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Brexpiprazole in Combination with Sertraline for Treatment of Adults with Post-Traumatic Stress Disorder (PTSD)

July 18, 2025

Psychopharmacologic Drugs Advisory Committee

Otsuka Pharmaceutical Co.

Lundbeck Inc.

Introduction

Mary Hobart, PhD

Senior Vice President, Global Regulatory Affairs

Otsuka Pharmaceutical

Post-Traumatic Stress Disorder (PTSD) – Serious and Chronic Psychiatric Disorder

One of most common mental health disorders in US[1]

Caused by traumatic event or circumstance, making it difficult to acknowledge and seek help

Most prevalent among civilian population[2]

1. Kessler et al 2005 ; 2. Lehavot et al 2018

Limited Treatment Options for PTSD

- Only 2 approved pharmacological treatments in US
  - Sertraline (Zoloft)* approved December 7, 1999
  - Paroxetine (Paxil)* approved December 14, 2001

Despite approved treatments, many do not experience adequate clinical response and additional treatment options are needed to address PTSD and its severe consequences

*Selective serotonin reuptake inhibitors (SSRIs)

Seeking Supplemental Application for Brexpiprazole

Proposed sNDA Indication

Brexpiprazole in combination with sertraline for treatment of PTSD in adults

Recommended Dosing

- Target Dose: Brexpiprazole 2 mg/day plus sertraline 150 mg/day
- Maximum Dose: Brexpiprazole 3 mg/day plus sertraline 200 mg/day

Brexpiprazole (REXULTI®) – Currently Approved in 3 Indications

2015
- Treatment of schizophrenia in adults
- Adjunctive therapy to antidepressants for treatment of major depressive disorder in adults

2021
- Treatment of schizophrenia in adolescents

2023
- Treatment of agitation associated with dementia due to Alzheimer's disease

1,689,049 patient-years experience from clinical trials and post-marketing experience

Brexpiprazole in Combination with Sertraline Provides Added Benefit in PTSD

PTSD is associated with abnormalities of norepinephrine, serotonin, and dopamine systems[1-5]

Sertraline[6]

- Selective serotonin reuptake inhibitor

+

Brexpiprazole[7]

- Partial agonist at dopamine D_2 receptors and serotonin 5-HT_{1A} receptors
- Antagonist at serotonin 5-HT_{2A} receptors and norepinephrine α_{1A}, α_{1B}, and α_{2C} receptors

1. Jain, 2024; 2. Strawn, 2008; 3. Young, 2004; 4. Torrisi, 2019; 5. Sherin, 2011; 6. Zoloft PI, 2023; 7. Rexulti PI, 2025

Brexpiprazole in Combination with Sertraline Clinical Program and Key FDA Regulatory Interactions

- **3 completed RCTs in US**
- **Largest PTSD program**
- **> 1,200 adults**

Phase 2 Trial 061
Flexible-dose
4-arm, randomized, controlled, double-blind, multicenter, 12 Weeks

Phase 3 Trial 071
Flexible-dose
2-arm, randomized, controlled, double-blind, multicenter, 12 Weeks

Phase 3 Trial 072
Fixed-dose
3-arm, randomized, controlled, double-blind, multicenter, 12 Weeks

EOP2: End of Phase 2 Meeting

Positive Benefit / Risk for Brexpiprazole in Combination with Sertraline for Treatment of PTSD

1. Only two approved treatments in past 25 years, both with modest and inconsistent efficacy in managing PTSD symptoms across all symptom clusters; many people continue suffering from PTSD and its severe consequences

2. Largest program in PTSD to date; combination treatment more effective in relieving symptoms of PTSD vs sertraline alone in 2 of 3 studies

3. Well tolerated and safety profile consistent with large database from clinical trials and extensive real-world usage in variety of psychiatric indications

4. Potential to address critical unmet clinical need and provide substantial improvement relative to currently approved and off-label treatments

Agenda

Unmet Need	**Arash Javanbakht, MD** Founding Director of the Stress, Trauma, and Anxiety Research Clinic (STARC), Wayne State University School of Medicine
Efficacy	**John Kraus, MD, PhD** Executive Vice President and Chief Medical Officer Otsuka Pharmaceutical
FDA Considerations	**Jason Connor, PhD** President and Lead Statistical Scientist ConfluenceStat, LLC
Safety	**Thomas Thompson, MD** Vice President, Global Clinical Development Therapeutic Head, CNS Otsuka Pharmaceutical
Clinical Perspective	**Kathleen Brady, MD, PhD** Distinguished University Professor and Director, South Carolina Clinical and Translational Research Institute, Medical University of South Carolina

Additional Experts

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Psychiatrist, Medical Director
Advanced Discovery Research

Jingli Song, PhD
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Background and Unmet Need

Arash Javanbakht, MD

Founding Director of the Stress, Trauma, and Anxiety Research Clinic (STARC)

Wayne State University School of Medicine

Post-Traumatic Stress Disorder – One of Most Common Mental Health Disorders in US

~13 million	US adults experience PTSD in a given **year**[1]
~6 of **100**	people will have PTSD in their **lifetime**[2]
~2x	more common in **females** than males[2]
30-59	years of age have **highest** prevalence[3]
86%	of US PTSD population are **civilian** rather than military[4]
$232 billion	annual economic **burden** of PTSD in US[4*]

1. National Center for PTSD 2025; 2. Goldstein 2016; 3. Kessler 2005; 4. Davis 2022; *data from 2018

Diagnostic Criteria for PTSD Include History of Exposure to Traumatic Event

Must experience symptoms from each of the 4 PTSD symptom clusters

Symptom Cluster	Symptom Examples
Intrusion (Re-experiencing) symptoms	Intrusive memories Traumatic nightmares Flashbacks
Persistent Avoidance of stimuli	Avoiding trauma-related thoughts or feelings Avoiding people, places, objects
Negative alterations in Cognition and Mood	Distorted beliefs Guilt, shame, numbing Feelings of alienation
Marked alterations in Arousal and Reactivity	Irritability Hypervigilance Sleep disturbance

Dysfunction and Distress

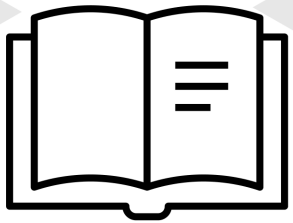
PTSD Is Associated with Considerable Humanistic and Clinical Burden

- ~80% of people with PTSD have a psychiatric comorbidity[1]
  - Depression, anxiety, and substance use disorder[2]
- Overall impaired psychosocial functioning and lowered QoL[3]
- Increased risk of cardiovascular disease, metabolic disorders, and chronic pain[4,5]
- Increased rates of suicide attempt (odds ratio = 5.1)[6]
- PTSD associated with 47% increase in mortality risk[7]
- Profound public health burden[8]

1. National Center for PTSD 2025; 2. Yehuda 2015; 3. Rodriguez 2012; 4. Goldstein 2016; 5. Sumner 2023; 6. Pietrzak 2011; 7. Nilaweera 2023; 8. Al Jowf 2022

Need for More and Better Pharmacologic Treatment Options for PTSD

Guidelines[1,2]



Psychotherapy

Including:

- Cognitive behavioral and processing therapy
- Prolonged exposure therapy
- Eye movement desensitization and reprocessing

Pharmacotherapy

If pharmacotherapy is indicated:

- **Sertraline** } **PTSD Approved ~25 years ago**
- **Paroxetine** }
- Venlafaxine
- Fluoxetine

Limitations

- Barriers prevent access to trauma-based psychotherapy[1]

- Improvements in some PTSD clusters (negative mood / cognition)[3]
- Individual trials fail to show consistent efficacy on PTSD symptom clusters, particularly intrusion and arousal[3]

Approximately ~70% of patients with PTSD experience residual symptoms after treatment[4-6]

1. American Psychological Association 2025; 2. Department of Veterans Affairs 2023; 3. Williams 2022; 4. Tripp 2020; 5. Schnurr 2019; 6. Kline 2024

PTSD Symptoms Often Managed Using Unapproved and Non-Evidence-Based Off-Label Treatments

- Only approximately 20% of patients on pharmacotherapy receive an FDA-approved treatment[1]
- Other SSRIs, SNRIs, benzodiazepines, anxiolytics or sedative hypnotics, alpha blockers, and antipsychotics[2]
- Following PTSD diagnosis, 41% of patients receive polypharmacy therapy in their first line of treatment[3]
- 7 out of 10 need to switch medicine in the first two years of treatment[4]

Most common reason for treatment change is "inadequate/suboptimal management of PTSD symptoms with prior treatment"[4]

1. Holder 2021; 2. Cook 2021; 3. Data on file; 4. Davis 2024

Summary of Unmet Need

1. PTSD is a debilitating, potentially lethal condition with high prevalence of serious comorbidities
2. Only 2 approved pharmacotherapy treatments with modest and varied response rates that do not address all PTSD symptom clusters
3. Trial-and-error polypharmacy with unapproved and non-evidence-based therapies come with notable safety problems
4. Need for effective, evidence-based, and tolerable options that better address patients' burdensome, heterogeneous, and complex symptoms

Efficacy

John Kraus, MD, PhD

Executive Vice President and Chief Medical Officer

Otsuka Pharmaceutical

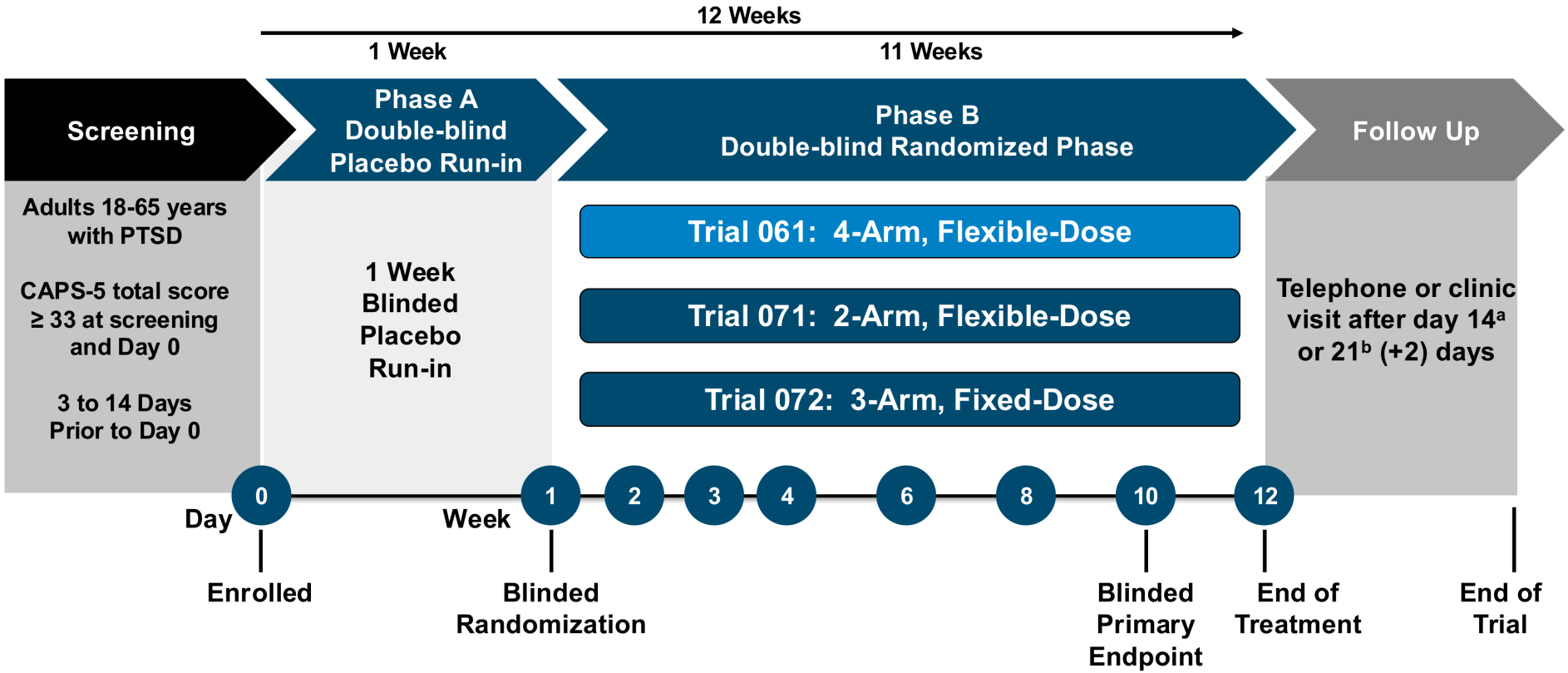
Brexpiprazole Plus Sertraline Clinical Development Program

