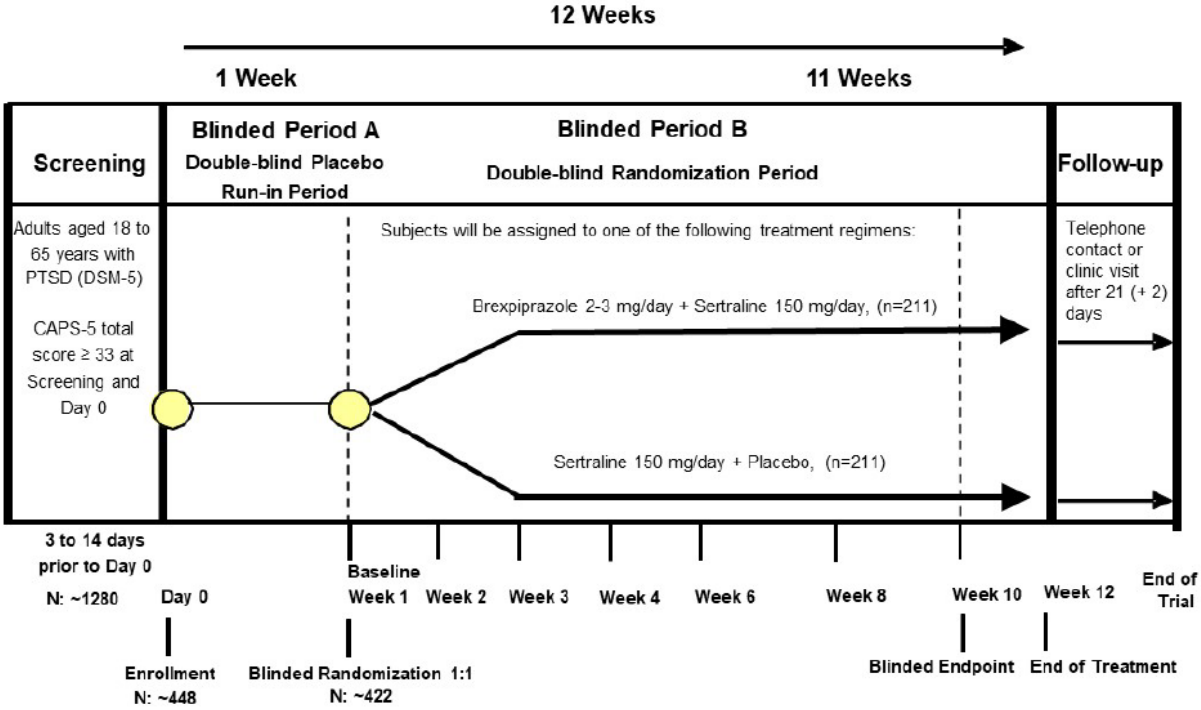
Both studies consisted of a 14-day screening period, a 12-week double-blind period, and a 21-day follow-up period. The 12-week double-blind period began with a 1-week double-blind placebo run-in period (Period A). The purpose of the placebo run-in period was to identify placebo responders. To identify placebo responders, the Applicant operationalized Enriched Subjects Criteria:

- CAPS-5 total score of at least 27 at the randomization visit (Week 1) AND
- Improvement (reduction) in CAPS-5 total score of less than 50% at the end of the placebo run-in period (from baseline [Day 0] to the randomization visit [Week 1]).

Following the placebo run-in period, subjects were randomized to the double-blind treatment (Period B) to one (Study 00071) or two dose (Study 00072) arms as per Figure 2 and Figure 3. Placebo responders were randomized and included in the study to maintain blinding and to collect additional safety data; however, they were excluded from the primary efficacy analysis. Randomization was stratified by site and whether a subject met the Enriched Subjects Criteria (placebo responders).

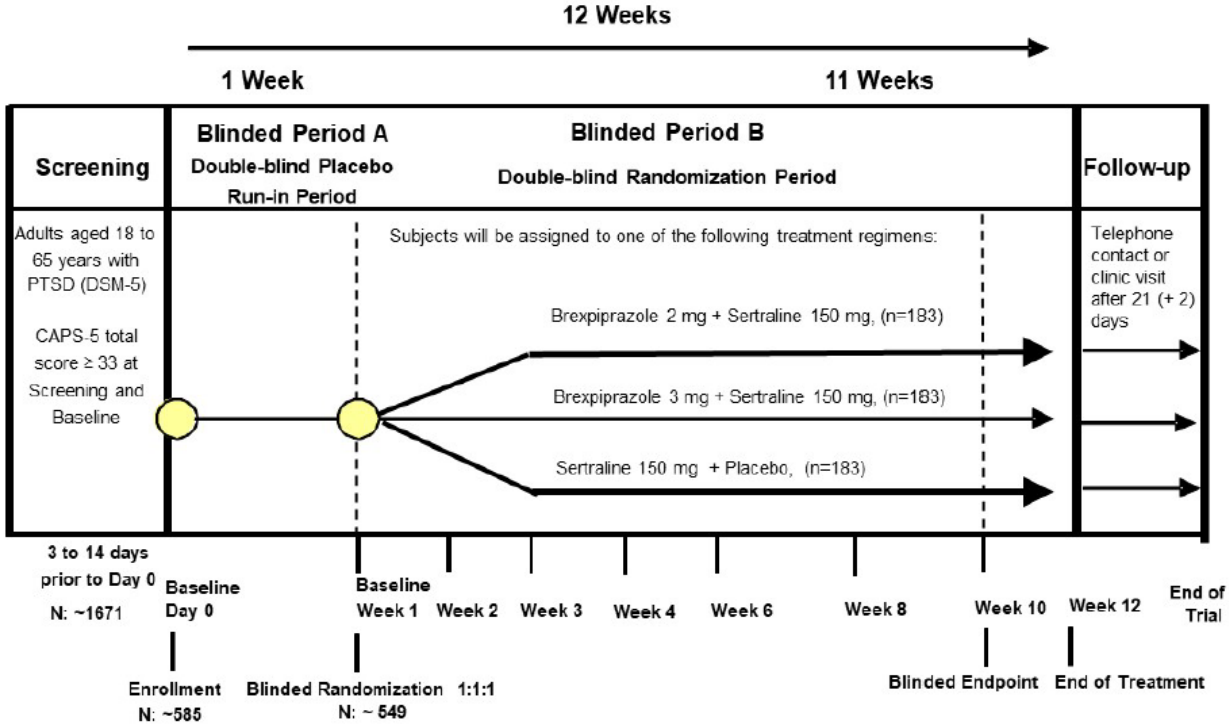
Site personnel were blinded to the placebo run-in period, the details of the timing of randomization, and the timing of the final efficacy assessments. To reduce expectation bias due to the absence of a true placebo arm, the actual list of treatment arms (active treatment arms only) was not disclosed in the trial protocol. The study designs for each study, as per protocol addendum, are shown in Figure 2 and Figure 3.

Figure 2. Study 00071 Unblinded Schema



Source: Applicant's Revised Clinical Protocol Addendum for Study 00071, Version 4.0, Amendment 3, dated January 4, 2023, Figure 3.1-1.
Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PTSD, post-traumatic stress disorder

Figure 3. Study 00072 Unblinded Schema



Source: Applicant's Revised Clinical Protocol Addendum for Study 00072, Version 4.0, Amendment 3, dated January 4, 2023, Figure 3.1-1.
Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PTSD, post-traumatic stress disorder

3.1.1.2.2 Dosages, Studies 00071 and 00072

In **Study 00071**, at Week 1, subjects assigned to brexpiprazole plus sertraline began dosing and had their dose increased up to the Week 3 visit in the following fixed forced titration sequence:

- Week 1: 0.5 mg/day brexpiprazole plus 50 mg/day sertraline.
- Week 2: 1 mg/day brexpiprazole plus 100 mg/day sertraline.
- Week 3: 2 mg/day brexpiprazole plus 150 mg/day sertraline.
- Week 4: The dosage could be maintained at 2 mg/day brexpiprazole plus 150 mg/day sertraline or further increased to 3 mg/day brexpiprazole plus 150 mg/day sertraline, based on the subject's efficacy and tolerability.

The brexpiprazole dose could be adjusted to optimize efficacy and safety/tolerability according to the following rules:

- No further dose increase was allowed after Week 4.
- Only a one-time dose decrease at scheduled or unscheduled visit for reasons of tolerability was allowed up to the Week 6 visit.
- Dose had to be maintained for the remainder of the treatment period after the Week 6 visit. If subjects were unable to maintain the Week 6 dose due to tolerability issues, the subject had to be withdrawn from the trial.

- After a dose reduction, subjects maintained the decreased dose for the remainder of the trial. All other subjects unable to tolerate their assigned dose were discontinued from the trial.
- The daily dose of sertraline remained fixed at 150 mg to avoid confounding by simultaneous titration of both drugs. This differs from Study 00061, where sertraline was administered at flexible doses from 100 mg to 200 mg.

In **Study 00072**, at Week 1, subjects were randomized in a 1:1:1 ratio to one of the following arms:

- Brexpiprazole 2 mg plus sertraline 150 mg.
- Brexpiprazole 3 mg plus sertraline 150 mg.
- Sertraline 150 mg plus placebo.

In the brexpiprazole 2 mg/day plus sertraline arm, the two drugs were titrated within the first 3 weeks of treatment using the fixed forced titration sequence described for Study 00071, whereas in the brexpiprazole 3 mg/day plus sertraline arm, there was an additional week of titration (total of 4 weeks of titration) to increase the brexpiprazole dose from 2 mg to 3 mg in Week 4. Subjects were assigned the Week 3 dose (or Week 4 dose, for combination brexpiprazole 3 mg plus sertraline) at all subsequent trial visits, through Week 12.

Brexpiprazole dose decreases were not permitted. If a subject was unable to maintain the dose due to tolerability issues, the subject had to be withdrawn from the trial.

As in Study 00071, and differently from Study 00061, the daily dose of sertraline remained fixed at 150 mg to avoid confounding by simultaneous titration of both drugs.

3.1.1.2.3 Population, Studies 00071 and 00072

The inclusion/exclusion criteria for the PTSD population were identical in Study 00071 and Study 00072.

The key inclusion criteria were:

- Male and female outpatients 18 to 65 years of age, inclusive, at the time of informed consent.
- PTSD diagnosed according to DSM-5, and confirmed by the MINI.
- CAPS-5 total score ≥33 at the screening and baseline visits (Day 0).
- Onset of PTSD symptoms for a minimum of 6 months prior to screening.
- Subjects willing to discontinue all prohibited medications to meet protocol-required washouts prior to and during the study period.

The key exclusion criteria were:

- Index traumatic event that led to development of PTSD took place >9 years before screening.
- Index traumatic event occurred before age 16 years.
- Subjects who have experienced a traumatic event within 3 months of screening.
- Subjects who meet the DSM-5 criteria for a current major depressive episode (i.e., currently symptomatic).
- Currently receiving sertraline with an adequate dose and duration (>50 mg/day for ≥8 weeks).
- Subjects 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.

- Subjects 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; subjects 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.
- Subjects who have a positive urine drug screen that could interfere with the interpretation of trial results.
- Subjects who have a history of moderate or severe head trauma as assessed by the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) 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 subject safety, in the investigator's opinion.
- Subjects 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 subjects with any suicidal behavior during the last year prior to the screening visit.
- Subjects with hypothyroidism or hyperthyroidism.
- Subjects 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, human immunodeficiency virus (HIV) seropositive status/acquired immunodeficiency syndrome, chronic hepatitis B or C or bariatric surgeries that may cause malabsorption.
- Subjects with diabetes mellitus, uncontrolled hypertension, with epilepsy or a history of seizures, and subjects with abnormal laboratory tests results, vital signs results, or electrocardiogram (ECG) findings.
- Subjects who received brexpiprazole in any prior clinical trial or subjects who have taken or are currently taking commercially available brexpiprazole (Rexulti).

As noted before, these studies enrolled participants willing to discontinue current antidepressants and excluded those on adequate sertraline doses, reflecting a shift from developing brexpiprazole as an adjunctive treatment to a combination therapy for PTSD. This change in approach meant that evidence of inadequate response to sertraline was not required for enrollment, deviating from typical adjunctive treatment study designs that focus on patients who have not benefited adequately from approved monotherapy.

Participants with a current major depressive episode were excluded from the studies to prevent confounding the treatment effect with improvements in depressive symptoms. This was an important consideration given that brexpiprazole is already approved as an adjunctive therapy to antidepressants for treating MDD in adults.

Prohibited Medications

The studies excluded all psychotropic agents (antipsychotic agents, anticonvulsants, antidepressants, mood stabilizers, benzodiazepines, hypnotics, opioid analgesics, and disulfiram, controlled stimulants, barbiturates), nutritional supplements and non-prescription herbal preparations with central nervous system effects, CYP2D6 inhibitors or CYP3A4 inhibitors and inducers, and any central nervous system-active drug that could have confounded the results. Benzodiazepines were allowed as needed when used to manage adverse events such as agitation and anxiety.

The protocols did not exclude drugs that may be associated with hypotension and dizziness and that are commonly used in PTSD, such as anti-adrenergic drugs (e.g., prazosin and propranolol; prazosin was allowed if used for an appropriate indication at a stable dose for at least 14 days prior to baseline visit) or drugs such as gabapentin. Inclusion of these drugs in the trials resembles clinical practice and allowed for the identification of potential drug-drug interactions of clinical significance.

3.1.1.2.4 Efficacy Assessment, Studies 00071 and 00072

The primary efficacy endpoint, consistent with Study 00061, was the change in the CAPS-5 total score from baseline (Week 1) to the end of the efficacy period (Week 10). Also similar to Study 00061, the protocols blinded the primary endpoint by decoupling the timing of the primary analysis from the duration of the studies; indeed, the total study duration was 12 weeks, but site personnel were blinded to the timing of the assessment of the primary endpoint, which occurred at Week 10.

For a description of CAPS-5, refer to Study 00061, Section 3.1.1.1.4.

The key secondary endpoints for which type I error was controlled were:

- CGI-S score from baseline (Week 1) to the end of the efficacy period (Week 10)
- Change of the Brief Inventory of Psychosocial Function (B-IPF) score from baseline (Week 1) to the end of the blind period (Week 12)

For a description of the CGI-S, refer to Section 3.1.1.1.4.

The B-IPF is a patient-reported outcome measure that evaluates PTSD-related psychosocial functional impairment on a 7-point Likert scale (0, not at all to 6, very much, and a not applicable option) within the last 30 days across seven functional domains (romantic relationships, family relationships, work, friendships and socializing, parenting, education, and self-care). Upon review of available quantitative and qualitative evidence, the Agency concluded that the B-IPF is not a fit-for-purpose measure of treatment benefit in the assessment of psychosocial functional impairment in PTSD. The discussion on fitness for purpose of secondary endpoints is outside the scope of this AC meeting; for completeness, the Agency presents the results of B-IPF secondary efficacy analyses in this section of the Briefing Document.