Phase 2 Trial 061
Flexible-dose
4-arm, randomized, controlled, double-blind, multicenter, 12 Weeks

Phase 3 Trial 071
Flexible-dose
2-arm, randomized, controlled, double-blind, multicenter, 12 Weeks

Phase 3 Trial 072
Fixed-dose
3-arm, randomized, controlled, double-blind, multicenter, 12 Weeks

Similar Clinical Trial Designs Across 3 Trials



a. Trial 061; b. Trial 071 & 072

Enrollment Criteria Generally Consistent Across 3 Trials

- 18-65 years of age
- Diagnosis of PTSD as defined in DSM-5 and confirmed by Mini International Neuropsychiatric Interview (MINI)
- Symptomatic for ≥ 6 months prior to screening
- CAPS-5 total score ≥ 33 at screening and Day 0
- Index traumatic event that led to development of PTSD
  - Within 15 years prior to screening for Trial 061
  - Within 9 years prior to screening for Trials 071 and 072
- No trauma types excluded

Same Prespecified Primary Endpoint Across 3 Trials

Primary Endpoint

Change from Baseline (Week 1) to Week 10 in Clinician-Administered PTSD Scale (CAPS-5) total score

- Clinician-reported outcome measure highly relevant to patients with PTSD
- Completed via structured interview by rigorously trained and certified interviewers
- Designed to assess severity of 20 PTSD symptoms, each on 0-4 scale

Similar Secondary Endpoints Across 3 Trials

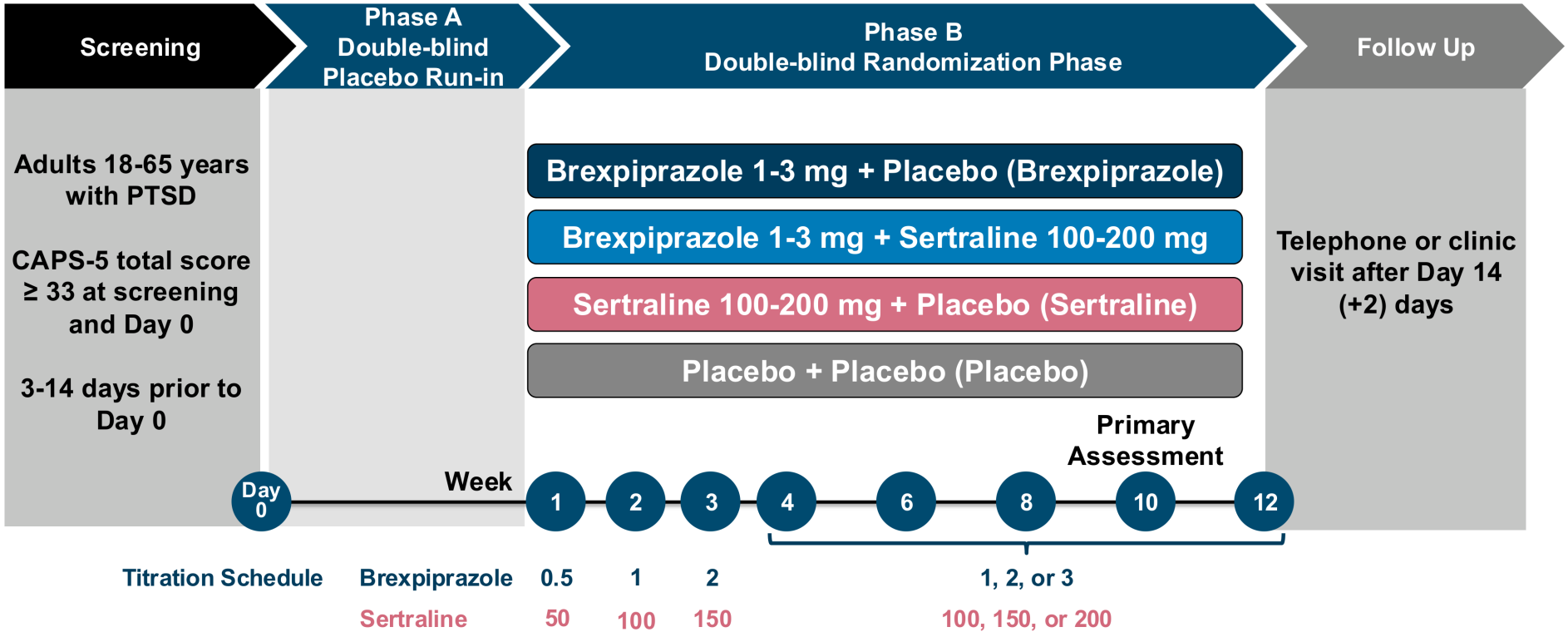
Endpoint	Clinician-Reported Outcomes
CGI-S Score (key secondary*)	Severity of illness
CAPS-5 Subscale – Intrusion	Severity of symptoms
CAPS-5 Subscale – Avoidance	Severity of symptoms
CAPS-5 Subscale – Cognition and Mood	Severity of symptoms
CAPS-5 Subscale – Arousal and Reactivity	Severity of symptoms
	Patient-Reported Outcomes
B-IPF Total Score (key secondary*)	Psychosocial functioning
PCL-5 Total Score	Severity of symptoms
HADS Subscale – Anxiety	Screening for symptoms of anxiety
HADS Subscale – Depression	Screening for symptoms of depression

CGI-S: Clinical Global Impression Severity; B-IPF: Brief Inventory of Psychosocial Function; PCL-5: PTSD Checklist for DSM-5; HADS: Hospital Anxiety and Depression Scale

*In Trial 061, CGI-S was included as other efficacy endpoint and B-IPF was not assessed

Phase 2 Trial 061

Trial 061: 4-Arm, Multifactorial Flexible-Dose



Trial 061: Original Protocol and Addendum

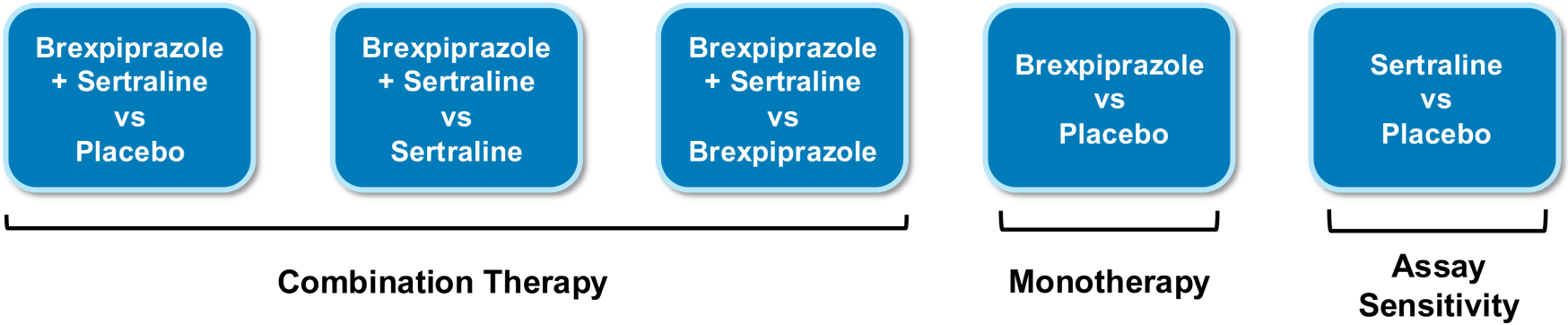
- **Original Protocol – September 2016**
  - Primary objective: evaluate efficacy of brexpiprazole as monotherapy or as combination treatment with sertraline
  - Protocol: hierarchical testing procedure, ordered 1, 2, 3

- **Revised Protocol Addendum – June 2017**
  - Additional test(s) might be added, and order of tests subject to change
  - Final order of hierarchical statistical testing procedure will be specified in SAP

SAP: Statistical Analysis Plan

Trial 061: Final SAP

- **Final SAP – November 2018**
  - Finalized prior to database lock and unblinding
  - Pre-specified 5 comparisons with no hierarchical testing to reduce risk of not being able to test combination



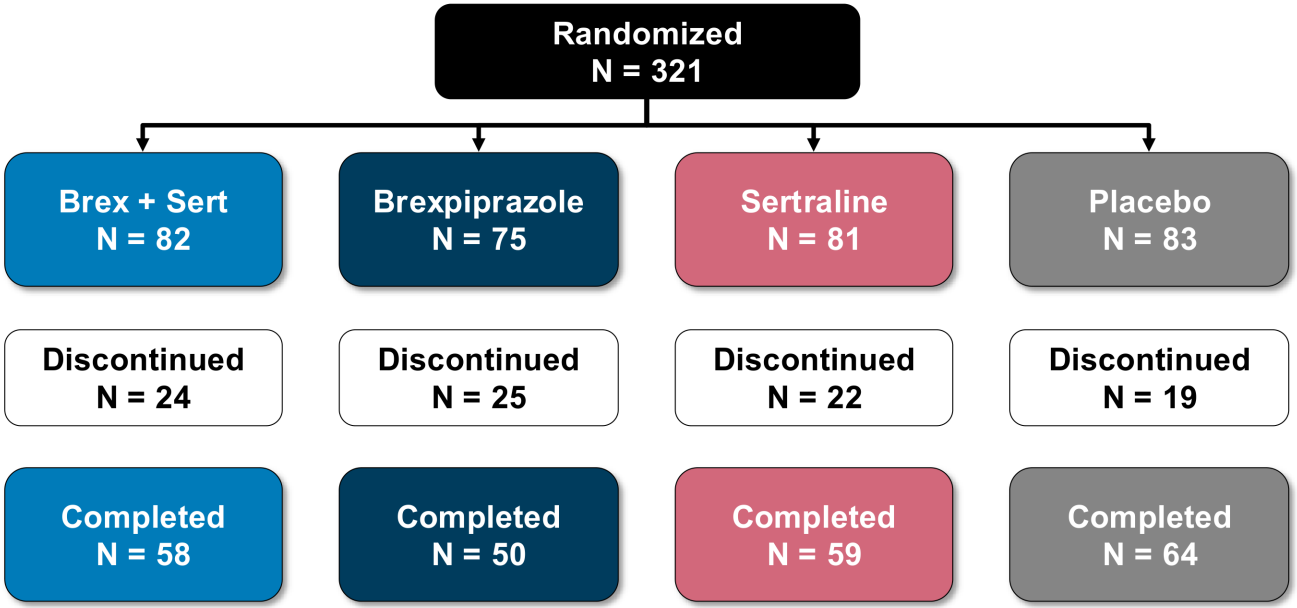
  - Powered for pairwise comparisons of primary endpoint
  - Prespecified sensitivity analyses to assess robustness of primary endpoint results under Missing at Random (MAR) assumption

Trial 061: Primary Efficacy Analysis Population

Full Analysis Set (FAS) – Efficacy Sample

- All patients randomized
  - Received ≥ 1 dose of treatment
  - Had baseline assessment and ≥ 1 post treatment assessment

Trial 061: Patient Disposition



Efficacy Analysis Sample
≥ 1 dose, ≥ 1 post treatment assessment

N = 79 | N = 72 | N = 77 | N = 80

Trial 061: Demographics Generally Balanced Across Groups and Representative of Intended Population

	Brex + Sert N = 82	Brexpiprazole N = 75	Sertraline N = 81	Placebo N = 83
Age (years), mean	38.4	39.3	38.6	40.3
Female	62%	65%	63%	58%
BMI (kg/m^2), mean	30	30	30	30
Race, White	67%	57%	65%	55%
Race, Black or African American	26%	31%	27%	31%
Ethnicity, Hispanic or Latino	16%	15%	14%	17%
Years since index traumatic event, mean	7	6	6	7
Treatment history				
Previous psychotherapy	35%	36%	38%	36%
Previous pharmacotherapy	44%	35%	48%	49%

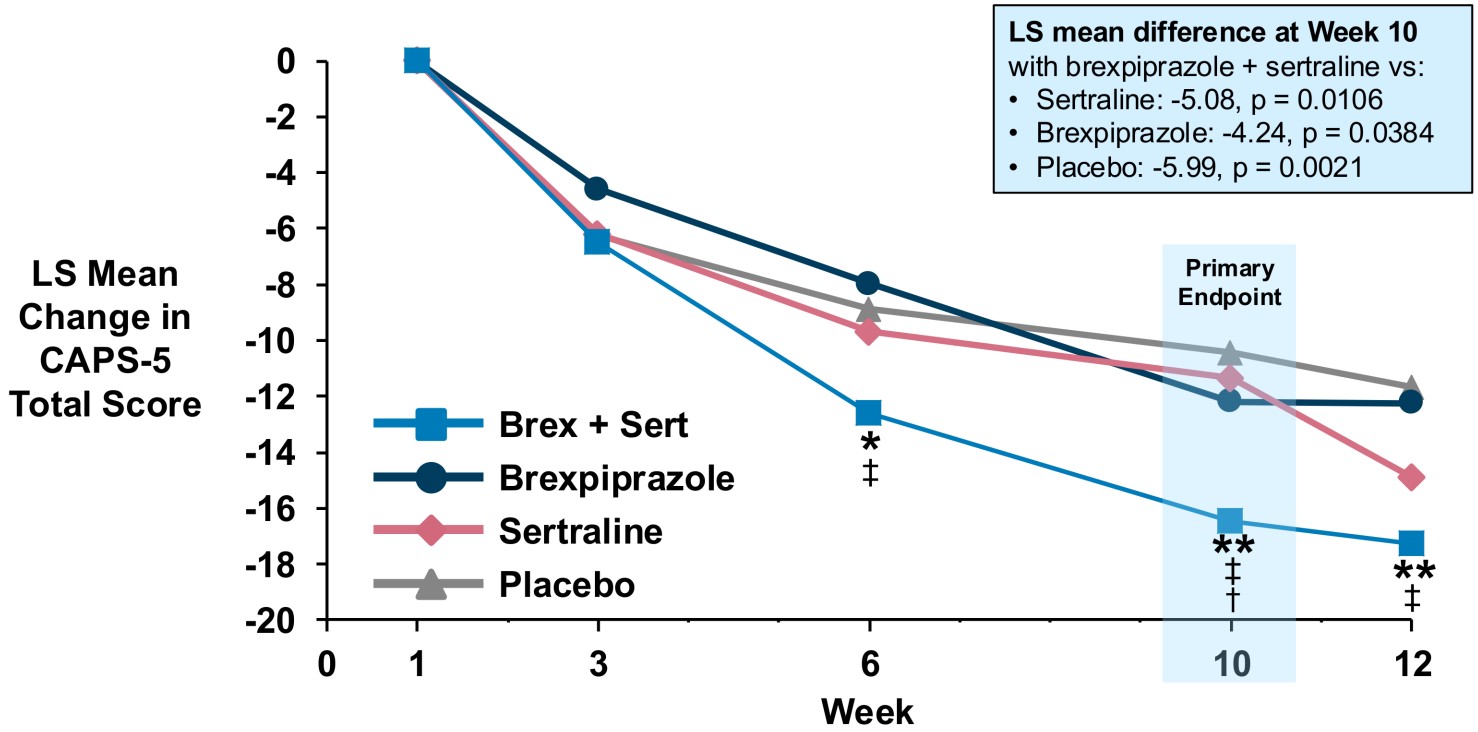
Randomized Sample

Trial 061: Baseline Efficacy Scale Scores Similar Across Treatment Groups

Baseline Score, Mean	Brex + Sert N = 79	Brexpiprazole N = 72	Sertraline N = 77	Placebo N = 80
CAPS-5 Total Score	35.5	34.2	36.8	35.3
CGI-S	4.4	4.3	4.4	4.4
PCL-5 Total Score	43.9	44.3	44.6	42.7

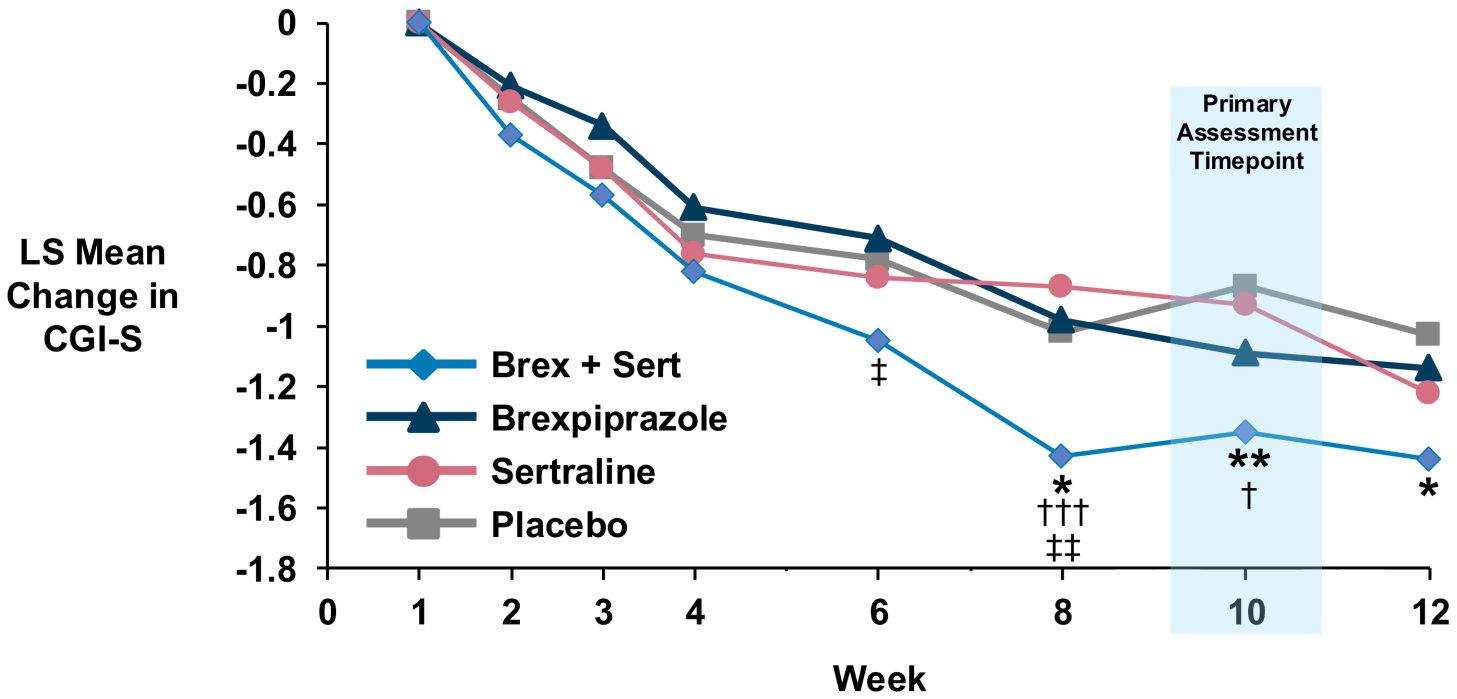
Efficacy Sample

Trial 061: Early and Consistent Benefit with Combination of Brexpiprazole Plus Sertraline in CAPS-5 Total Score



Nominal p-value vs placebo: *p <0.05, **p <0.01
Nominal p-value vs sertraline + placebo: † p <0.05;
Nominal p-value vs brex + placebo: ‡ p <0.05
Baseline CAPS-5 Placebo = 35.14, n = 78; Brexpiprazole = 33.88, n = 69; Sertraline = 36.51, n = 75; Brex + sert = 35.73, n = 77

Trial 061: CGI-S Score Consistent with CAPS-5 Combination Better vs All Other Treatment Arms



Nominal p-value vs placebo: *p <0.05, **p <0.01;
Nominal p-value vs sert + placebo: † p <0.05; ††† p <0.001;
Nominal p-value vs brex + placebo: ‡ p <0.05, ‡‡ p <0.01

Baseline CGI-S (at Week 1) Placebo = 4.38, n = 80, Brex = 4.26, n = 72, Sertraline = 4.38, n = 77 , Combo = 4.42, n = 78

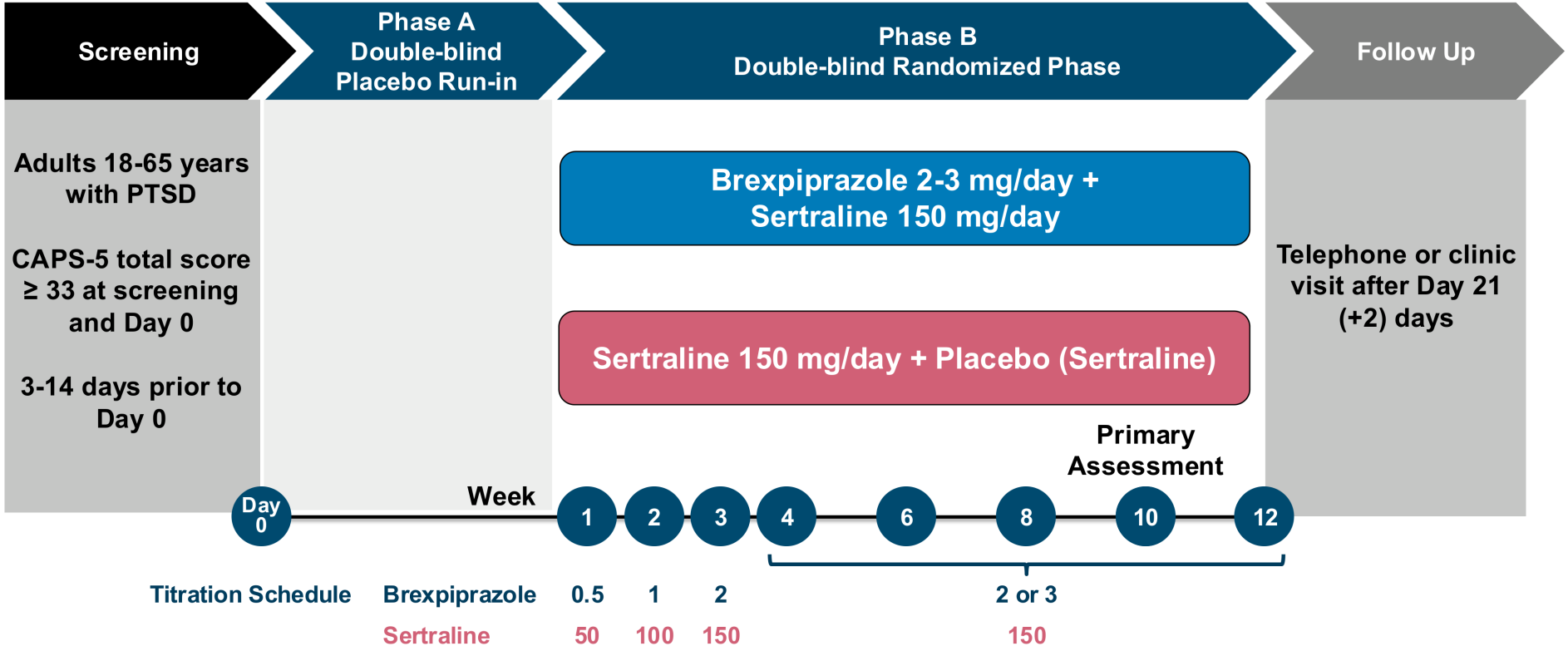
Trial 061: Treatment Benefit with Combination of Brexpiprazole Plus Sertraline Across Secondary Endpoints