Efficacy assessments were performed at the following visits:

- CAPS-5—Weeks 1, 3, 4, 6, 10, 12
- CGI-S—Weeks 1, 2, 3, 4, 6, 8, 10, 12
- B-IPF—Weeks 0, 8, 12

3.1.1.2.5 Efficacy Results Study 331-201-00071

Populations and Baseline Characteristics

In Study 00071, analysis populations were defined as follows:

- **Enrolled sample**—all subjects enrolled in placebo run-in period.
- **Randomized sample**—all subjects randomized into this trial.
- **Enriched randomized sample**—all subjects who were randomized satisfying the Enriched Subjects Criteria, defined as 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) in CAPS-5 total score of less than 50% at end of the placebo run-in phase (from baseline [Day 0] to randomization visit [Week 1]).
- **Full analysis set (FAS)**—all subjects in the randomized sample who took at least one dose of double-blind IMP and have a baseline value (Week 1) and at least one postbaseline evaluation of the CAPS-5 total score.
- **FAS for enriched subjects**—all subjects in the enriched randomized sample who received at least one dose of double-blind IMP, have a baseline value (Week 1) and at least one postbaseline efficacy evaluation for CAPS-5 total score. This is the primary efficacy analysis population.

As shown in Table 4, at the end of the 1-week placebo run-in period (Period A), a total of 416 subjects were randomized in Period B (214 subjects to the brexpiprazole plus sertraline group, and 202 to sertraline plus placebo), at 78 sites, all within the United States. The proportion of subjects who discontinued from Period B is high in both treatment arms, with a higher rate of discontinuation in the sertraline plus placebo group (44%) than in the brexpiprazole plus sertraline group (36%). In the enriched randomized sample, the proportion of subjects who discontinued is also high in both treatment arms, and again higher in the sertraline plus placebo group (33%) than the brexpiprazole plus sertraline group (28%). The primary efficacy analysis population (i.e., FAS for enriched subjects) included 149 subjects in the brexpiprazole plus sertraline group and 137 in the sertraline plus placebo group.

Table 4. Subject Disposition, Study 00071

Parameter	Brexpiprazole Plus Sertraline (N=214) n (%)[a]	Sertraline Plus Placebo (N=202) n (%)[a]	Total (N=416) n (%)[a]
Participants screened			1327
Screening failures			875
Period A			450[b]
Treated			433
Treated and discontinued			21
Not treated and discontinued			13
Period B randomized	214 (100)	202 (100)	416 (100)
Treated	205 (96)	196 (97)	401 (96)
Completed[c]	137 (64)	113 (56)	250 (60)
Discontinued	77 (36)	89 (44)	166 (40)

Parameter	Brexpiprazole Plus Sertraline (N=214) n (%)[a]	Sertraline Plus Placebo (N=202) n (%)[a]	Total (N=416) n (%)[a]
Enriched randomized[d]	160 (75)	150 (74)	310 (75)
Treated	155 (72)	146 (72)	301 (72)
Completed[c]	101 (47)	84 (42)	185 (44)
Discontinued	59 (28)	66 (33)	125 (30)
Analyzed for efficacy[e]	149 (70)	137 (68)	286 (69)
Analyzed for safety[f]	205 (96)	196 (97)	401 (96)

Source: Modified from Applicant's CSR for Study 00071 Table 10.1-1.

Period A, double-blind placebo run-in period; Period B, double-blind randomization period.

[a] Percentages are based on the number of randomized subjects.

[b] This number includes the following four subjects who were not treated during Period A: three subjects (due to site closure) and one subject was enrolled twice (i.e., second subject identity was not treated).

[c] Subjects completed Week 12 visit.

[d] Randomized subjects satisfying the criteria at randomization (Week 1) with CAPS-5 total score ≥27, and total score is <50% at end of the placebo run-in period (from Day 0 to randomization visit [Week 1]).

[e] Randomized and received at least one dose of study medication and had a Week 1 and one postbaseline CAPS-5 total score.

[f] Subjects receiving at least one dose of study medication are included in the safety analysis.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CSR, clinical study report; PTSD, post-traumatic stress disorder

For the FAS for enriched subjects, the overall discontinuation rate was higher in the sertraline plus placebo group (39%) compared to the brexpiprazole plus sertraline group (32%), possibly driven by lower discontinuations due to adverse events in the brexpiprazole plus sertraline group (4%) compared to sertraline plus placebo group (12%). Discontinuations due to protocol deviation were more commonly observed in the brexpiprazole plus sertraline group, although the percentage was low in both groups (5% versus 2%). All other reasons for discontinuation were balanced between the treatment groups (data not shown).

Overall, the baseline demographics and disease characteristics were balanced between participants who received brexpiprazole plus sertraline and participants who received sertraline plus placebo. A slightly higher number of participants in the brexpiprazole plus sertraline group had received SSRIs, including sertraline, and psychotherapy for PTSD in the past than in the sertraline group (SSRI 16% in the brexpiprazole plus sertraline group versus 14% in the sertraline plus placebo group, with 8% versus 6% on sertraline in the past; psychotherapy 40% versus 29%), but the difference was minimal and unlikely to have affected the results. Overall, baseline demographic, disease, and clinical characteristics were balanced between the treatment groups (see Table 15).

Like Study 00061, Study 00071 was conducted entirely in the United States, though had a larger proportion of female participants and had more White participants. However, the racial and ethnic composition of the two treatment groups was similar, making it unlikely that sociodemographic factors influenced the study results.

Primary Endpoint Analysis and Results

For analysis of Period B data, baseline is defined as the last available measurement prior to the first dose of double-blind IMP, scheduled at the Week 1 visit.

The primary efficacy analysis was performed by fitting a MMRM analysis with an unstructured variance covariance matrix in which the change from baseline in CAPS-5 total score during the double-blind

treatment phase was the dependent variable based on the observed cases (OC) data set. The OC data set consists of actual observations recorded at each visit during the double-blind treatment period and no missing data were imputed. The model included fixed class effect terms for treatment, pooled trial site, visit, previous pharmacological treatment intervention for PTSD (*Yes* or *No*), and an interaction term of treatment by visit, and an interaction term of baseline CAPS-5 total score by visit. The model included all visits with scheduled CAPS-5 evaluation after baseline during Period B (i.e., Weeks 3, 4, 6, 10 and 12). However, the primary comparison was performed at the Week 10 Visit.

As shown in Table 5, the estimated least squares mean change from baseline to Week 10 in the CAPS-5 total score was −19.2 (standard error [SE] 1.17) in the combination group and −13.6 (SE 1.24) in the sertraline group. For the primary efficacy endpoint, the difference between brexpiprazole plus sertraline versus sertraline plus placebo was statistically significant (i.e., treatment difference −5.6; 95% CI −8.79, −2.38; p=0.0007).

Table 5. LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00071, FAS for Enriched Subjects*

CAPS-5 Total Score	Brexpiprazole Plus Sertraline (N=149)	Sertraline Plus Placebo (N=137)
n	148	134
Mean at baseline (SD)	38.4 (7.18)	38.7 (7.75)
LS Mean change from baseline at Week 10 (SE)	−19.2 (1.17)	−13.6 (1.24)
Treatment difference (95% CI)	−5.6 (−8.79, −2.38)	
P-Value	0.0007	

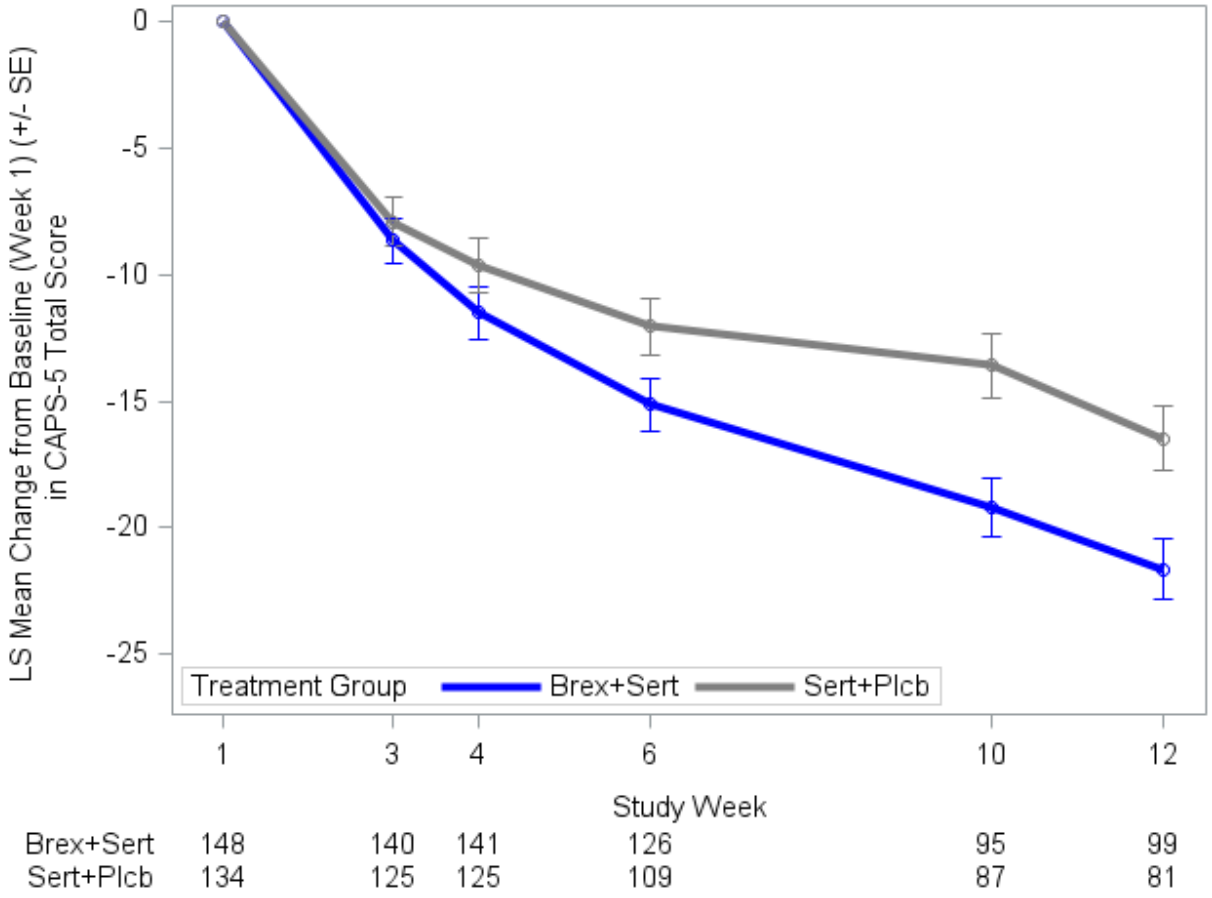
Source: Study 00071 Clinical Study Report CT-5.2.1.1, confirmed by the Statistical Reviewer.

* Four subjects in the FAS for Enriched Subjects were excluded from analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the primary efficacy analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Figure 4 displays the estimated least squares mean changes by treatment group from baseline (Week 1) in CAPS-5 total score throughout Period B (Week 1 to Week 12).

Figure 4. LS Mean Change From Baseline (Week 1) Trajectories in CAPS-5 Total Score, Study 00071, FAS for Enriched Subjects*



Source: Statistical Reviewer.

*Four subjects in the FAS for enriched subjects were excluded from analysis because of no valid postbaseline CAPS-5 measures.

Table shows the number of subjects included in the primary efficacy analysis at each study week, for each treatment group.

Abbreviations: Brex, brexpiprazole; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FAS, full analysis set; LS, least squares; Plcb, placebo; PTSD, post-traumatic stress disorder; SE, standard error; Sert, sertraline

Key Secondary Endpoint Analysis and Results

Both key secondary endpoints (change from Week 1 to Week 10 in CGI-S and change from Week 1 to Week 12 in B-IPF) were analyzed using an MMRM model similar to that prespecified for the primary

efficacy endpoint, correcting for the relevant values at randomization. The key secondary efficacy endpoints were tested at the same significance level as the primary endpoint.

To control the overall type I error when testing for both the primary efficacy endpoint and the key secondary efficacy endpoints, a stepwise hierarchical testing procedure was applied. The statistical testing was performed in the following order:

1. Primary efficacy endpoint for the comparison of brexpiprazole plus sertraline versus sertraline plus placebo based on the FAS for enriched subjects.
2. The first key secondary endpoint of the change from baseline (Week 1) to Week 10 in the CGI-S score for the comparison of brexpiprazole plus sertraline versus sertraline plus placebo based on the FAS for enriched subjects.
3. The second key secondary endpoint of the change from baseline (Week 1) to Week 12 in B-IPF score for the comparison of brexpiprazole plus sertraline versus sertraline plus placebo based on the FAS for enriched subjects.

As shown in Table 6, for the key secondary endpoint CGI-S, the brexpiprazole plus sertraline group is statistically superior to the sertraline plus placebo group (treatment difference −0.5 [95% CI −0.76, 0.17], p=0.0019).

Table 6. LS Mean Change From Baseline (Week 1) to Week 10 in CGI-S Score, Study 00071, FAS for Enriched Subjects*

CGI-S Score	Brexpiprazole Plus Sertraline (N=149)	Sertraline Plus Placebo (N=137)
n	148	137
Mean at baseline (SD)	4.6 (0.61)	4.6 (0.62)
LS Mean change from baseline at Week 10 (SE)	−1.5 (0.10)	−1.1 (0.11)
Treatment difference (95% CI)	−0.5 (−0.76, −0.17)	
P-Value	0.0019	

Source: Study 00071 Clinical Study Report Table CT-5.4.1.1, confirmed by the Statistical Reviewer.

* One subject in the FAS for enriched subjects were excluded from analysis because of no scheduled postbaseline CGI-S measures.

Abbreviations: CI, confidence interval; CGI-S, Clinical Global Impression Severity of Illness; FAS, full analysis set; LS, least squares; n, number of subjects included in the analysis in each treatment group; SE, standard error

As noted above (Section 3.1.1.2.4), after reviewing the available quantitative and qualitative evidence, the Agency concluded that the B-IPF is not a fit-for-purpose measure of treatment benefit in the assessment of psychosocial functional impairment in PTSD. The discussion on fitness for purpose of secondary endpoints is outside the scope of this AC meeting. However, for completeness of data presentation, the results for the B-IPF are reported in Table 7. The results favor the brexpiprazole plus sertraline group.

Table 7. LS Mean Change From Baseline (Week 1) to Week 12 in B-IPF Total Score, Study 00071, FAS for Enriched Subjects*

B-IPF Total Score	Brexpiprazole Plus Sertraline (N=149)	Sertraline Plus Placebo (N=137)
n	104	97
Mean at baseline (SD)	64.8 (21.21)	63.5 (23.24)
LS Mean change from baseline at Week 10 (SE)	−33.8 (2.84)	−21.8 (2.97)
Treatment difference (95% CI)	−12.0 (−19.44, −4.62)	
P-Value	0.0016	

Source: Study 00071 Clinical Study Report Table CT-5.5.1.1, confirmed by the Statistical Reviewer.

* Eighty-five subjects in the FAS for enriched subjects were excluded from analysis because of no scheduled postbaseline B-IPF measures.

Abbreviations: B-IPF, Brief Inventory of Psychosocial Function; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the analysis in each treatment group; SD, standard deviation; SE, standard error

3.1.1.2.6 Efficacy Results, Study 331-201-00072

Populations and Baseline Characteristics

The definition of the analysis populations for Study 00072 is identical to Study 00071.

The primary efficacy analysis population is the FAS for enriched subjects, i.e., all subjects in the enriched randomized sample (Enriched Subjects Criteria defined as a CAPS-5 total score of at least 27 at the randomization visit, and an improvement in CAPS-5 total score of less than 50% at end of the placebo run-in phase) who received at least one dose of double-blind IMP, have a baseline value (Week 1) and at least one post baseline efficacy evaluation for CAPS-5 total score.