Endpoint	Brexpiprazole + Sertraline vs Sertraline Treatment Difference (95% CI)	Nominal p-value
CGI-S	**-0.42** (-0.76, -0.08)	**0.0167**
CAPS-5 Subscale Intrusion (Re-Experiencing)	**-2.06** (-3.51, -0.60)	**0.0058**
CAPS-5 Subscale Avoidance	**-0.79** (-1.50, -0.09)	**0.0273**
CAPS-5 Subscale Negative Cognition / Mood	**-1.82** (-3.44, -0.19)	**0.0285**
CAPS-5 Subscale Arousal	**-0.56** (-1.69, 0.58)	**0.3325**
PCL-5	**-4.93** (-9.83, -0.03)	**0.0487**
HADS - Anxiety	**-1.55** (-2.92, -0.17)	**0.0274**
HADS - Depression	**-1.94** (-3.23, -0.65)	**0.0033**

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

Trial 071

Trial 071: 12-Week, Multicenter, Double-Blind, Randomized, 2-Arm, Flexible Dose



Trials 071 / 072: Primary Efficacy Analysis Population

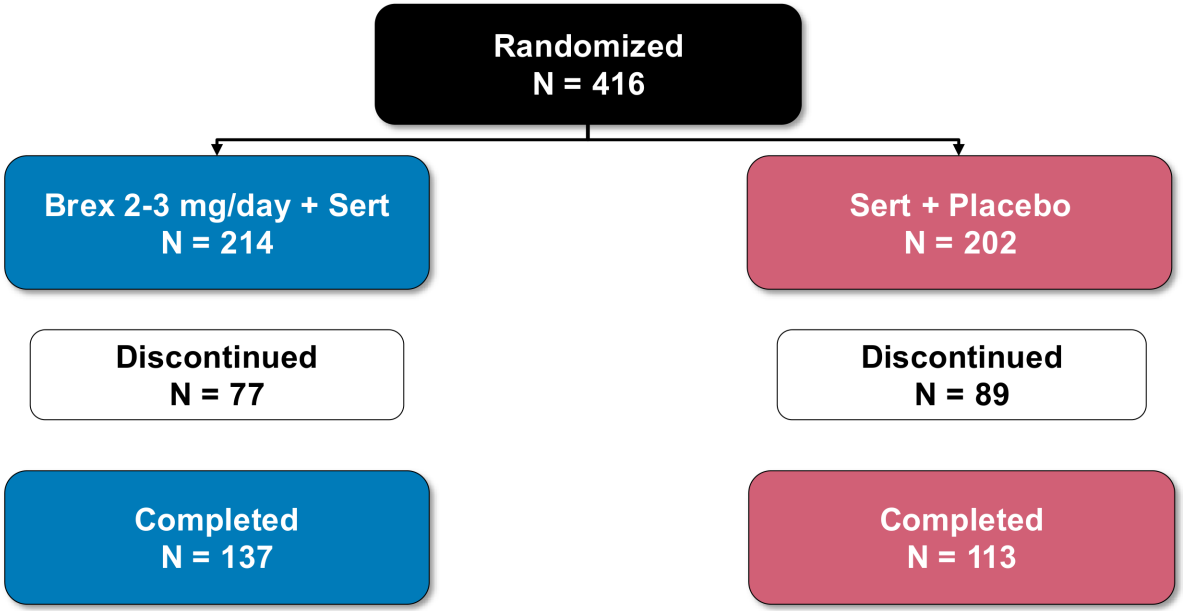
Full Analysis Set (FAS) – Efficacy Sample

- All patients randomized
  - Received ≥ 1 dose of randomized treatment
  - Had baseline assessment and ≥ 1 post treatment assessment

and

  - Met pre-specified Efficacy Sample criteria
    - CAPS-5 total score of ≥ 27 at randomization visit Week 1
    - Improvement in CAPS-5 total score of < 50% at end of placebo run-in phase (Week 1)

Trial 071: Patient Disposition



Pre-specified Efficacy Sample

≥ 1 dose, ≥ 1 post treatment assessment, < 50% CAPS-5 Change from Day 0 and CAPS-5 ≥ 27 at week 1

N = 149

N = 137

Trial 071: Demographics Balanced Between Groups

	Brex + Sert N = 214	Sertraline N = 202
Age (years), mean	38	37
Female	74%	75%
BMI (kg/m^2), mean	30	30
Race, White	69%	71%
Race, Black or African American	23%	19%
Ethnicity, Hispanic or Latino	14%	16%
Years since traumatic event, mean	4	4
Treatment history		
Previous psychotherapy	37%	29%
Previous pharmacotherapy	29%	25%

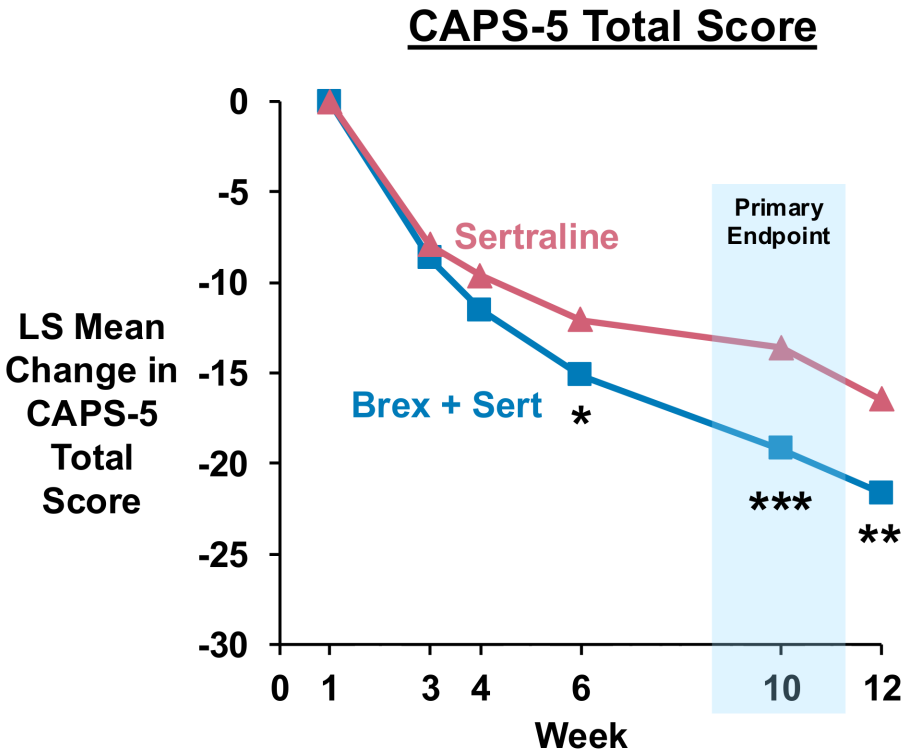
Randomized sample

Trial 071: Baseline Efficacy Scale Scores Balanced Between Treatment Groups

Clinical Characteristics, mean	Brex + Sert N = 149	Sertraline N = 137
CAPS-5 Total Score	38.3	38.8
CGI-S	4.6	4.6
B-IPF Total Score	65.2	64.3
PCL-5 Total Score	47.4	48.0

Efficacy sample

Trial 071: Met Primary Endpoint with Statistically Significant and Clinically Meaningful Reduction in CAPS-5



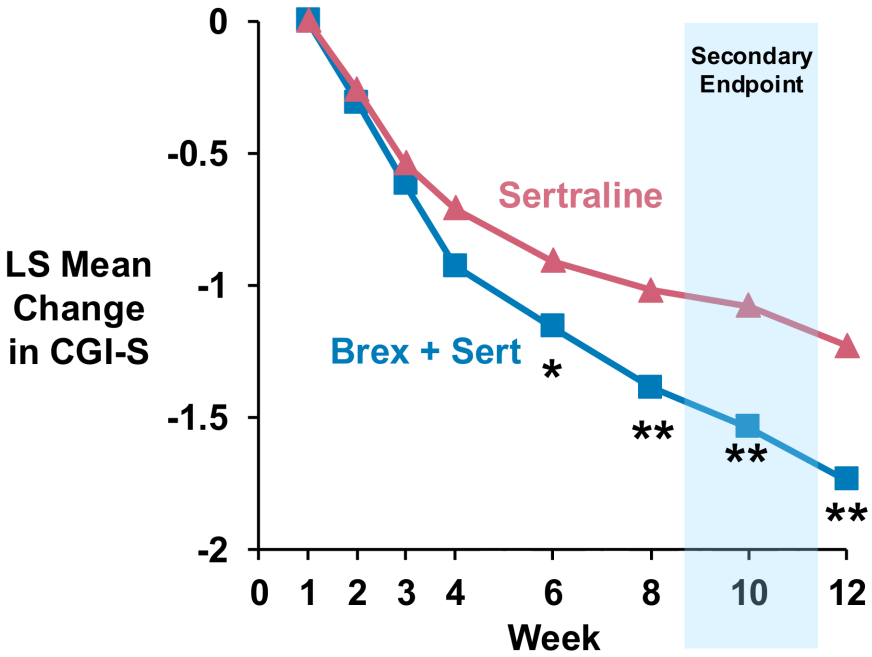
	Brexpiprazole + Sertraline	Sertraline
CAPS-5 Total score at Week 1, Mean (SD)	**38.35** (7.18)	**38.68** (7.75)
Mean Change in CAPS-5 Total score at Week 10, LS Mean (SE)	**-19.19** (1.17)	**-13.61** (1.24)
Treatment Difference at Week 10 (95% CI)	**-5.59** (-8.79, -2.38)	
p-value	**0.0007**	

Nominal *p <0.05, **p <0.01, ***p <0.001

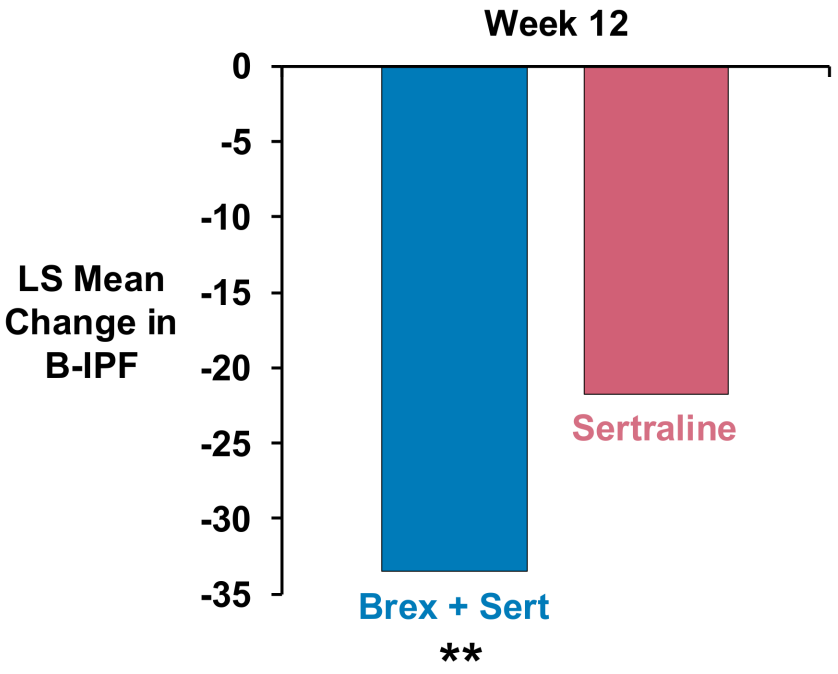
Baseline CAPS-5 Total Score: Brex + Sert = 38.35, n = 148; sertraline = 38.68, n = 134