As listed in Table 8, at the end of the 1-week placebo run-in period (Period A), a total of 553 subjects were randomized to Period B (191 to the brexpiprazole 2 mg plus sertraline, 185 subjects to brexpiprazole 3 mg plus sertraline and 177 to sertraline plus placebo), at 95 sites, all within the United States. The proportion of subjects who discontinued from Period B is high (34%) but balanced across treatment arms. In the enriched randomized sample, the proportion of subjects who discontinued is also high (26%), but similarly balanced among arms (27% in the brexpiprazole 2 mg plus sertraline group, 24% in the brexpiprazole 3 mg plus sertraline group, and 27% in the sertraline plus placebo group). The primary efficacy analysis population (i.e., FAS for enriched subjects) included 132 subjects in the brexpiprazole 2 mg plus sertraline group, 126 subjects in the brexpiprazole 3 mg plus sertraline group, and 130 subjects in the sertraline plus placebo group.

Table 8. Subject Disposition, Study 00072

Number of Subjects	Brexpiprazole 2 mg Plus Sertraline (N=191) n (%)[a]	Brexpiprazole 3 mg Plus Sertraline (N=185) n (%)[a]	Sertraline Plus Placebo (N=177) n (%)[a]	Total (N=553) n (%)[a]
Screened				1821
Screen failure				1230
Period A				591[b]
Treated				568
Treated and discontinued				18
Not treated and discontinued				20

Number of Subjects	Brexpiprazole 2 mg Plus Sertraline (N=191) n (%)[a]	Brexpiprazole 3 mg Plus Sertraline (N=185) n (%)[a]	Sertraline Plus Placebo (N=177) n (%)[a]	Total (N=553) n (%)[a]
Period B randomized sample	191 (100)	185 (100)	177 (100)	553[b] (100)
Treated	185 (97)	180 (97)	172 (97)	537 (97)
Completed[c]	126 (66)	123 (66)	116 (66)	365 (66)
Discontinued	65 (34)	62 (34)	61 (34)	188 (34)
Analyzed for efficacy[d]	177 (93)	167 (90)	165 (93)	509 (92)
Enriched randomized sample[e]	143 (75)	136 (74)	138 (78)	417 (75)
Treated	139 (73)	132 (71)	135 (76)	406 (73)
Completed[c]	92 (48)	91 (49)	91 (51)	274 (50)
Discontinued	51 (27)	45 (24)	47 (27)	143 (26)
Analyzed for efficacy[e]	132 (69)	126 (68)	130 (73)	388 (70)
Analyzed for safety[f]	185 (97)	180 (97)	172 (97)	537 (97)

Source: Modified from the Applicant's Clinical Study Report for Study 00072, Table 10.1-1.
Period A, double-blind placebo run-in period; Period B, double-blind randomization period.
Analyzed for efficacy under Period B randomized represents the full analysis set; Analyzed for efficacy under enriched randomized represents the full analysis set for enriched subjects.
[a] Percentages are based on the number of randomized subjects.
[b] This number includes three subjects who were not treated during Period A and randomized at the Week 1 visit.
[c] Subjects completed Week 12 visit.
[d] Randomized and received at least one dose of study medication and had a baseline (Week 1) and one postbaseline CAPS-5 total score.
[e] Randomized subjects satisfying the criteria at randomization (Week 1) with CAPS-5 total score ≥27, and total score is less than 50% at end of the placebo run-in period (from Day 0 to Randomization visit [Week 1]).
[f] Subjects receiving at least one dose of study medication are included in the safety analysis.
Abbreviation: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PTSD, post-traumatic stress disorder

For the FAS for enriched subjects (the primary efficacy analysis population), the overall discontinuation rates were very similar across all arms. The most common discontinuation reasons are lost to follow-up and withdrawal by subjects (data not shown).

Overall, the baseline demographics and disease characteristics were balanced between subjects who received brexpiprazole 2 mg plus sertraline, subjects who received brexpiprazole 3 mg plus sertraline, and those who received sertraline plus placebo. Study 00072 had a slightly higher percentage of subjects with Hispanic or Latino ethnicity than Study 00071 (24% versus 13%) and a lower percentage of subjects with previous pharmacological treatment for PTSD (20% versus 28%). However, the differences in these variables were minimal and unlikely to have influenced the results. Nonetheless, subgroup analyses based on ethnicity were explored for Study 00072 to rule out any effect of ethnicity (subgroup analyses in Section 4.3.3, Study 00072). In addition, the primary efficacy analysis model incorporated previous pharmacological treatment for PTSD (*Yes* or *No*) as a fixed class effect term, consistent with Study 00071. This inclusion ensured that the efficacy analysis was controlled for this variable. All other baseline demographics and disease characteristics were similar between the two phase 3 studies (see Table 16).

Studies 00061, 00071, and 00072 were conducted entirely in the United States. These studies consistently had a larger proportion of female subjects and a predominance of White subjects.

Primary Endpoint Analysis and Results

Similar to Study 00071, the primary efficacy analysis was performed by fitting a MMRM analysis with an unstructured variance covariance matrix in which the change from baseline in CAPS-5 total score during the double-blind treatment phase was the dependent variable. The model was the same as the one used in Study 00071, i.e., included fixed class effect terms for treatment, pooled trial site, visit, previous pharmacological treatment intervention for PTSD (*Yes* or *No*), and an interaction term of treatment by visit, an interaction term of baseline values of CAPS-5 total score by visit. All visits with scheduled CAPS-5 evaluation after baseline during Period B (i.e., Weeks 3, 4, 6, 10 and 12) were included in the model, but the primary comparison was performed at the Week 10 visit.

To control the overall Type I error for multiple doses compared with the control, a global test was first conducted by comparing the average effect of the two combination therapies (i.e., average of (a) brexpiprazole 2 mg plus sertraline and (b) brexpiprazole 3 mg plus sertraline) with the sertraline plus placebo. If the global test was statistically significant, each combination therapy was then compared with the sertraline plus placebo.

As shown in Table 9, based on the global test, the difference between the average effect of the two combination therapies versus the sertraline plus placebo was not statistically significant (i.e., treatment difference 0.2; 95% CI −2.56, 2.88; p=0.9073). Additionally, the subsequent pairwise comparisons were not nominally significant. The estimated least-squares mean change from baseline to Week 10 in CAPS-5 total score was −16.5 (SE 1.19) in the brexpiprazole 2 mg plus sertraline group; −18.3 (SE 1.23) in the brexpiprazole 3 mg plus sertraline group and −17.4 (SE 1.19) in the sertraline plus placebo group.

Table 9. LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS for Enriched Subjects*

CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Average (Brexpiprazole 2 mg Plus Sertraline and Brexpiprazole 3 mg Plus Sertraline)	Sertraline Plus Placebo (N=130)
n	132	124		130
Mean at baseline (SD)	38.8 (8.26)	37.9 (7.38)		39.3 (7.75)
LS mean change from baseline at Week 10 (SE)	−16.5 (1.19)	−18.3 (1.23)		−17.6 (1.19)
Treatment difference versus sertraline plus placebo (95% CI)	1.0 (−2.09, 4.16)	−0.7 (−3.88, 2.46)	0.2 (−2.56, 2.88)	
P-value	0.5165	0.6593	0.9073	

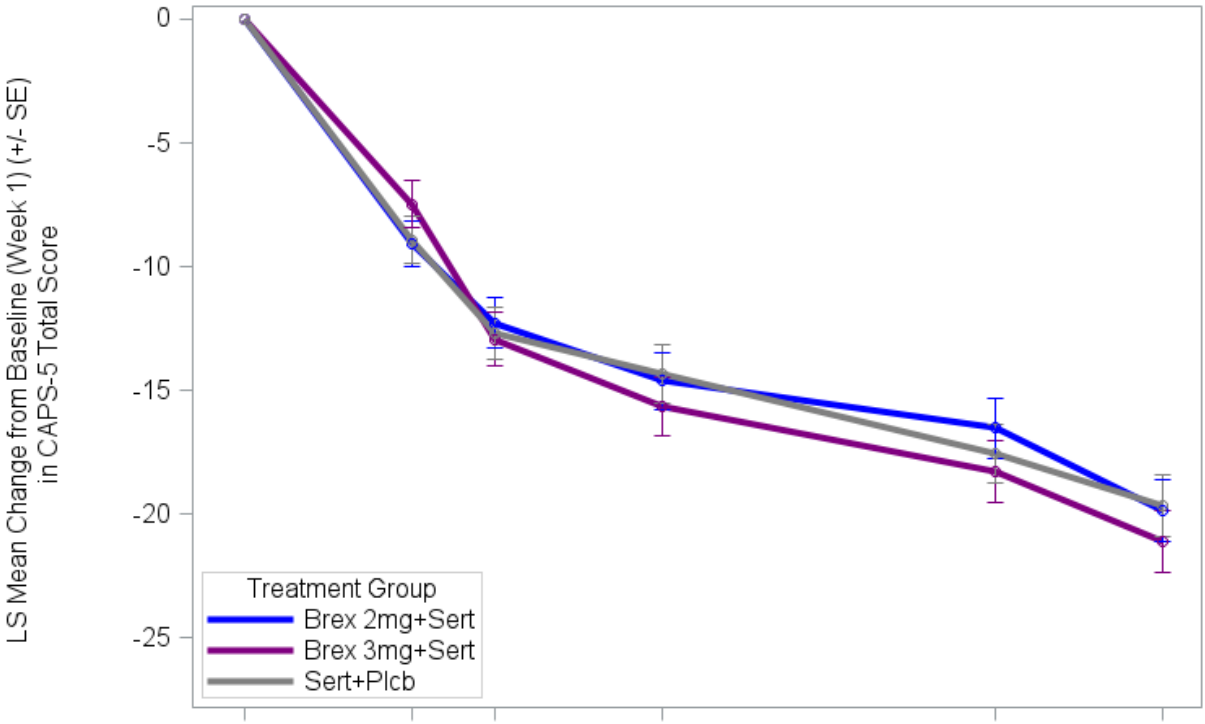
Source: Study 00072 Clinical Study Report Table CT-5.1.1, confirmed by the Statistical Reviewer.

* Two subjects in the FAS for enriched subjects were excluded from analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the primary efficacy analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Figure 5 displays the estimated least-squares mean changes by treatment group from baseline (Week 1) in CAPS-5 total score throughout Period B (Week 1 to Week 12).

Figure 5. LS Mean Change From Baseline (Week 1) Trajectories in CAPS-5 Total Score, Study 00072, FAS for Enriched Subjects*



Brex 2mg+Sert	132	124	123	115	90	86
Brex 3mg+Sert	124	115	120	109	86	81
Sert+Plcb	130	121	120	105	96	84

Source: Statistical Reviewer.

* Two subjects in the FAS for enriched subjects were excluded from analysis because of no valid postbaseline CAPS-5 measures. Table shows the number of subjects included in the primary efficacy analysis at each study week, for each treatment group.

Abbreviations: Brex, brexpiprazole; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FAS, full analysis set; LS, least squares; Plcb, placebo; PTSD, post-traumatic stress disorder; SE, standard error; Sert, sertraline

Key Secondary Endpoint Analysis and Results

To control the overall type I error when testing for both the primary efficacy endpoint and the key secondary efficacy endpoints, the same stepwise hierarchical testing procedure as in Study 00071 was applied, but for each efficacy endpoint a global test was first conducted before proceeding to the pairwise comparisons because there are two combination therapy groups.

For the key secondary endpoint change from Week 1 to Week 10 at the CGI-S, the average effect of the two combination therapies did not statistically differ from the sertraline plus placebo group (p=0.9795) (Table 10). Neither the subsequent pairwise comparisons were nominally significant.

Table 10. LS Mean Change From Baseline (Week 1) to Week 10 in CGI-S Score, Study 00072, FAS for Enriched Subjects*

CGI-S Score	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Average (Brexpiprazole 2 mg Plus Sertraline and Brexpiprazole 3 mg Plus Sertraline)	Sertraline Plus Placebo (N=130)
n	132	124		129
Mean at baseline (SD)	4.6 (0.67)	4.6 (0.67)		4.7 (0.69)
LS mean change from baseline at Week 10 (SE)	−1.3 (0.10)	−1.3 (0.11)		−1.3 (0.10)
Treatment difference versus sertraline plus placebo (95% CI)	0.03 (−0.25, 0.31)	−0.03 (−0.31, 0.26)	0.00 (−0.24, 0.25)	
P-value	0.8215	0.8584	0.9795	

Source: Study 00072 Clinical Study Report Table CT-5.4.1.1, confirmed by the Statistical Reviewer.

* Three subjects in the FAS for enriched subjects were excluded from analysis because of no valid postbaseline CGI-S measures.

Abbreviations: CGI-S, Clinical Global Impression - Severity; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the primary efficacy analysis in each treatment group; SD, standard deviation; SE, standard error

The results for the B-IPF are reported in Table 11. Nominally, the brexpiprazole 3 mg plus sertraline group, as well as the average of the two combination groups showed a statistical significance over the sertraline plus placebo group. However, as previously explained (Section 3.1.1.2.4, Efficacy Assessment for Studies 00071 and 00072), B-IPF was deemed not a fit-for-purpose measure of treatment benefit in the assessment of psychosocial functional impairment in PTSD.

Table 11. LS Mean Change From Baseline (Week 1) to Week 12 in B-IPF Total Score, Study 00072, FAS for Enriched Subjects*

B-IPF Total Score	Brexpiprazole 2 mg plus sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Average (Brexpiprazole 2 mg Plus Sertraline and Brexpiprazole 3 mg Plus Sertraline)	Sertraline Plus Placebo (N=130)
n	98	94		96
Mean at baseline (SD)	62.2 (19.03)	63.1 (21.53)		59.7 (20.96)
LS mean change from baseline at Week 10 (SE)	−27.1 (2.67)	−31.8 (2.86)		−23.0 (2.71)
Treatment difference (95% CI)	−4.2 (−11.00, 2.69)	−8.8 (−15.82, −1.85)	−6.5 (−12.47, −0.52)	
P-value	0.2331	0.0134	0.0332	

Source: Study 00072 Clinical Study Report Table CT-5.5.1.1, confirmed by the Statistical Reviewer.

* One-hundred subjects in the FAS for enriched subjects were excluded from the analysis because of no valid postbaseline B-IPF measures.

Abbreviations: B-IPF, Brief Inventory of Psychosocial Function; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the primary efficacy analysis in each treatment group; SD, standard deviation; SE, standard error

Discussion of the Phase 3 Studies

Studies 00071 and 00072 produced inconsistent outcomes despite similarities in design and population definition.

The demographic and clinical characteristics of the study populations were comparable, with approximately 75% female subjects and 70% White subjects in both studies. Study 00072 had a slightly higher percentage of Hispanic subjects (approximately 25%) compared to Study 00071 (approximately 15%). The distribution of traumatic event types was similar across both study populations, with an average of four years since the index trauma. Baseline PTSD severity, as measured by CAPS-5 and CGI-S, was comparable between studies. Study 00071 enrolled a marginally higher proportion of subjects with prior PTSD pharmacologic or nonpharmacologic prescription. For a comprehensive list of baseline demographics and clinical characteristics, refer to Table 15 and Table 16.

Additionally, plasma concentration ranges for brexpiprazole and sertraline were comparable between Studies 00071 and 00072.

Due to the lack of statistically significant difference in treatment response between brexpiprazole plus sertraline groups and sertraline plus placebo group in Study 00072, the review team conducted post hoc exploratory analyses to investigate potential subgroup differences in response.

Post hoc subgroup analyses by sex, ethnicity, prior PTSD treatment, and baseline severity revealed no nominal difference between the brexpiprazole plus sertraline groups and sertraline plus placebo in CAPS-5 total score change from baseline (Week 1) to Week 10, for the FAS for enriched subjects (primary efficacy population).