Trial 071: Statistically Significant Improvement on Both Key Secondary Endpoints

CGI-Severity Score

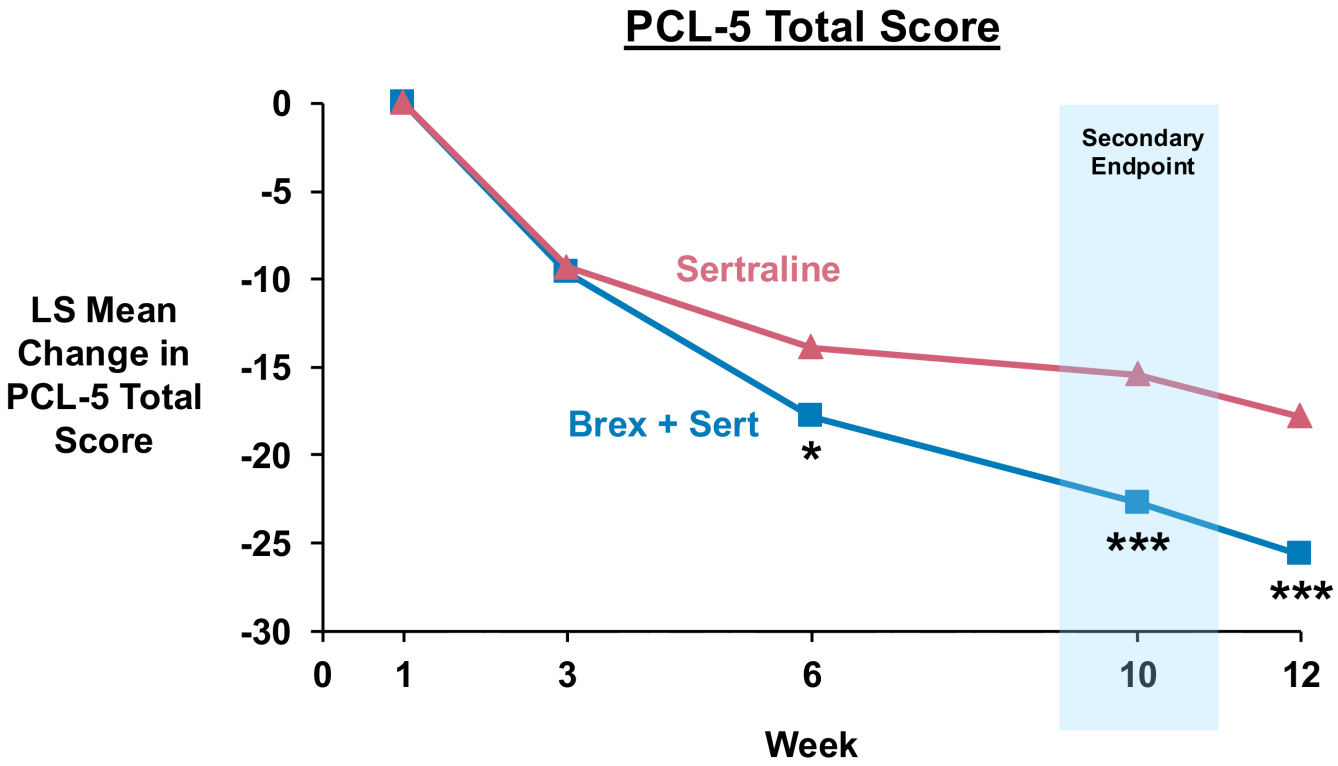


B-IPF Total Score



Nominal *p <0.05, **p <0.01

Trial 071: Statistically Significant Reduction in PCL-5 Total Score



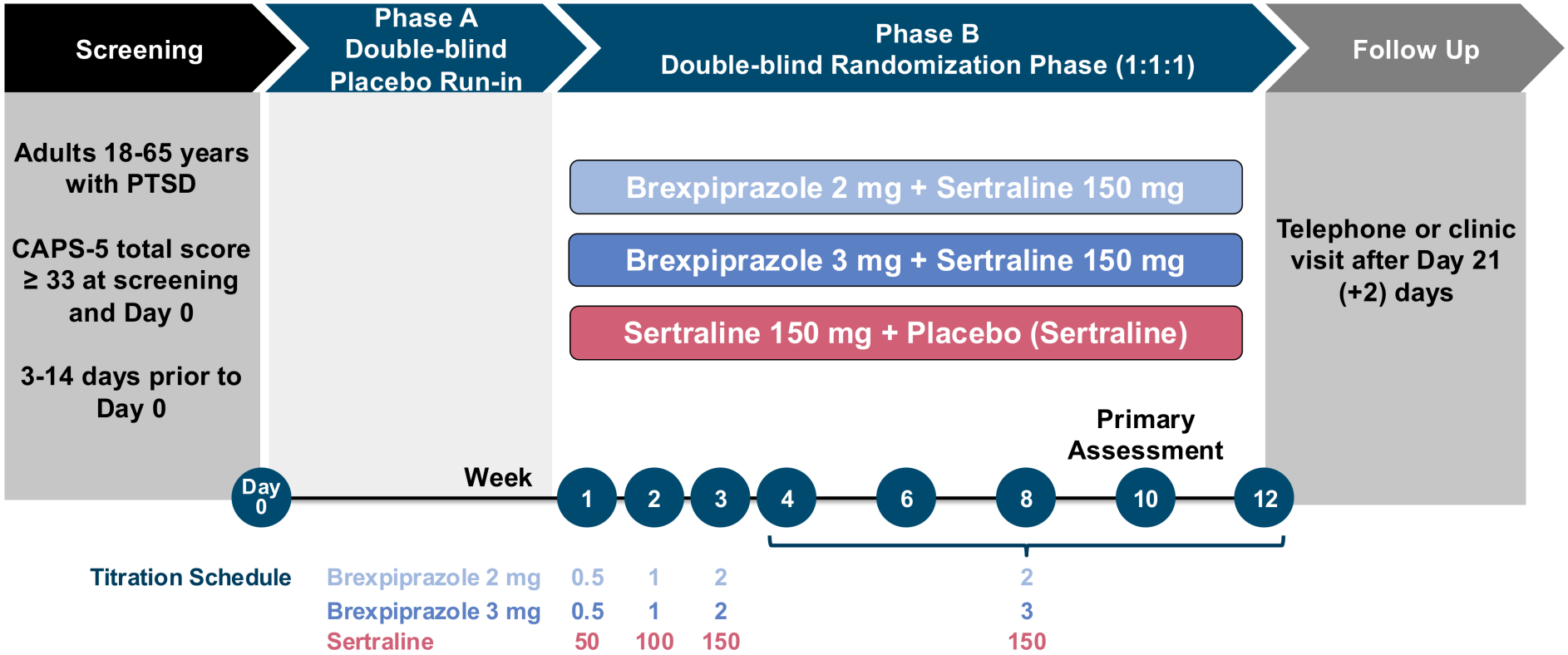
Nominal *p <0.05, ***p <0.001

Trial 071: Secondary Efficacy Endpoints

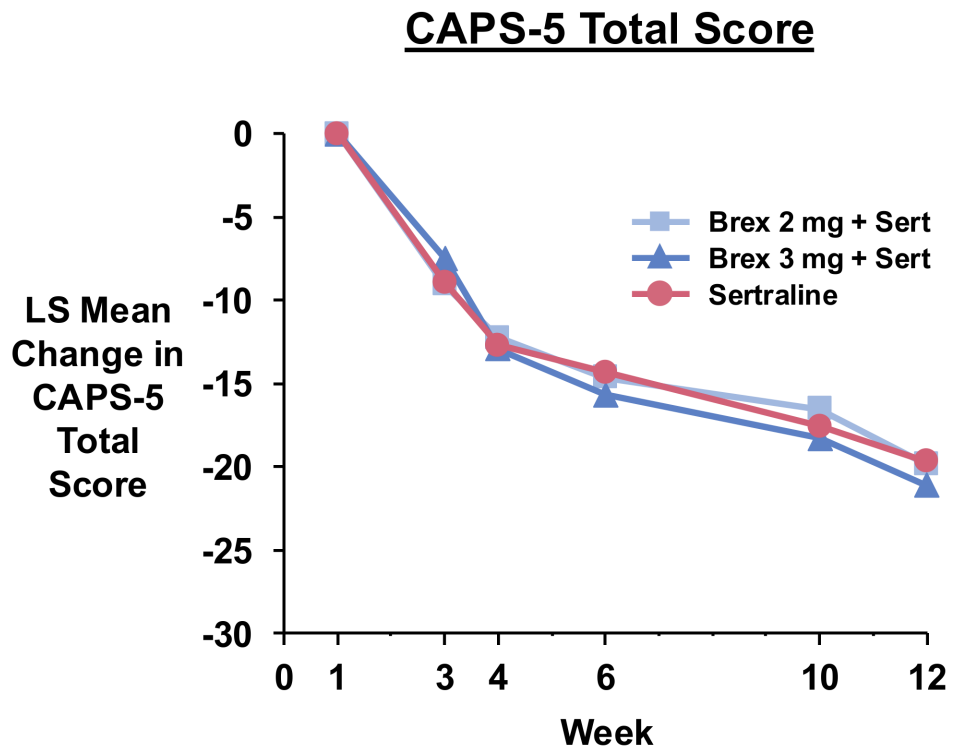
Endpoint	Brexpiprazole + Sertraline vs Sertraline LS Mean Change (95% CI)	p-value
CGI-S	**-0.47** (-0.76, -0.17)	**0.0019**
B-IPF	**-12.03** (-19.44, -4.62)	**0.0016**
CAPS-5 Subscale Intrusion (Re-experiencing)	**-1.69** (-2.76, -0.62)	**0.0022**
CAPS-5 Subscale Avoidance	**-0.74** (-1.32, -0.15)	**0.0134**
CAPS-5 Subscale Negative Cognition / Mood	**-1.94** (-3.33, -0.55)	**0.0065**
CAPS-5 Subscale Arousal	**-1.35** (-2.25, -0.45)	**0.0036**
PCL-5	**-7.28** (-11.50, -3.06)	**0.0008**
HADS - Anxiety	**-1.56** (-2.72, -0.41)	**0.0083**
HADS - Depression	**-1.34** (-2.49, -0.19)	**0.0223**

Trial 072

Trial 072: 12-Week, Multicenter, Double-Blind, Randomized, 3-Arm, Fixed Dose



Trial 072: Primary Efficacy Endpoint Not Met; Change in Combination Arm Consistent with Other Trials

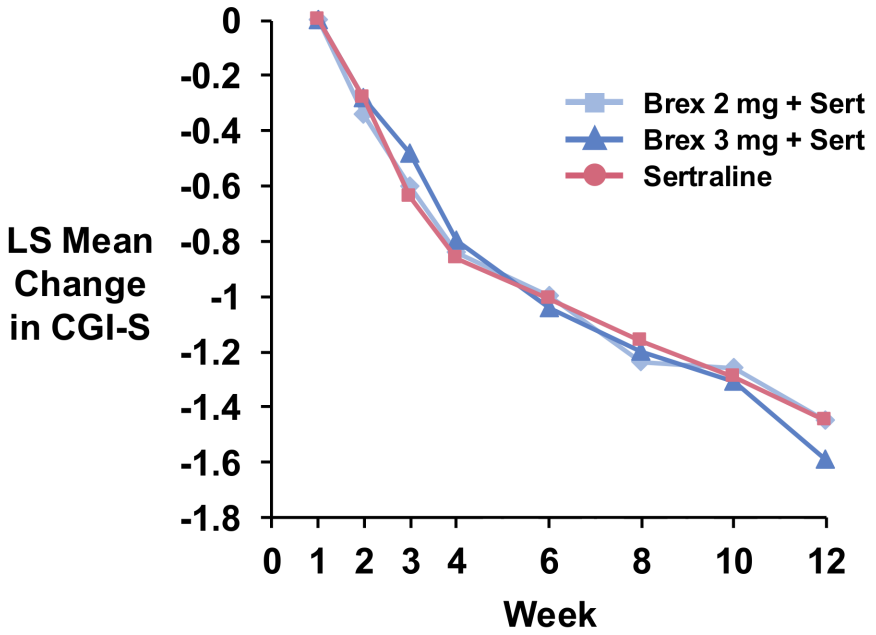


	Brex 2 mg + Sert N = 132	Brex 3 mg + Sert N = 124	Sertraline N = 130
CAPS-5 Total Score, MMRM			
Mean Baseline (SD)	**38.80** (8.26)	**37.88** (7.38)	**39.30** (7.75)
LS Mean Change at Week 10 (SE)	**-16.53** (1.19)	**-18.28** (1.23)	**-17.57** (1.19)
Treatment Difference (95% CI)	**1.03** (-2.09, 4.16)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