The same subgroup analyses conducted on the FAS, which included all randomized subjects including placebo responders, revealed a trend favoring the combination of brexpiprazole 3 mg and sertraline in the female subgroup of Study 00072. Additionally, in the FAS population, subjects without prior pharmacological intervention who received brexpiprazole 3 mg plus sertraline exhibited nominally significant superiority over sertraline plus placebo on the primary endpoint. Furthermore, in the FAS sample, participants of non-Hispanic or Latino ethnicity in the brexpiprazole 3 mg plus sertraline group exhibited nominally significant superiority over sertraline on the CAPS-5 total score.

The review team also analyzed CAPS-5 response based on baseline severity in Studies 00071 and 00072, categorizing the FAS for enriched sample population into three subgroups of increasing severity based on baseline CAPS-5 total score: 27 to 32, 33 to 42, and ≥43. In Study 00072, no difference was observed between the brexpiprazole plus sertraline group and sertraline plus placebo group across these baseline CAPS severity subgroups (see Table 27). This finding contrasts with results from Study 00071, where a larger treatment effect was noted in the highest severity subgroup.

The review team also analyzed CAPS-5 response based on baseline severity in Studies 00071 and 00072, categorizing the FAS for enriched sample population into three subgroups of increasing severity based on baseline CAPS-5 total score: 27 to 32, 33 to 42, and ≥43. In Study 00072, no difference was observed between the brexpiprazole plus sertraline group and sertraline plus placebo group across these baseline CAPS severity subgroups (see Table 27). This finding contrasts with results from Study 00071, where a larger treatment effect was noted in the highest severity subgroup.For a comprehensive list of post hoc exploratory analyses, please refer to the Appendix.

3.1.2 Efficacy Summary

The Applicant has completed two randomized, double-blind, placebo-controlled phase 3 clinical trials investigating the efficacy of brexpiprazole initiated concurrently with sertraline for the treatment of PTSD compared to sertraline alone.

The studies used the change from baseline to Week 10 at the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score as the primary endpoint.

Study 00071, which used a flexible-dosing strategy, demonstrated statistically significant improvements in PTSD symptoms with the brexpiprazole plus sertraline group compared to sertraline plus placebo group. The primary efficacy endpoint showed a treatment difference of −5.6 in CAPS-5 total score (p=0.0007), favoring the brexpiprazole plus sertraline group. Additionally, the key secondary endpoint measuring changes in the CGI-S scale also showed a statistically significant improvement for the brexpiprazole 3 mg plus sertraline group.

In contrast, Study 00072, which employed fixed doses of brexpiprazole (2 mg and 3 mg), did not show statistically significant differences between either of the brexpiprazole plus sertraline groups and sertraline plus placebo for the primary efficacy endpoint or the key secondary endpoint. The difference in CAPS-5 total score between the average effect of the brexpiprazole plus sertraline groups and sertraline plus placebo was not significant (p=0.9073). The review team conducted several post hoc exploratory analyses and could not find a subpopulation who responded to brexpiprazole plus sertraline better than to sertraline plus placebo in the primary efficacy population. The populations of Study 00071 and Study 00072 had some differences in geographic distribution and ethnicity. However, post hoc exploratory analyses indicated that these factors do not explain why Study 00072 was negative.

Because PTSD is a prevalent condition, the Agency would typically require at least two positive adequate and well-controlled investigations to reach a conclusion that a drug is effective. The usual requirement for more than one adequate and well-controlled investigation reflects the need for independent substantiation of experimental results. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

Studies 00071 and 00072 were both designed as adequate and well-controlled studies with considerably larger sample size compared to Study 00061. However, while Study 00071 was robustly positive (treatment difference −5.6; 95% CI −8.79, −2.38; p=0.0007), Study 00072 did not provide any evidence or even trends toward benefit of brexpiprazole plus sertraline, with an estimated average difference very close to zero (treatment difference 0.2; 95% CI −2.56, 2.88; p=0.9073). Given the conflicting results of these two adequate and well-controlled phase 3 studies, an additional adequate and well-controlled study is needed to provide independent substantiation of the positive results of Study 00071. To address this concern, the Applicant proposed that Study 00061, a phase 2 proof-of-concept study, could serve this purpose based on post-hoc multiple testing procedures to control the overall Type I error.

Study 00061 was a phase 2 proof-of-concept study aiming at investigating the effect of brexpiprazole either in monotherapy or in combination with sertraline and generating a hypothesis for the phase 3 study design. The trial yielded nominally significant results favoring the brexpiprazole plus sertraline over placebo plus placebo, sertraline plus placebo, and brexpiprazole plus placebo. However, these findings should be interpreted cautiously due to the lack of multiplicity control in the statistical analysis, as the study ultimately did not employ methods to control a priori for multiple comparisons.

The Agency reviewed the results from the proof-of-concept Study 00061; however, methodological and statistical issues, including lack of prespecified multiplicity adjustment, limit its interpretability and its ability to serve as independent substantiation of efficacy. The data raises questions as to whether the results from Study 00061 are capable of overcoming the clearly and convincingly negative results of

Study 00072, to provide independent substantiation of Study 00071 and meet the evidentiary standard of substantial evidence of effectiveness for brexpiprazole, when initiated concurrently with sertraline, for the treatment of PTSD.

3.1.3 Efficacy Issues in Detail

Interpretability of Results of Study 00061

Study 00061 was an exploratory phase 2 study designed to evaluate the efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline in adult subjects with PTSD. The study was intended by the Applicant to generate hypotheses and inform the design of the phase 3 studies. In particular, the study would have investigated the contribution of the single brexpiprazole and sertraline monotherapy components to the overall effect of the combination. Because the study was intended by the Applicant as a proof-of-concept study, no adjustment for multiple comparisons was made.

The initial protocol addendum (dated September 29, 2016) proposed a hierarchical testing procedure. This approach would first establish a hierarchy of endpoints based on their importance or relevance to the trial objective, then evaluate each endpoint in succession at the prespecified significance level (0.05). By terminating the procedure at the first nonsignificant hypothesis and refraining from testing subsequent hypotheses, the overall false positive rate for multiple comparisons is controlled. According to the protocol addendum, the statistical testing would follow a hierarchical procedure in this order:

1. Comparison of brexpiprazole plus sertraline versus placebo plus placebo.
2. Comparison of brexpiprazole plus placebo versus placebo plus placebo.
3. Comparison of brexpiprazole plus sertraline versus sertraline plus placebo.

The Applicant further specified in protocol addendum Amendment 1 (dated June 8, 2017) that additional test(s) might be incorporated, and the order of tests was subject to modification. The addendum stipulated that the final order of the hierarchical statistical testing procedure would be delineated in the SAP. However, prior to data unblinding, the final SAP did not include any multiplicity control methods due to the exploratory nature of this study.

If this hierarchical testing procedure from the protocol had been implemented, the annotated table below would illustrate the testing order of three comparisons under multiplicity control. Following this testing order, statistical significance could only be claimed for the first comparison: brexpiprazole plus sertraline versus placebo plus placebo.

Table 12. LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score With the Protocol Addendum Specified Hierarchical Testing Procedure, Study 00061, ITT Population*

CAPS-5 Total Score	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)
n	77	69	75	78
Mean at baseline (SD)	35.7 (11.50)	33.9 (13.31)	36.5 (10.19)	35.1 (10.68)
LS mean change from baseline at Week 10 (SE)	−16.4 (1.43)	−12.2 (1.57)	−11.4 (1.46)	−10.5 (1.40)
Treatment difference versus placebo plus placebo (95% CI)	**1** −6.0 (−9.79, −2.19)	**2** −1.7 (−5.70, 2.22)		
Nominal p-value	0.0021	0.3868		
Treatment difference brexpiprazole plus sertraline versus sertraline plus placebo (95% CI)	**3** −5.1 (−8.96, −1.20)			
Nominal p-value	0.0106			

Source: Statistical Reviewer.

Numbers 1, 2, and 3 in the table indicate the hierarchical testing order pre-specified in the protocol addendum.

* Nine subjects in the ITT population were excluded from analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; ITT, intent-to-treat; LS, least squares; n, number of subjects included in the primary efficacy analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Instead, the SAP defined five treatment group comparisons to be analyzed, without a hierarchical testing procedure:

1. Brexpiprazole plus sertraline versus placebo plus placebo.
2. Brexpiprazole plus sertraline versus sertraline plus placebo.
3. Brexpiprazole plus sertraline versus brexpiprazole plus placebo.
4. Brexpiprazole plus placebo versus placebo plus placebo.
5. Sertraline plus placebo versus placebo plus placebo.

The Applicant presented the results of these five comparisons and the nominal p-values in their submitted clinical study report (Table 3).

Given the failure of one of the two phase 3 studies, the Applicant sought evidence from this phase 2 study to support the effectiveness of the brexpiprazole plus sertraline for the treatment of PTSD. The Applicant first argued that three of the five comparisons analyzed in Study 00061 were the most relevant to evaluate the effects of brexpiprazole for PTSD, specifically:

1. Brexpiprazole plus sertraline versus sertraline plus placebo.
2. Brexpiprazole plus sertraline versus placebo plus placebo.
3. Brexpiprazole plus placebo versus placebo plus placebo.

The Applicant further selected three post hoc multiplicity control methods: a) Bonferroni procedure, b) Holm step-down procedure, and c) Hochberg step-up procedure to control the overall Type I error of these three comparisons. Among these three methods, the Bonferroni procedure is generally the most conservative. The Holm stepdown and Hochberg step-up procedures are very similar to the Bonferroni procedure, but slightly less stringent. These two methods make stepwise (either step down or step up) adjustments to the significance threshold.

The primary comparison of clinical interest in the phase 3 studies (i.e., brexpiprazole plus sertraline versus sertraline plus placebo) remained statistically significant after these three multiplicity control methods were implemented.

However, the primary comparison of clinical interest was no longer statistically significant when using a different multiplicity control method, such as the hierarchical testing procedure, which was once prespecified in the Study 00061 protocol addendum.

The hierarchical testing procedure is highly dependent on a predetermined testing order, which usually corresponds to the study objective and clinical importance. As shown in Table 12 and Table 13 according to the testing order prespecified in the protocol addendum, the testing would stop at the second comparison (i.e., brexpiprazole plus placebo versus placebo plus placebo). Thus, there was no alpha left for the current primary comparison of interest, brexpiprazole plus sertraline versus sertraline plus placebo. As a result, one cannot claim statistical significance for the comparison of brexpiprazole plus sertraline versus sertraline plus placebo based on this hierarchical testing procedure.

To summarize, the primary objective of Study 00061 was not to compare brexpiprazole plus sertraline with sertraline plus placebo, but to select the most plausible hypothesis to investigate in future phase 3 clinical studies. The objectives of Study 00061 were reflected in the prespecified hierarchical testing order in the protocol addendum, in which the brexpiprazole plus sertraline was first tested against placebo plus placebo. In this same prespecified hierarchical testing order, the subsequent test was intended to investigate the effect of brexpiprazole plus placebo compared to placebo plus placebo. In essence, because the study was exploratory, at the time of protocol development, the Applicant had selected the comparisons most relevant to inform phase 3 studies, including assessing the contribution of individual components to the treatment effect. Thus, the comparison between the brexpiprazole plus placebo and placebo plus placebo was higher in the sequence than the comparison between the brexpiprazole plus sertraline and sertraline plus placebo. Most likely, because the brexpiprazole plus placebo did not show efficacy in the phase 2 study, the Applicant decided to investigate the brexpiprazole plus sertraline combination therapy and, following the Agency's recommendation, abandoned the placebo plus placebo arm in the following phase 3 studies.

Although the combination therapy remained statistically significantly superior to sertraline after applying three multiplicity control methods proposed by the Applicant, the retrospective selection of hypotheses of research interest and the use of post hoc multiple testing procedures after data unblinding raises concerns about inflation of the overall Type I error rate, which is a critical statistical criterion required to demonstrate drug effectiveness.

Table 13. Post Hoc Analyses Adjusting for Multiplicity, Study 00061

Variable	Brexpiprazole Plus Sertraline Versus Sertraline Plus Placebo	Brexpiprazole Plus Sertraline Versus Placebo Plus Placebo	Brexpiprazole Plus Placebo Versus Placebo Plus Placebo
ITT population*, N=308			
Nominal p-value	0.0106	0.0021	0.3868
Post hoc multiple testing procedures[1]			
Bonferroni procedure	Pass	Pass	Fail
Holm step-down procedure	Pass	Pass	Fail
Hochberg step-up procedure	Pass	Pass	Fail
Hierarchical testing procedure	Fail	Pass	Fail

Source: Statistical Reviewer.

* Nine subjects in the ITT population were excluded from the analysis because of no valid postbaseline CAPS-5 measures.

[1] There are three targeted comparisons as the Applicant defined in their Summary of Clinical Efficacy. For the Bonferroni procedure, each p-value is to be compared with significance level of 0.0167 (=0.05/3). For the Holm step-down procedure, the three p-values are ranked from smallest to largest, then they would be compared with the significance level of 0.0167 (=0.05/3), 0.025 (=0.05/2) and 0.05, sequentially. The test would proceed until one fails to reject the H_0, all hypotheses that have been rejected prior to this step are significant. For the Hochberg step-up procedure, the three p-values are ranked from largest to smallest, then they would be compared with the significance level of 0.05, 0.025 (=0.05/2) and 0.0167 (=0.05/3). The test would proceed until one can reject the H_0, all remaining hypotheses in the sequence would also be rejected.

The hierarchical testing procedure used the prespecified order in protocol: 1) brexpiprazole plus sertraline versus placebo; 2) brexpiprazole versus placebo; 3) brexpiprazole plus sertraline versus sertraline.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ITT, intent-to-treat; PTSD, post-traumatic stress disorder

An additional concern in the interpretation of results from Study 00061 is the lack of a nominally superior difference between the sertraline plus placebo arm over the placebo plus placebo arm. The failure of sertraline to demonstrate superiority over placebo raises questions about the ability of Study 00061, as designed, to detect a treatment effect.

3.1.4 Safety Issues—Adverse Events and Investigations

The safety of brexpiprazole and sertraline are well-characterized, with their safety in a monotherapy context described in current labeling for each.

Brexpiprazole has boxed warnings for increased risk of death in dementia-related psychosis and for suicidal ideation and behavior in pediatric and young adult patients. The brexpiprazole label lists a number of additional warnings, including cerebrovascular adverse reactions including stroke in elderly patients with dementia-related psychosis; neuroleptic malignant syndrome; tardive dyskinesia; metabolic changes; pathological gambling and other compulsive behaviors; leukopenia, neutropenia, and agranulocytosis; orthostatic hypotension and syncope; falls; seizures; body temperature dysregulation; dysphagia; and potential for cognitive and motor impairment. The most common adverse reactions associated with brexpiprazole treatment vary by indication, but include weight gain, somnolence, akathisia, extrapyramidal symptoms, nasopharyngitis, and dizziness.

Sertraline has a boxed warning for suicidal ideation and behavior in pediatric and young adult patients. The sertraline label lists additional warnings for serotonin syndrome, increased risk of bleeding, activation of mania or hypomania, discontinuation syndrome, seizures; angle-closure glaucoma, hyponatremia, false-positive effects on screening tests for benzodiazepines, QTc prolongation, and sexual dysfunction. The most common adverse reactions associated with sertraline treatment include

nausea, diarrhea/loose stool, tremor, dyspepsia, decreased appetite, hyperhidrosis, ejaculation failure, and decreased libido.