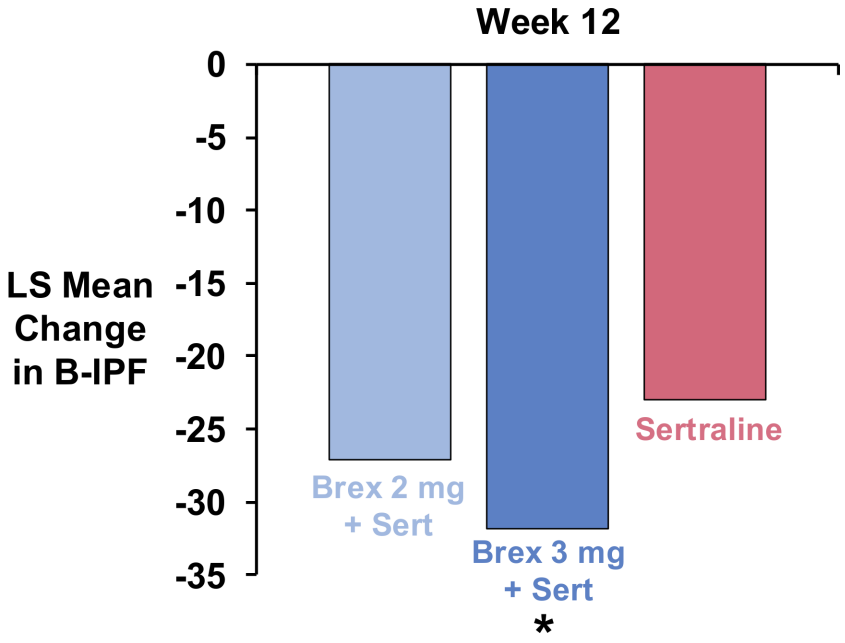
Baseline CAPS-5 Brex 2 mg = 38.80, n = 132; Brex 3 mg = 37.88, n = 124; Sertraline = 39.30, n = 130

Trial 072: Key Secondary Endpoints Showed Numerical Improvement with Brexpiprazole 3 mg

CGI-Severity Score

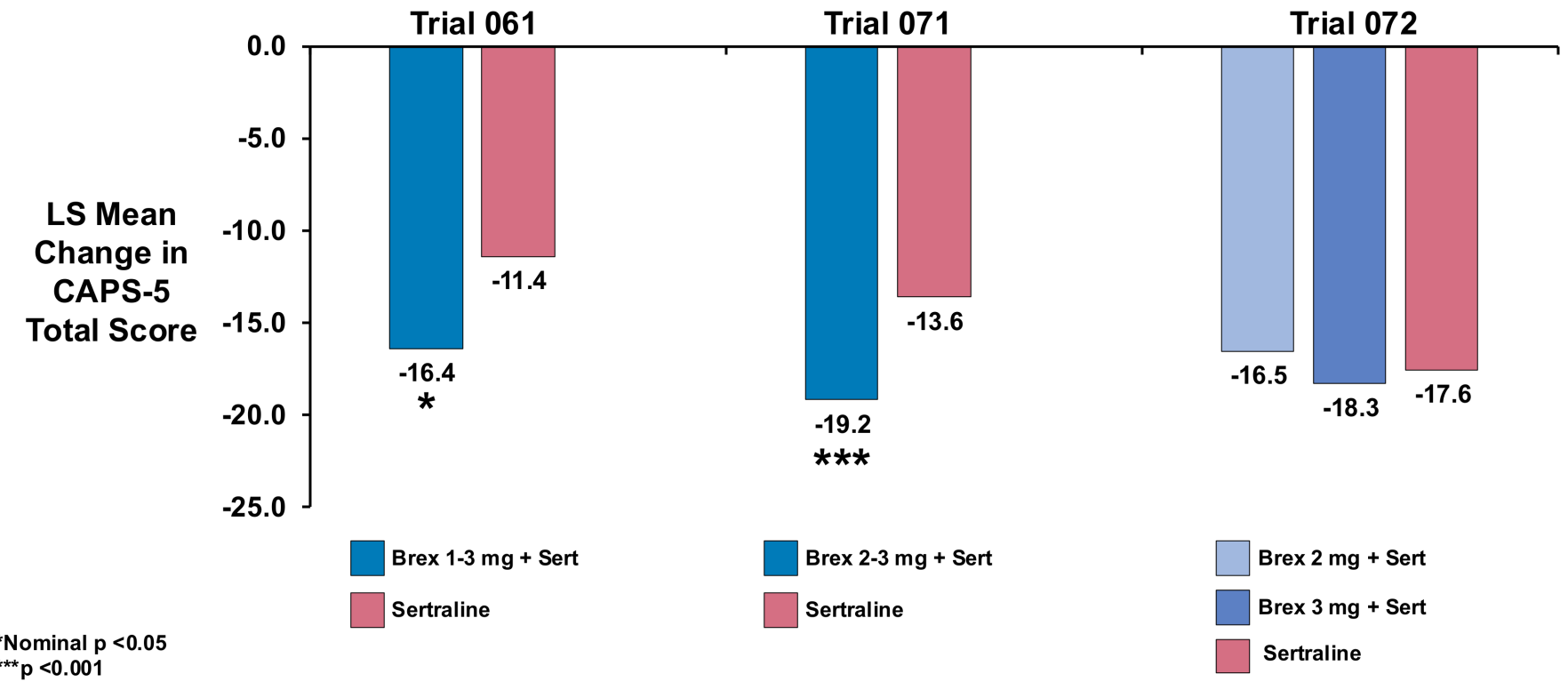


B-IPF Total Score



*p <0.05

Demonstrated Benefit with Combination Treatment on Primary Endpoint



*Nominal p <0.05
***p <0.001

Trial 061 FDA Statistical Considerations

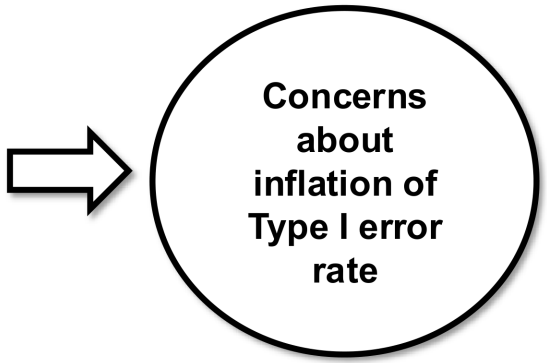
Jason Connor, PhD

President and Lead Statistical Scientist

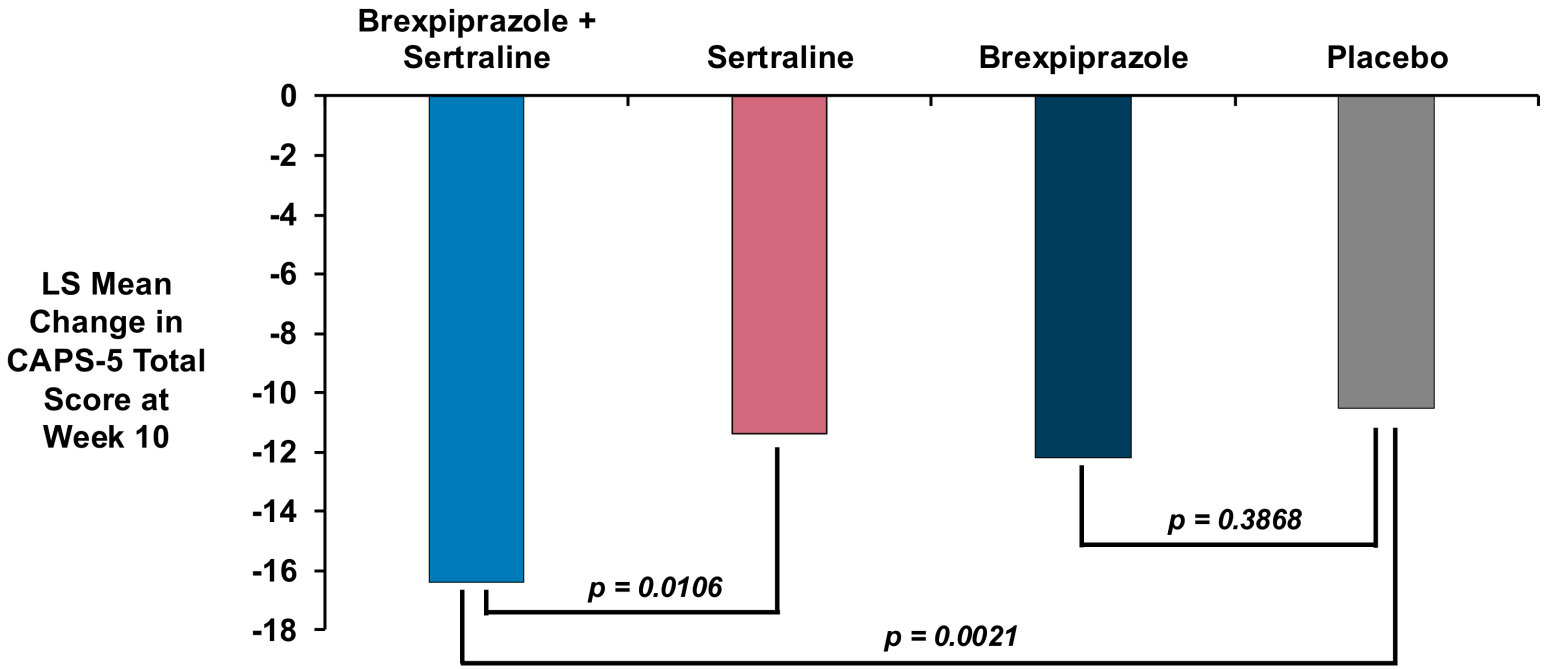
ConfluenceStat, LLC

Trial 061: FDA Considerations

FDA Considerations
Study 061, originally designed as an exploratory phase 2 study, was retrospectively analyzed to provide additional efficacy evidence.
Post hoc application of multiplicity control methods.
Retrospective selection of comparisons of interest.
Deviation from originally prespecified hierarchical testing procedure.