The safety profile of brexpiprazole plus sertraline initiated concurrently per the proposed treatment was similar to that of each drug individually. There were no novel or unexpected safety findings in the development program; however, subjects experienced adverse reactions consistent with both medications.

Deaths

During the development program, three deaths occurred across different treatment groups: one in the brexpiprazole plus sertraline group, one in the sertraline plus placebo group, and one in the placebo plus placebo group. All three fatalities were assessed as either unrelated or unlikely to be related to the study drug. Specifically, in Study 00072, a subject in the 2 mg/day brexpiprazole plus sertraline dose group died from drowning. This individual had discontinued the investigational medicinal product prior to the incident and had demonstrated poor overall compliance, including attendance at study visits. In Study 00071, a death was reported in the sertraline group, attributed to toxicity from various agents, with cocaine being of particular significance. Lastly, in Study 00061, a fatality occurred in the placebo arm due to a bile duct stone.

Serious Adverse Events (SAEs)

The incidence of SAEs was relatively low and comparable between the combination therapy group and the sertraline monotherapy group. Specifically, 1% of subjects in the brexpiprazole plus sertraline group experienced SAEs, compared to 2% in the sertraline plus placebo group. In the combination therapy group, the SAEs that occurred were assessed as unlikely to be related to the study drug and did not raise specific safety concerns. These SAEs included one case of cyst rupture, one case of gastroenteritis, one instance of back pain, and two suicide attempts. Notably, one of the suicide attempts occurred in a participant who had not yet initiated the IMP. This distribution and nature of SAEs suggest that the combination therapy did not substantially increase the risk of serious adverse events compared to sertraline monotherapy.

Adverse Events Leading to Treatment Discontinuation

Treatment discontinuation due to adverse events (AEs) occurred less frequently in the brexpiprazole plus sertraline group compared to the sertraline plus placebo group (4% versus 7%, respectively).

Treatment-Emergent Adverse Events (TEAEs)

No new safety signals were identified in the study. However, the combination of brexpiprazole plus sertraline demonstrated a clinically relevant difference in weight gain compared to sertraline plus placebo, with 5% of subjects in the brexpiprazole plus sertraline group experiencing weight gain versus 1% in the sertraline plus placebo group. Additionally, somnolence was observed more frequently in the brexpiprazole plus sertraline group (4%) than in the sertraline plus placebo group (3%). It is important to note that both of these TEAEs are expected and are already documented in the brexpiprazole labeling.

Topics of Interest

The incidences of TEAEs of topics of interest were similar between the two groups (extrapyramidal symptoms; orthostatic hypotension including dizziness and syncope; metabolic changes; hepatic impairment; rhabdomyolysis and CPK elevation; suicidality). Other TEAEs of interest, such as hematopoietic and leukopenia events, neuroleptic malignant syndrome, overdose, QT prolongation, seizure, and thrombotic and embolic events did not occur in either group.

Investigations (Laboratory Tests, Vital Signs)

As anticipated, the incidence of potentially clinically relevant prolactin levels was higher in the brexpiprazole plus sertraline group compared to the sertraline plus placebo group. This difference was observed in both males (22% versus 6%, respectively) and females (23% versus 3%, respectively). However, it is noteworthy that no TEAEs associated with prolactin were reported.

Other safety parameters, including laboratory assessments, vital signs, and physical examinations, showed no significant differences between the groups. These findings were generally consistent with the known safety profile of brexpiprazole.

3.2 Risk Mitigation

The FDA is not considering risk evaluation and mitigation strategies for this supplemental application.

3.3 References

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4 Appendix

4.1 Demographic and Clinical Characteristics

4.1.1 Study 00061

Table 14. Baseline Demographics and Clinical Characteristics, Study 00061, ITT Population

Characteristic	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)	Total (N=308)
Sex, n (%)					
Male	30 (38)	24 (33)	28 (36)	33 (41)	115 (37)
Female	49 (62)	48 (67)	49 (64)	47 (59)	193 (63)
Age, years					
Mean (SD)	38.5 (12.0)	39.3 (10.7)	38.9 (10.9)	40.3 (11.0)	39.3 (11.1)
Median (min, max)	35.0 (18, 65)	38.0 (20, 61)	39.0 (20, 62)	39.0 (19, 65)	38.0 (18, 65)
Age group (years), n (%)					
<55	68 (86)	63 (88)	68 (88)	68 (85)	267 (87)
≥55	11 (14)	9 (13)	9 (12)	12 (15)	41 (13)
Height, cm					
Mean (SD)	168.4 (10.2)	166.5 (8.4)	170.4 (10.9)	169.3 (9.1)	168.7 (9.8)
Median (min, max)	168.0 (136.0, 192.0)	165.0 (150.0, 188.0)	170.0 (130.0, 198.0)	168.0 (149.0, 190.0)	168.0 (130.0, 198.0)
Weight, kg					
Mean (SD)	85.5 (24.2)	82.9 (22.8)	87.6 (23.5)	85.7 (17.2)	85.5 (22.0)
Median (min, max)	83.0 (45.5, 147.6)	77.8 (47.0, 165.2)	81.1 (51.0, 160.0)	85.7 (47.0, 127.0)	82.0 (45.5, 165.2)
BMI, kg/m^2					
Mean (SD)	30.0 (7.1)	29.8 (7.0)	30.2 (7.6)	30.1 (6.1)	30.1 (6.9)
Median (min, max)	29.3 (16.9, 50.3)	29.1 (16.0, 51.0)	28.7 (18.3, 63.4)	29.8 (17.7, 45.7)	29.3 (16.0, 63.4)
Waist circumference, cm					
Mean (SD)	95.6 (18.5)	95.5 (15.2)	97.0 (15.6)	97.9 (13.6)	96.5 (15.8)
Median (min, max)	97.0 (38.0, 138.0)	96.5 (66.0, 146.0)	94.0 (69.0, 156.0)	97.0 (64.0, 135.0)	97.0 (38.0, 156.0)
Race, n (%)					
White	52 (66)	40 (56)	50 (65)	44 (55)	186 (60)
Black or African American	21 (27)	23 (32)	22 (29)	25 (31)	91 (30)
American Indian or Alaska Native	1 (1)	1 (1)	0 (0)	2 (3)	4 (1)
Asian	1 (1)	2 (3)	0 (0)	1 (1)	4 (1)
Native Hawaiian or other Pacific Islander	1 (1)	1 (1)	0 (0)	0 (0.0)	2 (1)
Other	3 (4)	5 (7)	5 (6)	8 (10)	21 (7)
Ethnicity, n (%)					
Hispanic or Latino	13 (16)	11 (15)	9 (12)	14 (18)	46 (15)
Not Hispanic or Latino	65 (82)	61 (85)	68 (88)	66 (83)	261 (85)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (1)	0 (0)	0 (0)	0 (0)	1 (0)
Clinical baseline					
Baseline index traumatic event type, n (%)					
Combat-related	19 (24)	11 (15)	16 (21)	17 (21)	63 (20)
Not combat-related	60 (76)	61 (85)	61 (79)	63 (79)	245 (80)
Number of years since index traumatic event that led to development of PTSD, mean (SD)	6.7 (4.3)	5.9 (4.2)	5.5 (4.1)	6.7 (4.3)	6.2 (4.2)

Characteristic	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)	Total (N=308)
Baseline psychiatric scale evaluation, mean (SD)					
CAPS-5 total score	35.5 (11.4)	34.2 (13.2)	36.8 (10.2)	35.3 (10.6)	35.5 (11.4)
CGI Severity of Illness score, mean (SD)	4.4 (0.9)	4.3 (1.0)	4.4 (1.0)	4.4 (0.8)	4.4 (0.9)
Any prescription medication for PTSD based on E-TRIP, n (%)	34 (43.0)	24 (33.3)	37 (48.1)	40 (50.0)	135 (40.8)
SSRI	14 (18)	13 (18)	23 (30)	23 (29)	73 (24)
Sertraline	5 (6)	3 (4)	7 (9)	12 (15)	27 (9)
Any psychotherapy received for PTSD based on E-TRIP, n (%)	27 (34)	24 (33)	30 (39)	29 (36)	110 (36)

Source: Statistical Reviewer.

Abbreviations: BMI, body mass index; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CGI, Clinical Global Impression; E-TRIP, Emory Treatment Resistance Interview for PTSD; ITT, intent-to-treat; N, number of subjects in each treatment arm; n, number of subjects with given characteristic; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor

4.1.2 Study 00071

Table 15. Baseline Demographic and Clinical Characteristics, Study 00071, FAS for Enriched Subjects

Characteristic	Brexpiprazole Plus Sertraline (N=149)	Sertraline Plus Placebo (N=137)	Total (N=286)
Sex, n (%)			
Male	38 (26)	26 (19)	64 (22)
Female	111 (74)	111 (81)	222 (78)
Age, years			
Mean (SD)	38.7 (11.9)	37.4 (12.7)	38.1 (12.3)
Median (min, max)	37.0 (19, 65)	35.0 (18, 65)	36.0 (18, 65)
Age group (years), n (%)			
<55	132 (89)	119 (87)	251 (88)
≥55	17 (11)	18 (13)	35 (12)
Height, cm			
Mean (SD)	169.2 (9.6)	167.9 (9.4)	168.6 (9.5)
Median (min, max)	168.0 (134.6, 192.0)	167.6 (147.0, 202.2)	167.6 (134.6, 202.2)
Weight, kg			
Mean (SD)	86.6 (20.1)	84.0 (21.9)	85.4 (21.0)
Median (min, max)	86.7 (44.8, 139.5)	81.9 (45.0, 150.0)	82.9 (44.8, 150.0)
BMI, kg/m^2			
Mean (SD)	30.5 (6.7)	29.7 (7.0)	30.1 (6.9)
Median (min, max)	30.1 (18.2, 48.9)	28.9 (18.3, 50.2)	29.4 (18.2, 50.2)
Waist circumference, cm			
Mean (SD)	96.3 (15.6)	94.7 (18.4)	95.5 (17.0)
Median (min, max)	96.5 (66.5, 142.0)	92.7 (61.0, 148.0)	95.0 (61.0, 148.0)
Race, n (%)			
American Indian or Alaska Native	6 (4)	2 (1)	8 (3)
Asian	3 (2)	7 (5)	10 (3)
Black or African American	30 (20)	24 (18)	54 (19)
Native Hawaiian or other Pacific Islander	1 (1)	0 (0)	1 (0)
White	108 (72)	97 (70.8)	205 (73)
Other	1 (0)	7 (5.1)	8 (3)

Characteristic	Brexpiprazole Plus Sertraline (N=149)	Sertraline Plus Placebo (N=137)	Total (N=286)
Ethnicity, n (%)			
Hispanic or Latino	17 (11)	20 (15)	37 (13)
Not Hispanic or Latino	130 (87)	115 (84)	245 (86)
Unknown	0 (0)	1 (1)	1 (0)
Other	2 (1)	1 (1)	3 (1)
Baseline index traumatic event type, n (%)			
Assault (with or without weapon)	49 (33)	60 (44)	109 (38)
Captivity	0 (0)	1 (1)	1 (0)
Combat or exposure to war-zone	4(3)	3 (2)	7 (2)
Exposure to sudden death	19 (13)	10 (7)	29 (10)
Life-threatening illness or injury	7 (5)	4 (3)	8 (3)
Motor vehicle or other transportation accident	13 (9)	17 (12)	30 (10)
Natural disaster, fire, or explosion	4 (3)	4 (3)	8 (3)
Serious harm or death for which you are responsible	1 (1)	0 (0)	1 (0)
Serious non-transportation accident	1 (1)	1 (1)	2 (1)
Sexual trauma	40 (27)	29 (21)	69 (24)
Other	11 (7)	8 (6)	19 (7)
Number of years since index traumatic event that led to development of PTSD, mean (SD)	4.3 (2.5)	4.0 (2.4)	4.1 (2.5)
Baseline psychiatric scale evaluations, mean (SD)			
CAPS-5 total score	38.3 (7.2)	38.8 (8.0)	38.6 (7.6)
CGI severity of illness score	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)
HADS subscale anxiety score	14.0 (3.9)	14.1 (3.3)	14.1 (3.6)
HADS subscale depression score	11.0 (3.7)	10.7 (3.8)	10.8 (3.8)
Any prescription medication for PTSD based on E-TRIP, n (%)	46 (31)	35 (26)	81 (28)
SSRI	24 (16)	19 (14)	43 (15)
Sertraline	12 (8)	8 (6)	20 (7)
Any psychotherapy received for PTSD based on E-TRIP, n (%)	59 (40)	40 (29)	99 (35)

Source: Applicant's Clinical Study Report for Study 00071, Table CT-3.1.1, CT-3.5.2, CT-3.2.4.3, CT-3.4.1.1 and the Statistical Reviewer.
Abbreviations: BMI, body mass index; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CGI, Clinical Global Impression; E-TRIP, Emory Treatment Resistance Interview for PTSD; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; N, number of subjects in each treatment arm; n, number of subjects with given characteristic; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor

4.1.3 Study 00072

Table 16. Baseline Demographics and Clinical Characteristics, Study 00072, FAS for Enriched Subjects

Characteristic	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Sertraline Plus Placebo (N=130)	Total (N=388)
Sex, n (%)				
Male	33 (25)	29 (23)	36 (28)	98 (25)
Female	99 (75)	97 (77)	94 (72)	290 (75)
Age (years)				
Mean (SD)	38.7 (12.4)	35.8 (11.6)	37.9 (12.9)	37.1 (12.3)
Median (min, max)	36.5 (18, 65)	32.5 (18, 61)	35.5 (18, 65)	35.0 (18, 65)
Age group (years), n (%)				
<55	117 (89)	115 (91)	111 (85)	343 (88)
≥55	15 (11)	11 (9)	19 (15)	45 (12)

Characteristic	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Sertraline Plus Placebo (N=130)	Total (N=388)
Height, cm				
Mean (SD)	167.0 (9.2)	167.5 (10.5)	168.7 (9.5)	167.7 (9.7)
Median (min, max)	165.1 (149.0, 190.5)	167.0 (125.0, 195.6)	169.5 (147.3, 195.4)	167.6 (125.0, 195.6)
Weight, kg				
Mean (SD)	81.8 (21.0)	82.7 (21.9)	82.2 (21.3)	82.0 (21.3)
Median (min, max)	76.5 (39.6, 149.0)	77.7 (42.8, 148.0)	78.0 (45.7, 130.5)	77.4 (39.6, 149.0)
BMI, kg/m^2				
Mean (SD)	29.0 (6.6)	29.3 (6.8)	28.8 (6.2)	29.0 (6.5)
Median (min, max)	27.9 (17.4, 53.1)	28.5 (16.3, 48.1)	27.9 (18.2, 46.8)	28.0 (16.3, 53.1)
Waist circumference, cm				
Mean (SD)	92.3 (17.4)	93.0 (16.1)	93.0 (15.3)	92.8 (16.3)
Median (min, max)	88.9 (57.2, 139.7)	91.4 (61.0, 134.6)	91.4 (63.5, 135.0)	91.4 (57.2, 139.7)
Race, n (%)				
American Indian or Alaska Native	1 (1)	1 (1)	1 (1)	3 (1)
Asian	5 (4)	6 (5)	4 (3)	15 (4)
Black or African American	25 (19)	29 (23)	28 (22)	82 (21)
Native Hawaiian or other Pacific Islander	2 (2)	1 (1)	0 (0)	3 (1)
White	96 (73)	84 (67)	95 (73)	275 (71)
Other	3 (2)	5 (4)	2 (2)	10 (3)
Ethnicity, n (%)				
Hispanic or Latino	35 (27)	29 (23)	28 (22)	92 (24)
Not Hispanic or Latino	97 (73)	95 (75)	102 (78)	294 (76)
Unknown	0 (0)	1 (1)	0 (0)	1 (0)
Other	0 (0)	1 (1)	0 (0)	1 (0)
Baseline index traumatic event type, n (%)				
Assault (with or without weapon)	46 (35)	42 (33)	53 (41)	141 (36)
Captivity	4 (3)	0 (0)	1 (1)	5 (1)
Combat or exposure to war-zone	2 (2)	1 (1)	1 (1)	4 (1)
Exposure to sudden death	22 (17)	28 (22)	17 (13)	67 (17)
Life-threatening illness or injury	8 (6)	3 (2)	6 (5)	17 (4)
Motor vehicle or other transportation accident	17 (13)	12 (10)	14 (11)	43 (11)
Natural disaster, fire, or explosion	1 (1)	1 (1)	5 (4)	7 (2)
Serious non-transportation accident	2 (2)	1 (1)	0 (0)	3 (1)
Sexual trauma	24 (18)	29 (23)	24 (18)	77 (20)
Other	6 (4)	9 (7)	8 (6)	23 (6)