Trial 061: 10 Week Improvement Is Highest in Combination of Brexpiprazole Plus Sertraline Group



Nominal p-values
Baseline CAPS-5 Placebo = 35.14, n = 78; Brex = 33.88, n = 69; Sertraline = 36.51, n = 75; Brex + sert = 35.73, n = 77

Type 1 Error Is Question of Replicability

FDA Considerations
Study 061, originally designed as an exploratory phase 2 study, was retrospectively analyzed to provide additional efficacy evidence.
Post hoc application of multiplicity control methods.
Retrospective selection of comparisons of interest.
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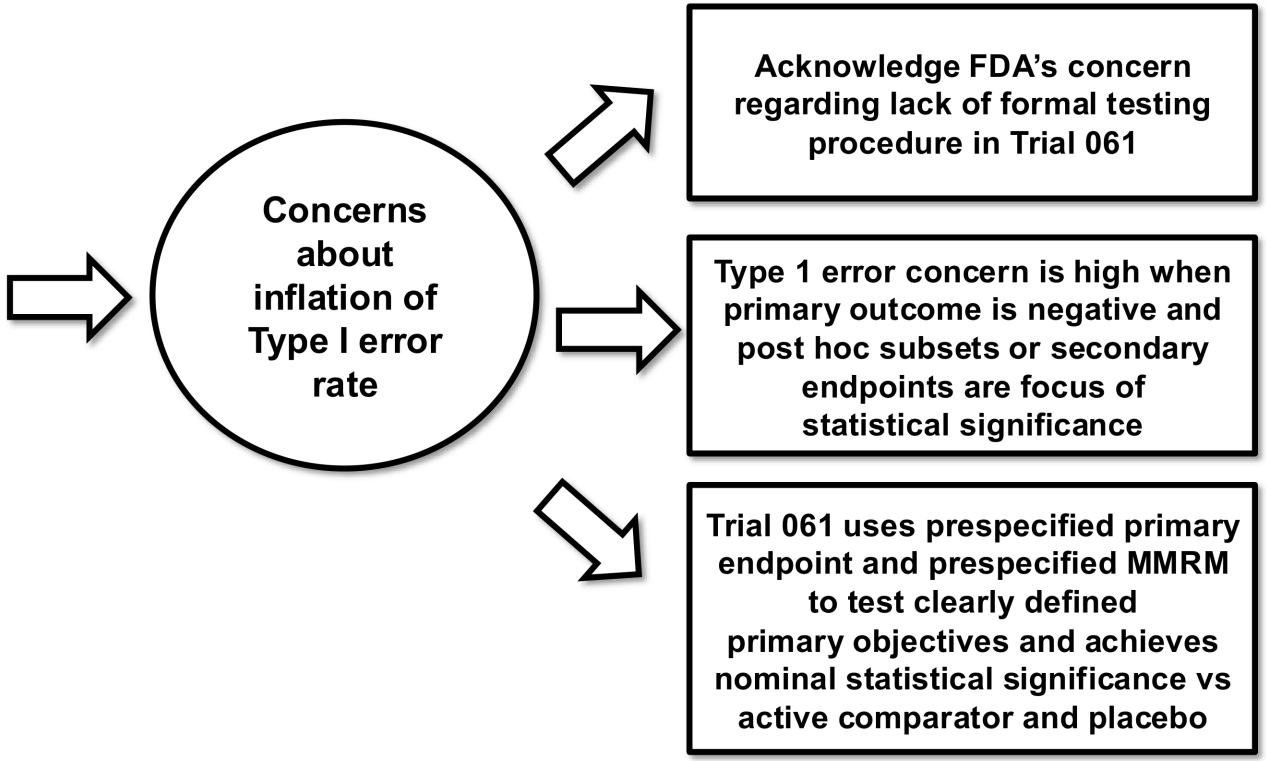
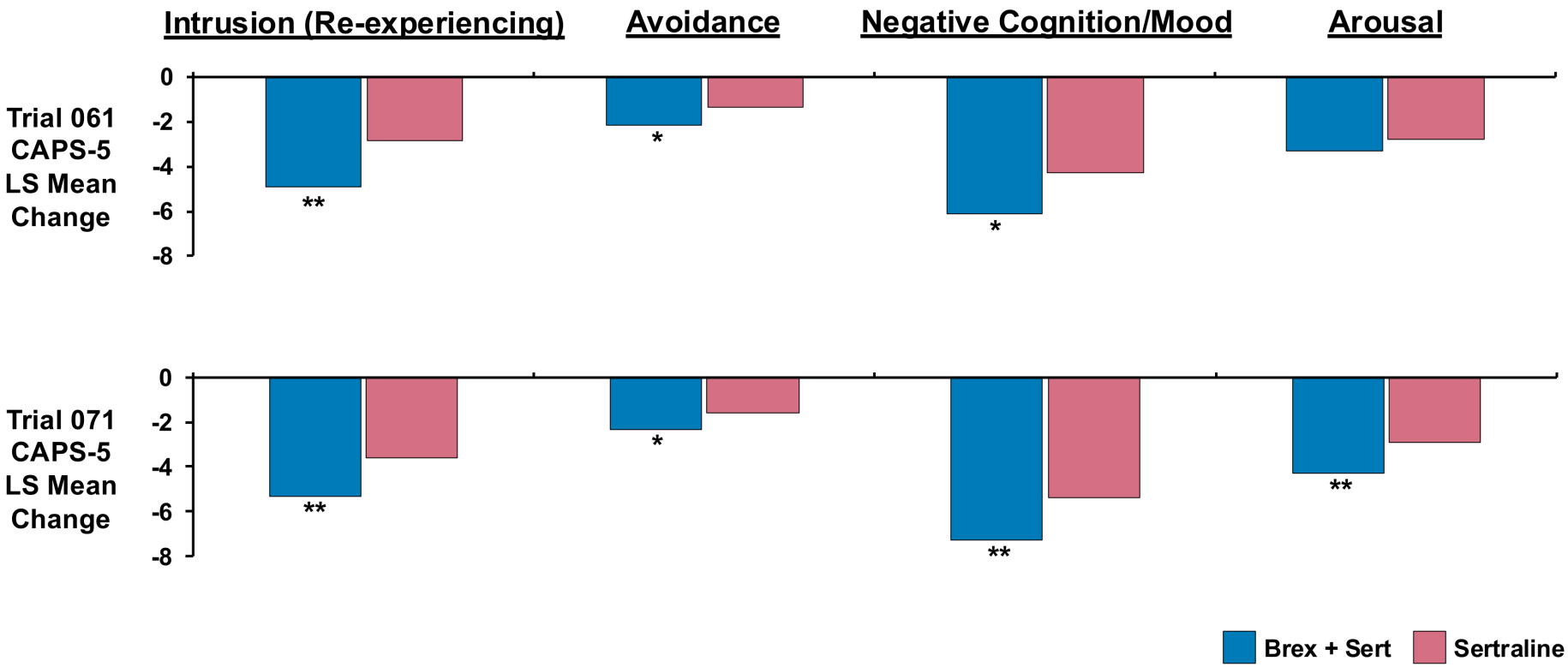


Trial 061 Results Consistently Replicated by 071

Endpoint	Trial 061		Trial 071	
	Treatment Difference	p-value	Treatment Difference	p-value
CAPS-5	-5.08	0.0106	-5.59	0.0007
CGI-S	-0.42	0.0167	-0.47	0.0019
CAPS-5 Subscale Intrusion (Re-experiencing)	-2.06	0.0058	-1.69	0.0022
CAPS-5 Subscale Avoidance	-0.79	0.0273	-0.74	0.0134
CAPS-5 Subscale Negative Cognition / Mood	-1.82	0.0285	-1.94	0.0065
CAPS-5 Subscale Arousal	-0.56	0.3325	-1.35	0.0036
PCL-5	-4.93	0.0487	-7.28	0.0008
HADS - Anxiety	-1.55	0.0274	-1.56	0.0083
HADS - Depression	-1.94	0.0033	-1.34	0.0223

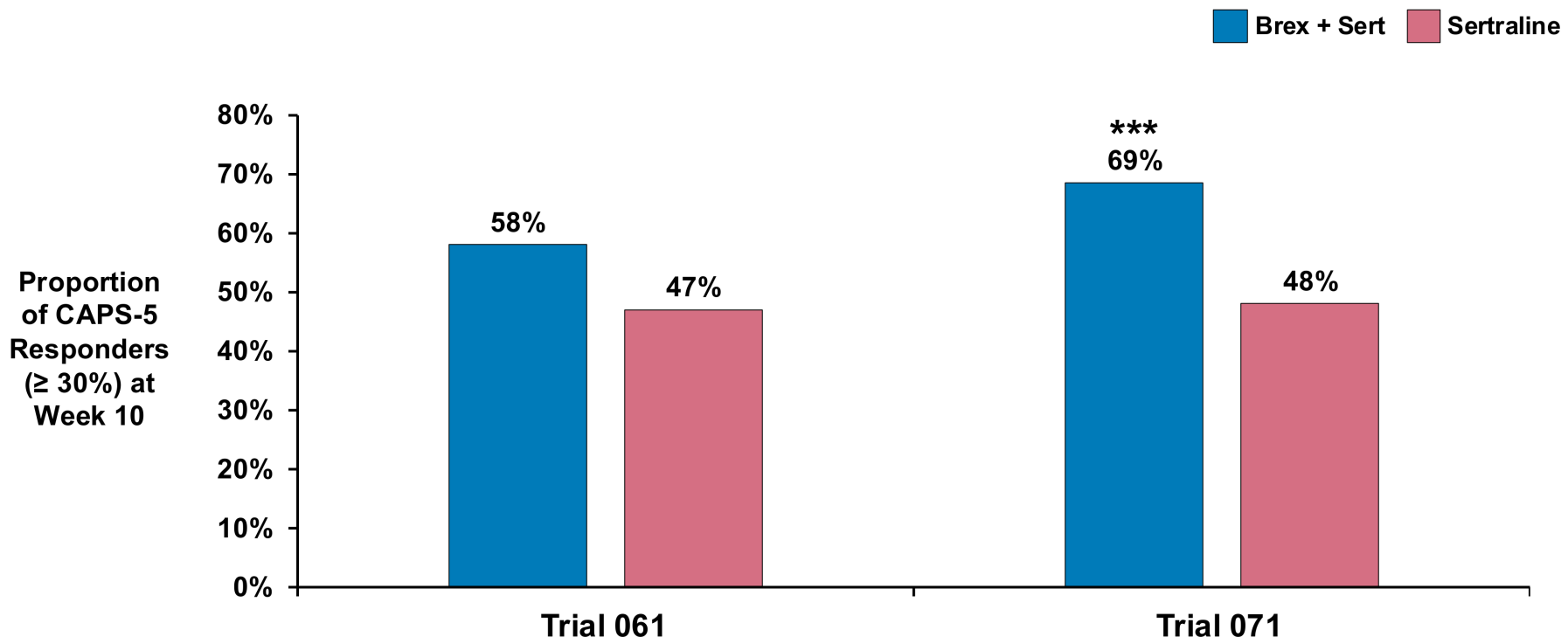
Clinical Relevance of Data

Brexpiprazole Plus Sertraline Demonstrated Greater Improvements vs Sertraline Alone in Symptom Clusters



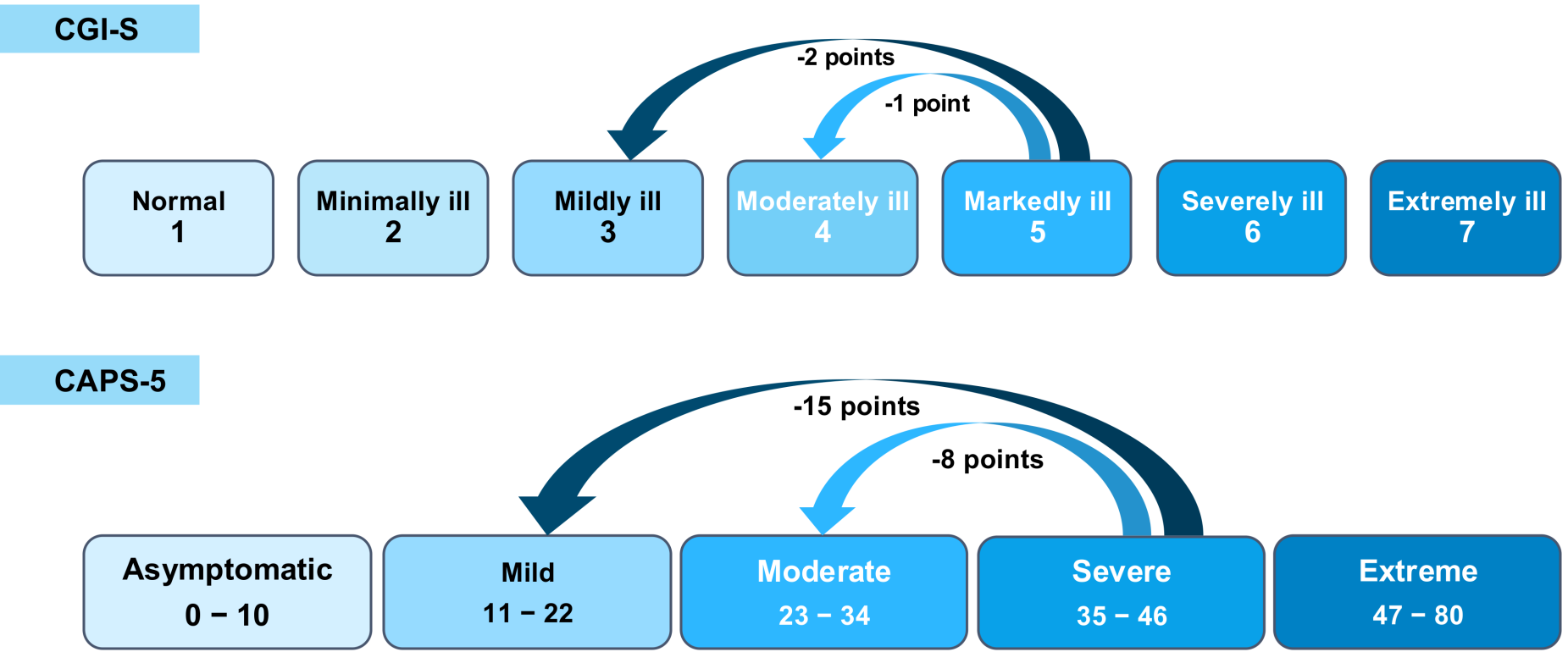
Nominal *p <0.05, **p <0.01

Prespecified Responder Analysis for CAPS-5 Showed Higher Proportion of Response with Combination Treatment