Characteristic	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Sertraline Plus Placebo (N=130)	Total (N=388)
Number of years since index traumatic event that led to development of PTSD, mean (SD)	4.1 (2.6)	4.0 (2.4)	3.9 (2.2)	4.0 (2.4)
Baseline psychiatric scale evaluations, mean (SD)				
CAPS-5 total score	38.8 (8.3)	37.8 (7.3)	39.3 (7.8)	38.7 (7.8)
CGI severity of illness score	4.6 (0.7)	4.5 (0.7)	4.7 (0.7)	4.6 (0.7)
HADS subscale anxiety score	13.3 (3.6)	13.3 (3.6)	13.1 (3.9)	13.2 (3.7)
HADS subscale depression score	10.5 (3.4)	9.9 (4.1)	9.6 (3.9)	10.0 (3.8)
Any prescription medication for PTSD based on E-TRIP, n (%)	28 (21)	23 (18)	26 (20)	77 (20)
SSRI	16 (12)	16 (13)	15 (12)	47 (12)
Sertraline	4 (3)	6 (5)	7 (5)	17 (4)
Any psychotherapy received for PTSD based on E-TRIP, n (%)	38 (29)	40 (32)	38 (29)	116 (30)

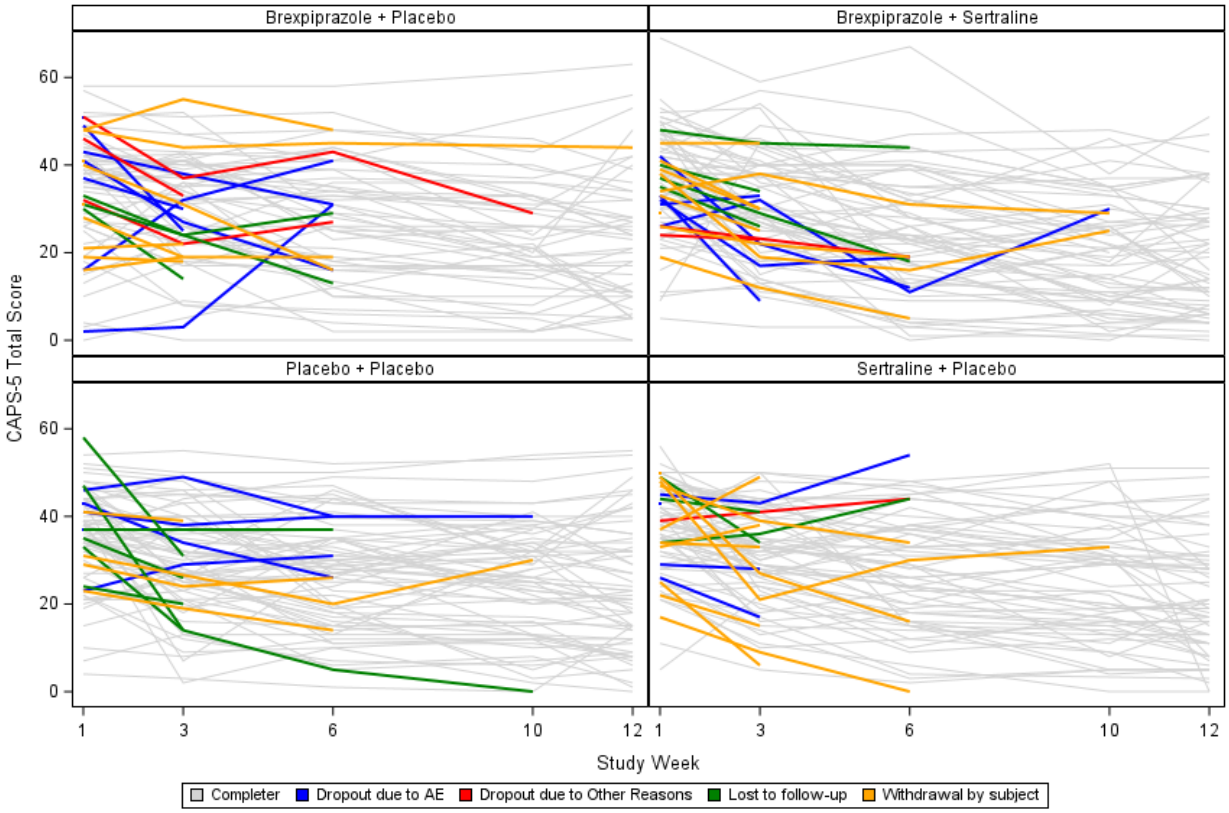
Source: Applicant's Clinical Study Report for Study 00072, Table CT-3.1.1, CT-3.5.2, CT-3.2.4.3, CT-3.4.1.1 and the Statistical Reviewer.
Abbreviations: BMI, body mass index; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CGI, Clinical Global Impression; E-TRIP, Emory Treatment Resistance Interview for PTSD; FAS, full analysis set; HADS, Hospital Anxiety and Depression Scale; N, number of subjects in each treatment arm; n, number of subjects with given characteristic; PTSD, post-traumatic stress disorder; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor

4.2 Missing Data and Additional Analyses

4.2.1 Study 00061

In Study 00061, 77 (25%) subjects in the ITT population discontinued the study. Specifically, 21 (27%) in the brexpiprazole plus sertraline group, 22 (31%) in the brexpiprazole plus placebo, 18 (23%) in the sertraline plus placebo, and 16 (20%) in the placebo plus placebo group. Figure 6 displays the individual trajectories of CAPS-5 total scores by completion status and discontinuation reason. Most subjects discontinued due to withdrawal by subjects (10%). Overall, there does not seem to be remarkable differences in the response trajectories between the completers and dropouts in each treatment group. There seems to be no evidence against the missing at random (MAR) assumption used in the primary efficacy analysis. Sensitivity analyses (such as tipping point analyses) exploring the impact of missing data generally supported the findings from the primary analysis, either for the brexpiprazole plus sertraline vs sertraline plus placebo comparison or the brexpiprazole plus sertraline vs placebo plus placebo comparison.

Figure 6. Individual CAPS-5 Total Score Trajectories by Completion Status and Discontinuation Reason, Study 00061, ITT Population



Source: Statistical Reviewer.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ITT, intent-to-treat; PTSD, post-traumatic stress disorder

Although no key secondary endpoints were defined for Study 00061, the changes from baseline in CGI-S scores were analyzed to facilitate the comparison between Study 00061 and the phase 3 studies. The results are presented in Table 17. A treatment difference of −0.4 (95% CI −0.76, −0.08; p=0.0167) was observed between the brexpiprazole plus sertraline group and the sertraline plus placebo group. Again, given that this analysis was not prespecified, the results are considered exploratory and should be interpreted cautiously.

Table 17. LS Mean Change From Baseline (Week 1) to Week 10 in CGI-S, Study 00061, ITT Population*

CGI-S Score	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)
n	78	72	77	80
Mean at baseline (SD)	4.4 (0.86)	4.3 (1.03)	4.4 (0.97)	4.4 (0.82)
LS mean change from baseline at Week 10 (SE)	−1.4 (0.12)	−1.1 (0.13)	−0.9 (0.13)	−0.9 (0.12)
Treatment difference vs. placebo plus placebo (95% CI)	−0.5 (−0.81, −0.14)	−0.2 (−0.56, 0.13)	−0.1 (−0.39, 0.28)	
Nominal p-value	0.0056	0.2278	0.7368	

CGI-S Score	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)
Treatment difference brexpiprazole plus sertraline vs. sertraline plus placebo (95% CI)	−0.4 (−0.76, −0.08)			
Nominal p-value	0.0167			
Treatment difference brexpiprazole plus sertraline vs. brexpiprazole plus placebo (95% CI)	−0.3 (−0.61, 0.09)			
Nominal p-value	0.1480			

Source: Study 00061 Clinical Study Report Table CT 5.4.1, verified by the Statistical Reviewer.

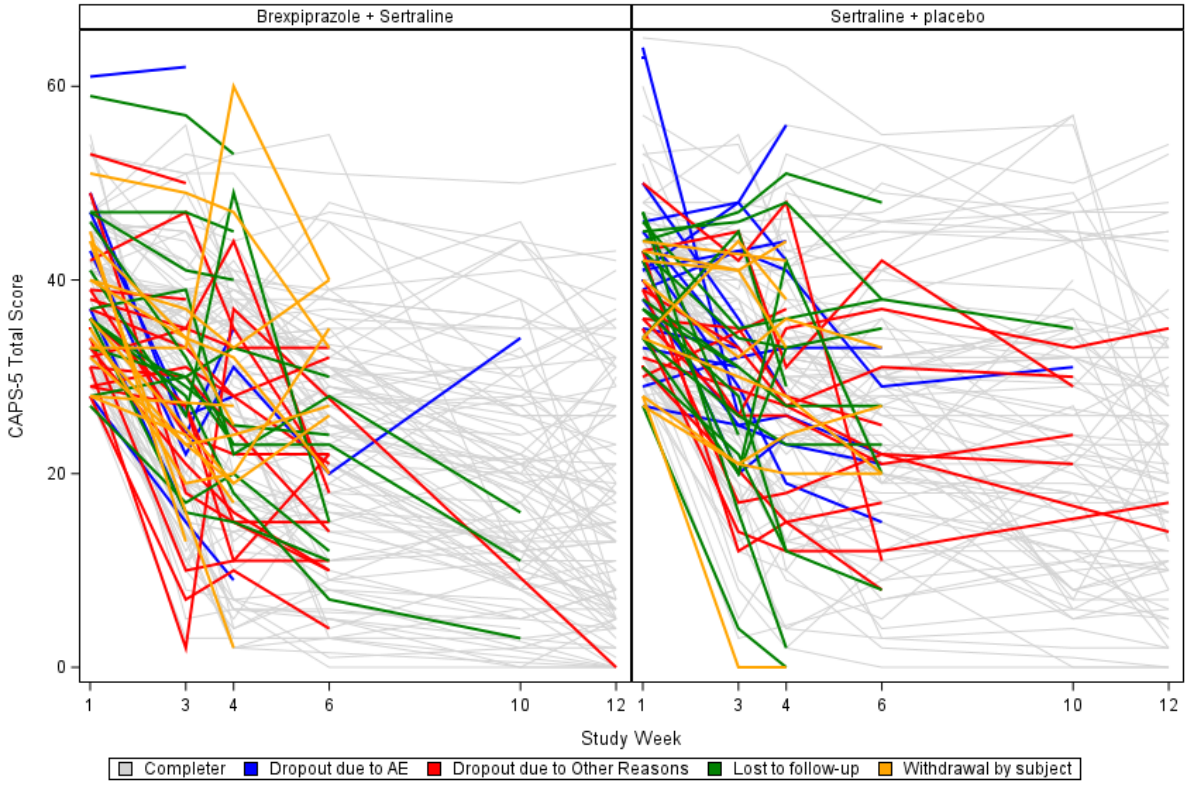
* One subject in the ITT population was excluded from the analysis because of no valid postbaseline CGI-S measures.

Abbreviations: CI, confidence interval; CGI-S, Clinical Global Impression Severity of Illness; ITT, intent-to-treat; LS, least squares; n, number of participants included in the analysis in each treatment group; SD, standard deviation; SE, standard error

4.2.2 Study 00071

In Study 00071, 101 (35%) subjects in the FAS for enriched subjects discontinued the study. Specifically, 48 (32%) in the brexpiprazole plus sertraline group and 53 (39%) in the sertraline plus placebo group. Figure 7 shows the individual trajectories of CAPS-5 total score by completion status and discontinuation reasons. No subjects discontinued the study due to lack of efficacy. Most subjects who discontinued were lost to follow-up (9%). Overall, there do not seem to be remarkable differences in the response trajectories between the completers and dropouts in each treatment group. There seems to be no evidence against the MAR assumption used in the primary efficacy analysis. Sensitivity analyses (such as tipping point analyses) exploring the impact of missing data generally supported the findings from the primary analysis.

Figure 7. Individual CAPS-5 Total Score Trajectories by Completion Status and Discontinuation Reason, Study 00071, FAS for Enriched Subjects



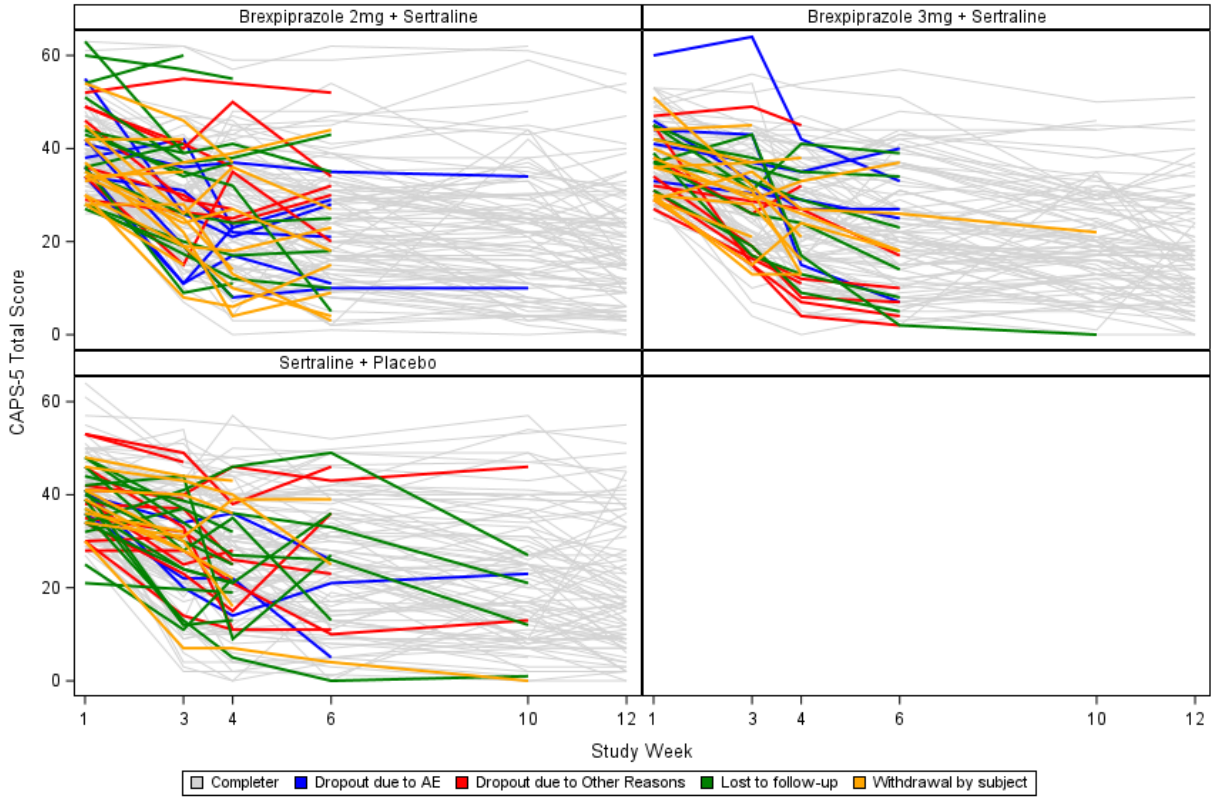
Source: Statistical Reviewer.

Abbreviations: AE, adverse event; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FAS, full analysis set; PTSD, post-traumatic stress disorder

4.2.3 Study 00072

In Study 00072, 143 (26%) subjects in the FAS for enriched subjects discontinued the study. Specifically, 51 (27%) in the brexpiprazole 2 mg plus sertraline group, 45 (24%) in the brexpiprazole 3 mg plus sertraline group, and 47 (27%) in the sertraline plus placebo group. Figure 8 shows the individual trajectories of CAPS-5 total score by completion status and discontinuation reasons. No subjects in the FAS for Enriched Subjects discontinued the study due to lack of efficacy. Most subjects who discontinued were lost to follow-up (9%). Overall, there do not seem to be remarkable differences in the response trajectories between the completers and dropouts in each treatment group. There seems to be no evidence against the MAR assumption used in the primary efficacy analysis.

Figure 8. Individual CAPS-5 Total Score Trajectories by Completion Status and Discontinuation Reason, Study 00072, FAS for Enriched Subjects



Source: Statistical Reviewer.

Abbreviations: AE, adverse event; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FAS, full analysis set; PTSD, post-traumatic stress disorder

4.3 Subgroup Analyses and Other Post Hoc Exploratory Analyses

Because these studies were not designed for subgroup analyses, all subgroup analyses are considered exploratory. If subjects are not randomized within each subgroup, the lack of randomization may lead to imbalance of confounding effects, whether identifiable or not, between treatment groups. The likelihood of a chance finding is increased with a small sample size due to its large variation, so subgroup analysis results should be considered descriptive and interpreted with caution.

4.3.1 Study 00061

Review Team's Other Post Hoc Analyses

Analyses in the Enriched Subgroup

Given that the primary efficacy analyses in Studies 00071 and 00072 were conducted after excluding placebo responders, we performed a further subgroup analysis by applying the same enriched criteria to Study 00061 as were used in Studies 00071 and 00072.

As shown in Table 18, analyses in the enriched population subgroup showed similar results to those observed in the ITT population i.e., the brexpiprazole plus sertraline group showed superiority to the sertraline plus placebo group on the primary endpoint.

Table 18. LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00061, Enriched Population*

CAPS-5 Total Score	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)
n	61	50	61	61
Mean at baseline (SD)	40.0 (8.06)	40.5 (7.20)	40.1 (6.99)	39.6 (6.64)
LS Mean change from baseline at Week 10 (SE)	−18.5 (1.67)	−14.1 (1.89)	−11.7 (1.69)	−12.7 (1.66)
Treatment difference versus Placebo (95% CI)	−5.8 (−10.24, −1.29)	−1.4 (−6.17, 3.30)	1.0 (−3.44, 5.47)	
Nominal p-value	0.0119	0.5511	0.6550	
Treatment difference brexpiprazole plus sertraline versus sertraline (95% CI)	−6.8 (−11.28, −2.27)			
Nominal p-value	0.0034			
Treatment difference brexpiprazole plus sertraline versus brexpiprazole (95% CI)	−4.3 (−9.12, 0.45)			
Nominal p-value	0.0758			

Source: Module 2.7.3 Summary of Clinical Efficacy Table CT-STAT-1.2.1, verified by the Statistical Reviewer.

* Nine subjects in the enriched population were excluded from the analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; LS, least squares; n, number of subjects included in the analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Subgroup Analysis by Baseline PTSD Severity

In order to identify potential subgroup populations that could benefit from brexpiprazole plus sertraline versus sertraline plus placebo, the review team conducted post hoc sensitivity analyses by baseline severity as measured by the baseline CAPS-5 total score. Subjects in the ITT population were divided into three severity subgroups: 1) CAPS-5 total score 0 to 32, 2) CAPS-5 total score 33 to 42, and 3) CAPS-5 total score ≥43. This subgroup analysis used a similar MMRM analysis as for the primary efficacy analysis but only adjusted for visit, treatment, and an interaction between visit and treatment. A trend for a larger treatment effect of sertraline compared to placebo was observed in subjects in the first group corresponding to mild severity of PTSD symptoms (Table 19 and Figure 9), but not in the other two groups. On the other hand, a larger treatment effect of the combination therapy compared to sertraline was observed in the severe severity of PTSD symptoms group (Table 19 and Figure 9).

Although this subgroup analysis could suggest that the most severe patients do not respond to sertraline but could benefit from the combination, its interpretation requires caution because the study was not designed for subgroup analyses, these analyses were conducted post hoc, had very small sample sizes, and had an arbitrary cut-off of baseline CAPS-5 scores.

Table 19. Subgroup Analysis by Baseline CAPS-5 Total Scores—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00061, ITT Population*

Subgroup	CAPS-5 Total Score	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)
Baseline CAPS-5 0 to 32	n	28	26	22	23
	Mean at baseline (SD)	24.1 (7.74)	19.9 (9.72)	23.9 (6.50)	22.0 (7.29)
	LS Mean change from baseline at Week 10 (SE)	−7.4 (1.76)	−6.4 (1.98)	−9.4 (2.03)	−2.5 (1.91)
	Treatment difference vs. placebo (95% CI)	−4.9 (−10.11, 0.25)	−3.9 (−9.33, 1.60)	−6.9 (−12.43, −1.32)	
	Treatment difference vs. sertraline plus placebo (95% CI)	1.9 (−3.37, 7.25)			
	Treatment difference vs. brexpiprazole plus placebo (95% CI)	−1.1 (−6.38, 4.25)			
Baseline CAPS-5 33 to 42	n	28	24	30	34
	Mean at baseline (SD)	37.3 (3.09)	38.1 (2.65)	37.2 (2.85)	36.6 (2.55)
	LS Mean change from baseline at Week 10 (SE)	−15.0 (2.43)	−12.5 (2.50)	−12.9 (2.22)	−11.1 (2.08)
	Treatment difference vs. placebo (95% CI)	−3.9 (−10.28, 2.43)	−1.4 (−7.89, 5.18)	−1.8 (−7.86, 4.27)	
	Treatment difference vs. sertraline plus placebo (95% CI)	−2.1 (−8.67, 4.40)			
	Treatment difference vs. brexpiprazole plus placebo (95% CI)	−2.6 (−9.49, 4.33)			

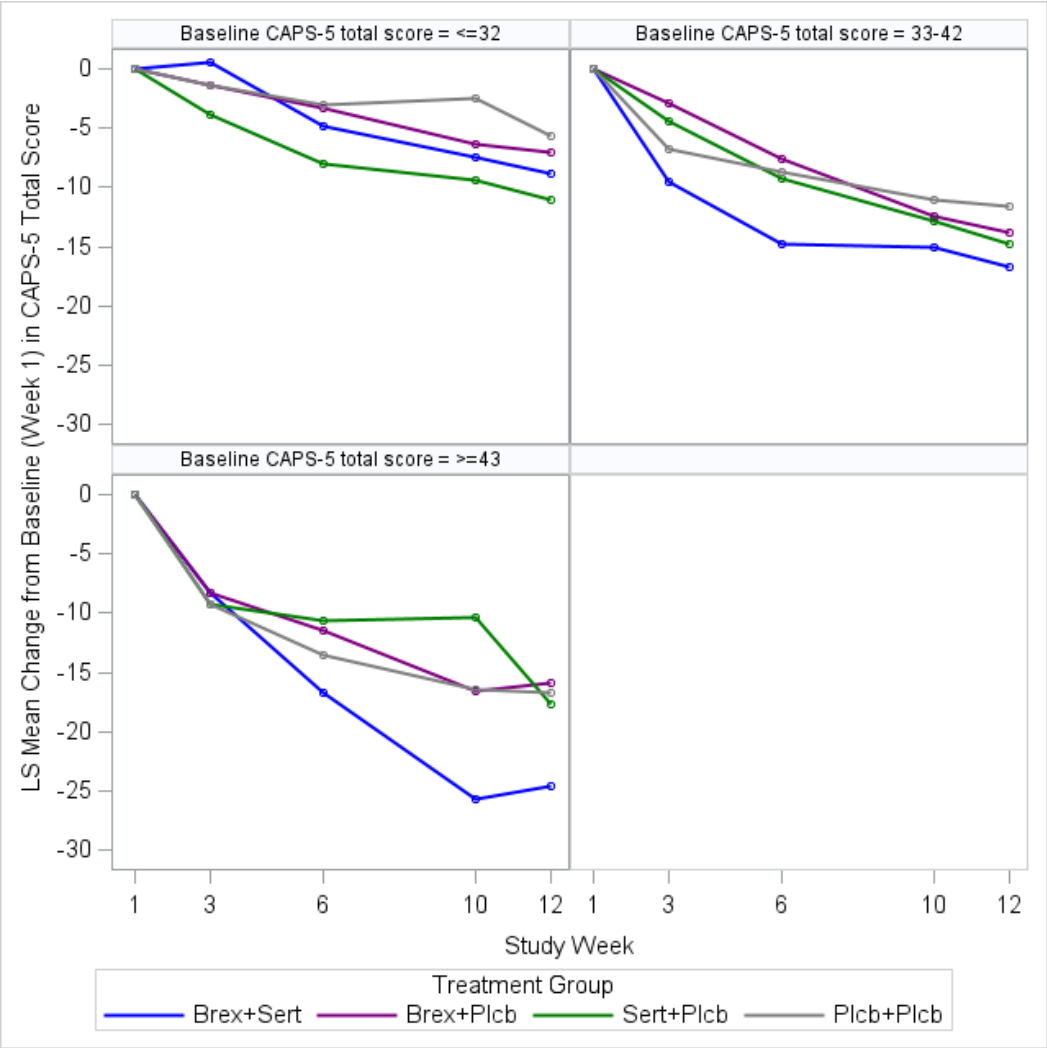
Subgroup	CAPS-5 Total Score	Brexpiprazole Plus Sertraline (N=79)	Brexpiprazole Plus Placebo (N=72)	Sertraline Plus Placebo (N=77)	Placebo Plus Placebo (N=80)
Baseline CAPS-5 ≥43	n	21	19	23	21
	Mean at baseline (SD)	49.1 (5.61)	47.7 (4.51)	47.7 (3.05)	47.2 (3.93)
	LS Mean change from baseline at Week 10 (SE)	−25.7 (2.94)	−16.6 (3.20)	−10.3 (2.87)	−16.4 (3.00)
	Treatment difference vs. placebo (95% CI)	−9.3 (−17.78, −0.85)	−0.2 (−8.97, 8.50)	6.1 (−2.18, 14.33)	
	Treatment difference vs. sertraline plus placebo (95% CI)	−15.4 (−23.60, −7.19)			
	Treatment difference vs. brexpiprazole plus placebo (95% CI)	−9.1 (−17.76, −0.41)			

Source: Statistical Reviewer.

* Nine subjects in the ITT population were excluded from the analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; ITT, intent-to-treat; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group ; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Figure 9. LS Mean Change in CAPS-5 Total Score Based on Baseline CAPS-5 Severity, Study 00061, ITT Population



Source: Statistical Reviewer.
Abbreviations: Brex, brexpiprazole; CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ITT, intent-to-treat; LS, least squares; Plcb, placebo; PTSD, post-traumatic stress disorder; Sert, sertraline

4.3.2 Study 00071

For all subgroup analyses, the Applicant prespecified a similar MMRM analysis as for the primary efficacy analysis except excluding the fixed class effect pooled trial center and previous pharmacological treatment intervention for PTSD (*Yes* or *No*). Subgroup analysis results are considered descriptive and should be interpreted with caution because these studies were not designed nor powered for formal subgroup analyses.

Subgroup Analysis by Baseline PTSD Severity

The review team examined whether the severity of baseline PTSD symptoms, as measured by the CAPS-5, might have led to a different response. As reported in Table 20, we found treatment differences of −8.0; 95% CI −15.34, −0.68) between the combination group and the sertraline monotherapy group in

the population with high severity baseline CAPS-5 total score; there were no treatment differences between the two groups in the population with mild baseline CAPS-5 total score (treatment difference −1.8; 95% CI −6.93, 3.37). The treatment difference between combination therapy and sertraline monotherapy in the population with moderate baseline CAPS-5 total score was intermediate between these two subgroups (treatment difference −5.8; 95% CI −10.37, −1.13).

Table 20. Subgroup Analysis by Baseline CAPS-5 Total Score—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00071, FAS for Enriched Subjects*

Subgroup	CAPS-5 Total Score	Brexpiprazole Plus Sertraline (N=149)	Sertraline Plus Placebo (N=137)
Baseline CAPS-5 27 to 32	n	34	33
	Mean at baseline (SD)	29.9 (1.74)	29.5 (1.84)
	LS Mean change from baseline at Week 10 (SE)	−15.3 (1.85)	−13.5 (1.77)
	Treatment difference vs. sertraline plus placebo (95% CI)	−1.8 (−6.93, 3.37)	
Baseline CAPS-5 33 to 42	n	74	58
	Mean at baseline (SD)	37.1 (2.84)	37.5 (2.90)
	LS Mean change from baseline at Week 10 (SE)	−19.2 (1.51)	−13.4 (1.77)
	Treatment difference vs. sertraline plus placebo (95% CI)	−5.8 (−10.37, −1.13)	
Baseline CAPS-5 ≥43	n	40	43
	Mean at baseline (SD)	47.9 (4.26)	47.3 (5.57)
	LS Mean change from baseline at Week 10 (SE)	−23.0 (2.66)	−15.0 (2.53)
	Treatment difference vs. sertraline plus placebo (95% CI)	−8.0 (−15.34, −0.68)	

Source: Statistical Reviewer.

* Four subjects in the FAS for enriched subjects were excluded from the analysis due to no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for DSM-5; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

4.3.3 Study 00072

Study 00072 did not demonstrate superiority of brexpiprazole plus sertraline over sertraline plus placebo for PTSD symptoms. Given that Study 00072 is almost identical to Study 00071 except for the fixed-dose design, the review team conducted several subgroup analyses to explore possible factors that may have contributed to the negative results. This section describes these subgroup analyses.

For all subgroup analyses, the Applicant prespecified a similar MMRM analysis as for the primary efficacy analysis except excluding the fixed class effect pooled trial center and previous pharmacological treatment intervention for PTSD (*Yes* or *No*). Subgroup analysis results are considered descriptive and should be interpreted with caution because these studies were not designed nor powered for formal subgroup analyses.

Most subgroup analyses showed no nominal differences between subgroups, with three exceptions described below: sex, prior pharmacologic treatment, and ethnicity. Note that although the primary analysis population is FAS for enriched subjects, nominally significant results were only observed in

specific subgroups of the full analysis set, not of the primary analysis population. Below, we present subgroup analyses with both the FAS and FAS for enriched subjects for completeness.

Sex

When analyzing data from both sexes combined, Study 00072 demonstrated no significant treatment effect in the change of CAPS-5 total score from Week 1 to Week 10.

As PTSD is more common in women than men, the majority (approximately 75%) of participants in Studies 00071 and 0072 were women. Post hoc exploratory analyses revealed no statistically significant difference between the combination therapies and sertraline on the CAPS-5, in the FAS for enriched sample (primary efficacy population, Table 22) and in the FAS sample (all randomized subjects, Table 21). However, in the FAS sample and only in the 3 mg/day brexpiprazole plus sertraline group (n=125) there was a trend favoring brexpiprazole plus sertraline in females (treatment difference brexpiprazole 3 mg plus sertraline versus sertraline plus placebo=−3.2 [95% CI −6.32, 0.01]), though this was not statistically significant.

The difference between the FAS and the FAS for enriched sample is the inclusion of placebo responders; therefore, the clinical interpretation is difficult and possibly not meaningful.

Table 21. Subgroup Analysis by Sex—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS*

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=177)	Brexpiprazole 3 mg Plus Sertraline (N=167)	Sertraline Plus Placebo (N=165)
Female	n	129	125	118
	Mean at baseline (SD)	34.9 (12.31)	33.6 (10.69)	35.1 (11.30)
	LS Mean change from baseline at Week 10 (SE)	−14.5 (1.11)	−17.7 (1.12)	−14.5 (1.16)
	Treatment difference vs. sertraline plus placebo (95% CI)	0.0 (−3.14, 3.16)	−3.2 (−6.32, 0.01)	
Male	n	48	39	47
	Mean at baseline (SD)	29.2 (11.64)	31.9 (11.27)	34.4 (11.31)
	LS Mean change from baseline at Week 10 (SE)	−13.5 (1.88)	−14.1 (2.04)	−15.7 (1.89)
	Treatment difference vs. sertraline plus placebo (95% CI)	2.3 (−3.07, 7.66)	1.7 (−3.87, 7.17)	

Source: Statistical reviewer, results are consistent with Study 00072 CSR CT-6.1.1.2, CT-6.1.2.2.

*Three subjects in the FAS were excluded from analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Table 22. Subgroup Analysis by Sex—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS for Enriched Subjects*

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Sertraline Plus Placebo (N=130)
Female	n	99	95	94
	Mean at baseline (SD)	39.9 (8.59)	38.3 (7.06)	39.4 (7.58)
	LS Mean change from baseline at Week 10 (SE)	−17.2 (1.33)	−19.0 (1.35)	−16.8 (1.36)
	Treatment difference vs. sertraline plus placebo (95% CI)	−0.4 (−4.14, 3.32)	−2.2 (−5.97, 1.57)	
Male	n	33	29	36
	Mean at baseline (SD)	35.7 (6.32)	36.7 (8.38)	38.9 (8.28)
	LS Mean change from baseline at Week 10 (SE)	−14.0 (2.37)	−16.0 (2.48)	−19.4 (2.15)
	Treatment difference vs. sertraline plus placebo (95% CI)	5.5 (−0.95, 11.86)	3.5 (−3.11, 10.01)	

Source: Statistical Reviewer, results are consistent with Study 00072 CSR CT-6.1.1.1, CT-6.1.2.1.

* Two subjects in the FAS for enriched subjects were excluded from analysis because of no valid postbaseline CAPS-5 measures.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Prior Pharmacological Intervention Yes/No

In the FAS sample (Table 23), but not in the FAS for enriched subjects sample (Table 24), the subgroup of subjects without prior pharmacological intervention who received brexpiprazole 3 mg plus sertraline (n=134) showed nominally significant superiority over those who received sertraline plus placebo (n=131) on the primary endpoint (CAPS-5 total score treatment difference −3.2; 95% CI −6.22, −0.10). Conversely, among subjects who had received prior pharmacological intervention, the improvement in CAPS-5 total score from Week 1 to Week 10 in the brexpiprazole 2 mg plus sertraline group was comparable to that observed in the sertraline plus placebo group.

Table 23. Subgroup Analysis by Prior Pharmacological Treatment Intervention (Yes/No) for PTSD—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS*

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=177)	Brexpiprazole 3 mg Plus Sertraline (N=167)	Sertraline Plus Placebo (N=165)
With previous pharmacological treatment intervention for PTSD	n	36	30	34
	Mean at baseline (SD)	36.6 (12.40)	34.8 (10.52)	35.6 (10.83)
	LS Mean change from baseline at Week 10 (SE)	−15.7 (2.42)	−19.2 (2.87)	−21.2 (2.52)
	Treatment difference vs. sertraline plus placebo (95% CI)	4.9 (−0.66, 10.54)	1.9 (−4.08, 7.96)	
Without previous pharmacological treatment intervention for PTSD	n	141	134	131
	Mean at baseline (SD)	32.5 (12.26)	32.8 (10.89)	34.8 (11.42)
	LS Mean change from baseline at Week 10 (SE)	−14.3 (1.09)	−16.8 (1.08)	−13.6 (1.11)
	Treatment difference vs. sertraline plus placebo (95% CI)	−0.7 (−3.80, 2.34)	−3.2 (−6.22, −0.10)	

Source: Statistical reviewer, results are consistent with Study 00072 CSR CT-6.4.1.2, CT-6.4.2.2.

* Three subjects in the FAS were excluded from analysis because of no valid postbaseline CAPS-5 measures.
Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Table 24. Subgroup Analysis by Prior Pharmacological Treatment Intervention (Yes/No) for PTSD—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS for Enriched Subjects*

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Sertraline Plus Placebo (N=130)
With previous pharmacological treatment intervention for PTSD	n	28	23	26
	Mean at baseline (SD)	42.0 (7.50)	39.4 (7.05)	40.4 (6.81)
	LS Mean change from baseline at Week 10 (SE)	−15.7 (2.42)	−19.2 (2.87)	−21.2 (2.52)
	Treatment difference vs. sertraline plus placebo (95% CI)	5.5 (−1.49, 12.52)	2.0 (−5.63, 9.62)	
Without previous pharmacological treatment intervention for PTSD	n	104	101	104
	Mean at baseline (SD)	37.9 (8.28)	37.5 (7.45)	39.0 (7.98)
	LS Mean change from baseline at Week 10 (SE)	−16.6 (1.32)	−18.2 (1.30)	−16.7 (1.29)
	Treatment difference vs. sertraline plus placebo (95% CI)	0.1 (−3.56, 3.74)	−1.5 (−5.15, 2.08)	

Source: Statistical reviewer, results are consistent with Study 00072 Clinical Study Report CT-6.4.1.1, CT-6.4.2.1.
* Two subjects in the FAS for enriched subjects were excluded from analysis because of no valid postbaseline CAPS-5 measures.
Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Ethnicity

In the FAS sample (Table 25), but not in the FAS for enriched subjects sample (Table 26), the subgroup of participants of Not Hispanic or Latino ethnicity in the combination therapy group of brexpiprazole 3 mg plus sertraline (n=32) showed nominally significant superiority over sertraline (n=34) on the CAPS-5 total scores (treatment difference −3.4; 95% CI −6.30, −0.44). This was not observed for Hispanic or Latino ethnicity in either the 2 mg subgroup in FAS sample.

Table 25. Subgroup Analysis by Ethnicity—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS*

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=177)	Brexpiprazole 3 mg Plus Sertraline (N=167)	Sertraline Plus Placebo (N=165)
Hispanic or Latino	n	46	32	34
	Mean at baseline (SD)	32.7 (13.48)	37.3 (9.01)	35.6 (10.56)
	LS Mean change from baseline at Week 10 (SE)	−13.1 (2.19)	−13.6 (2.48)	−16.9 (2.48)
	Treatment difference vs. sertraline plus placebo (95% CI)	3.8 (−2.75, 10.40)	3.3 (−3.68, 10.21)	

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=177)	Brexpiprazole 3 mg Plus Sertraline (N=167)	Sertraline Plus Placebo (N=165)
Not Hispanic or Latino	n	131	130	131
	Mean at baseline (SD)	33.5 (11.99)	32.1 (11.08)	34.8 (11.48)
	LS Mean change from baseline at Week 10 (SE)	−14.9 (1.04)	−17.6 (1.05)	−14.3 (1.05)
	Treatment difference vs. sertraline plus placebo (95% CI)	−0.6 (−3.52, 2.31)	−3.4 (−6.30, −0.44)	

Source: Statistical Reviewer.

* Three subjects in the FAS were excluded from the analysis due to no valid postbaseline CAPS-5 measures. Two subjects with ethnicities of *Other* and *Unknown* were excluded from this subgroup analysis.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; FAS, full analysis set; LS, least square; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Table 26. Subgroup Analysis by Ethnicity—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS for Enriched Subjects*

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Sertraline Plus Placebo (N=130)
Hispanic or Latino	n	35	29	28
	Mean at baseline (SD)	38.6 (8.38)	39.1 (7.14)	39.3 (7.08)
	LS Mean change from baseline at Week 10 (SE)	−15.4 (2.49)	−14.9 (2.62)	−19.7 (2.74)
	Treatment difference vs. sertraline plus placebo (95% CI)	4.2 (−3.15, 11.60)	4.8 (−2.78, 12.32)	
Not Hispanic or Latino	n	97	93	102
	Mean at baseline (SD)	38.9 (8.26)	37.5 (7.53)	39.3 (7.96)
	LS Mean change from baseline at Week 10 (SE)	−16.9 (1.29)	−19.5 (1.32)	−17.0 (1.24)
	Treatment difference vs. sertraline plus placebo (95% CI)	0.1 (−3.45, 3.60)	−2.5 (−6.05, 1.11)	

Source: Statistical Reviewer, results are consistent with Applicant's Summary of Clinical Efficacy, CT-7.4.1.

* Two subjects in the FAS for enriched subjects were excluded from the analysis due to no valid postbaseline CAPS-5 measures. Two subjects with ethnicities of *Other* and *Unknown* were excluded from this subgroup analysis.

Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

Baseline PTSD Severity

We also examined whether the severity of baseline PTSD symptoms, as measured by the CAPS-5, might have led to a different response. As listed in Table 27, we found no significant difference between groups within each subgroup based on the baseline PTSD severity.

Table 27. Subgroup Analysis by Baseline CAPS-5 Total Score—LS Mean Change From Baseline (Week 1) to Week 10 in CAPS-5 Total Score, Study 00072, FAS for Enriched Subjects*

Subgroup	CAPS-5 Total Score	Brexpiprazole 2 mg Plus Sertraline (N=132)	Brexpiprazole 3 mg Plus Sertraline (N=126)	Sertraline Plus Placebo (N=130)
Baseline CAPS-5 27 to 32	n	28	37	28
	Mean at baseline (SD)	29.0 (1.62)	29.5 (1.85)	29.7 (2.40)
	LS Mean change from baseline at Week 10 (SE)	−12.6 (2.12)	−14.0 (1.82)	−15.1 (2.09)
	Treatment difference vs. sertraline plus placebo (95% CI)	2.5 (−3.45, 8.46)	1.4 (−4.37, 7.23)	
Baseline CAPS-5 33 to 42	n	67	54	61
	Mean at baseline (SD)	37.0 (3.00)	37.7 (2.91)	37.7 (3.15)
	LS Mean change from baseline at Week 10 (SE)	−17.5 (1.46)	−19.2 (1.63)	−17.3 (1.57)
	Treatment difference vs. sertraline plus placebo (95% CI)	−0.2 (−4.41, 4.07)	−1.9 (−6.35, 2.58)	
Baseline CAPS-5 ≥43	n	37	33	41
	Mean at baseline (SD)	49.5 (5.75)	47.6 (3.79)	48.3 (4.88)
	LS Mean change from baseline at Week 10 (SE)	−18.3 (2.83)	−20.3 (2.88)	−19.8 (2.43)
	Treatment difference vs. sertraline plus placebo (95% CI)	1.5 (−5.88, 8.94)	−0.5 (−7.99, 6.95)	

Source: Statistical Reviewer.

* Two subjects in the FAS for enriched subjects were excluded from the analysis because of no valid postbaseline CAPS-5 measures.

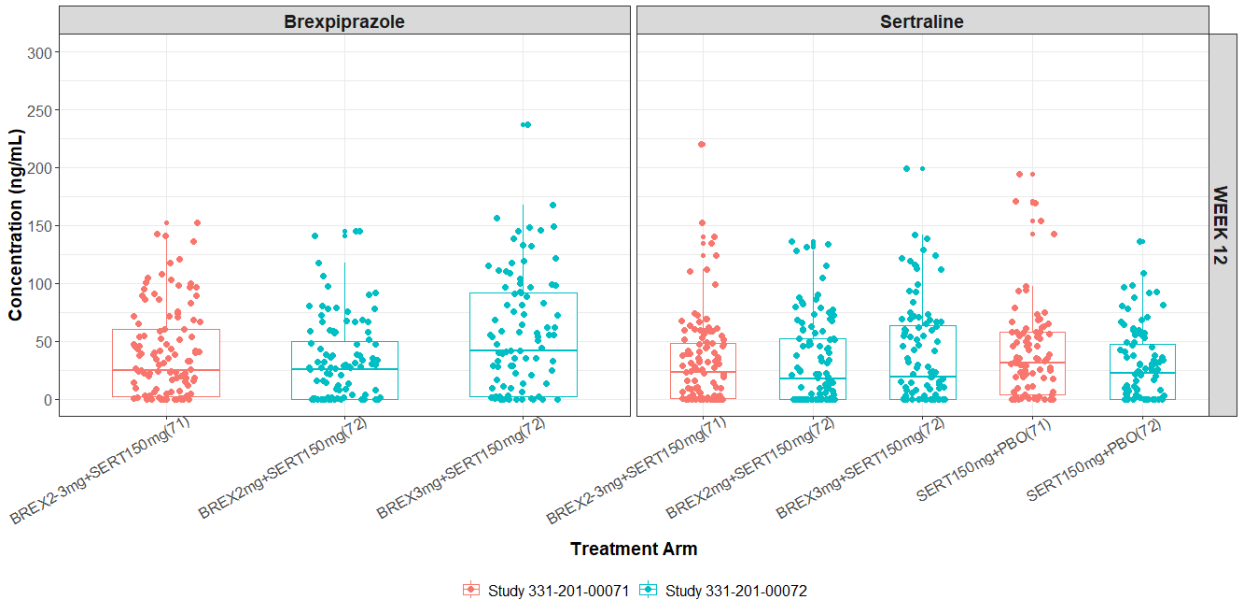
Abbreviations: CAPS-5, Clinician-Administered PTSD Scale for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; CI, confidence interval; FAS, full analysis set; LS, least squares; n, number of subjects included in the subgroup analysis in each treatment group; PTSD, post-traumatic stress disorder; SD, standard deviation; SE, standard error

As mentioned in previous paragraphs, similar analyses in Study 00061 and Study 00071 yielded different results (see Table 18 for Study 00061 and Table 20 for Study 00071).

4.3.4 Pharmacokinetics of Brexpiprazole and Sertraline in Study 00071 and Study 00072

In Studies 00071 and 00072, two postdose pharmacokinetic samples were collected from each subject at Week 6 and Week 12 or at the early termination visit. The plasma concentration ranges for brexpiprazole and sertraline were similar in Studies 00071 and 00072 (Figure 10).

Figure 10. Comparison of Brexpiprazole and Sertraline Concentrations Between Treatment Groups at Week 12 (Studies 00071 and 00072)



Source: Clinical Pharmacology Reviewer.
Abbreviations: BREX, brexpiprazole; PBO, placebo; Sert, Sertraline;71, Study 00071; 72, Study 00072