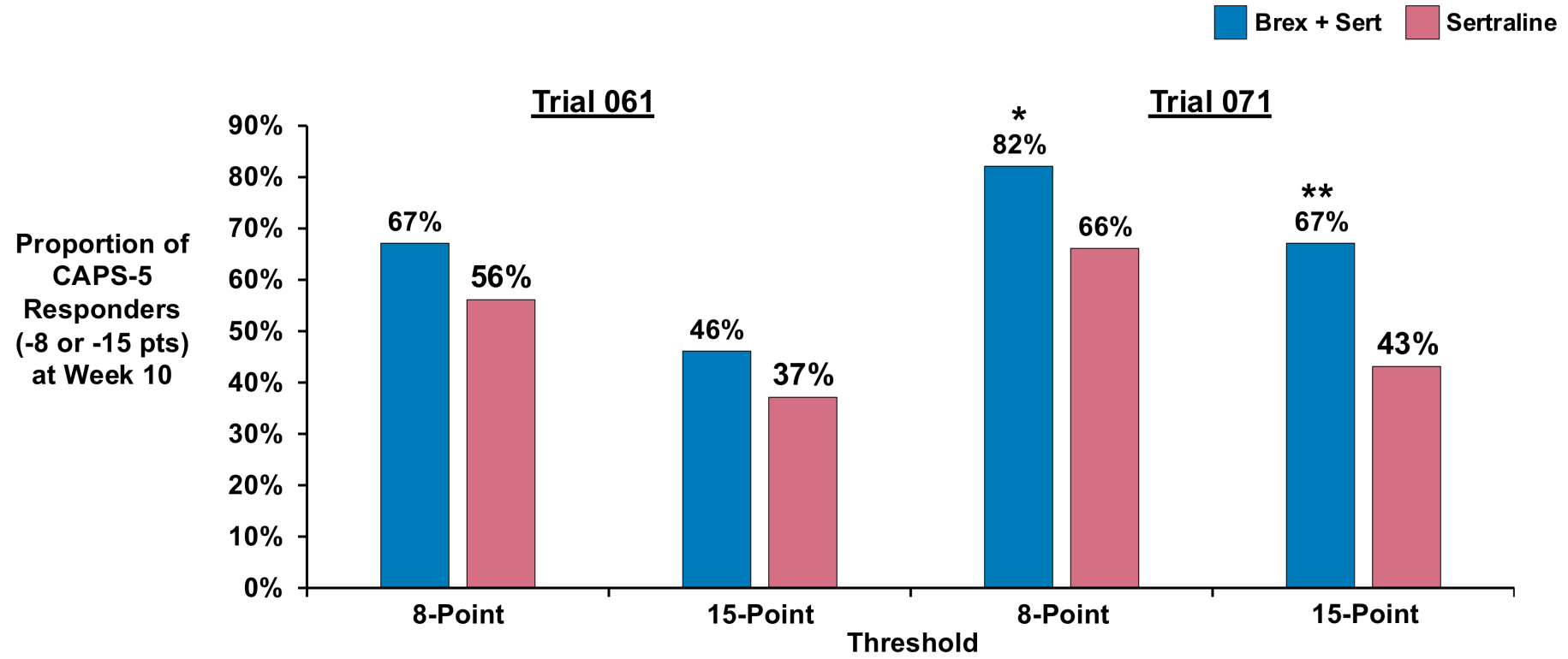


LOCF ***p <0.001

Defining CAPS-5 Responders Using CGI-S as Anchor



Responder Analysis Using MWPC Thresholds Showed Higher Proportion of Response with Combination Treatment



OC **p <0.01; *p <0.05

MWPC: Meaningful within-patient change

Summary of Efficacy

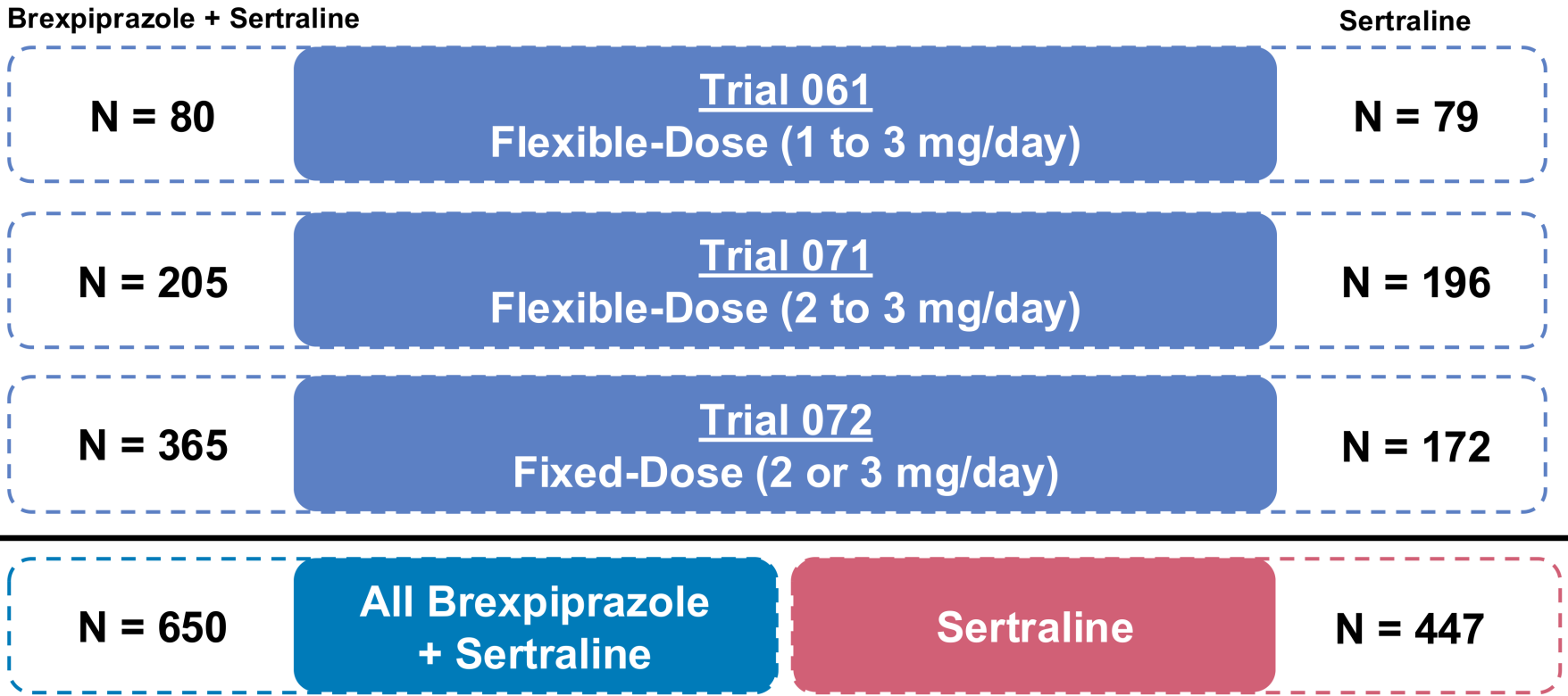
1. 2 of 3 trials were positive
2. Trial 071 provides statistically significant results that brexpiprazole plus sertraline is superior to sertraline alone
3. Trial 061 provides strong supportive evidence; results replicated in Trial 071
4. Trial 072 did not separate brexpiprazole plus sertraline from sertraline
5. Greater proportion of patients with brexpiprazole plus sertraline met clinically meaningful improvement thresholds and achieved ≥ 30% clinical response

Safety

Thomas Thompson, MD

Vice President, Global Clinical Development Therapeutic Head, CNS
Otsuka Pharmaceutical

Overall Safety Population



Trial 061: Brexpiprazole monotherapy (75), placebo only group (82) were also evaluated for safety; not included in the pooled safety analysis
Safety sample includes all randomized patients who received at least 1 dose of randomized treatment

Combination Treatment Was Generally Well Tolerated in Patients with PTSD

n (%)	Brex 2 mg + Sert N = 185	Brex 3 mg + Sert N = 180	Brex 1-3 mg + Sert N = 285	All Brex + Sert N = 650	Sertraline N = 447
Any AE	95 **(51%)**	87 **(48%)**	179 **(63%)**	361 **(56%)**	251 **(56%)**
Any Serious AE	1 **(0.5%)**	1 **(0.6%)**	3 **(1%)**	5 **(0.8%)**	7 **(2%)**
Any AE leading to discontinuation	5 **(3%)**	8 **(4%)**	13 **(5%)**	26 **(4%)**	31 **(7%)**
Deaths	1 **(0.5%)**	**0**	**0**	1 **(0.2%)**	1 **(0.2%)**

1 additional death in placebo group was reported in Trial 061

AEs Similar Between Combination Treatment and Sertraline Groups

Preferred Term ≥ 5% in any treatment group, n (%)	All Brexpiprazole + Sertraline N = 650	Sertraline N = 447
Nausea	52 **(8%)**	50 **(11%)**
Headache	36 **(6%)**	34 **(8%)**
Weight increased	34 **(5%)**	6 **(1%)**
Diarrhea	31 **(5%)**	27 **(6%)**

Serious Adverse Events Were Low in Frequency

Preferred Term, n (%)	All Brexpiprazole + Sertraline N = 650	Sertraline N = 447
Any SAE	5 **(0.8%)**	7 **(2%)**
Back pain	1 **(0.2%)**	**0**
Cyst rupture	1 **(0.2%)**	**0**
Drowning	1 **(0.2%)**	**0**
Gastroenteritis	1 **(0.2%)**	**0**
Suicide attempt	1 **(0.2%)**	**0**
Cerebrovascular accident	**0**	1 **(0.2%)**
Diverticulitis	**0**	1 **(0.2%)**
Hepatic enzyme increased	**0**	1 **(0.2%)**
Hypertension	**0**	1 **(0.2%)**
Mania	**0**	1 **(0.2%)**
Suicidal ideation	**0**	1 **(0.2%)**
Toxicity to various agents	**0**	1 **(0.2%)**

Important Safety Topics of Interest Generally Balanced Across Arms

Incidence of Adverse Events, n (%) (Grouping of relevant AEs)	All Brexpiprazole + Sertraline N = 650	Sertraline N = 447
Extrapyramidal symptoms (EPS)	60 **(9%)**	39 **(9%)**
Effect on weight*	43 **(7%)**	10 **(2%)**
Somnolence	34 **(5%)**	20 **(5%)**
Orthostatic hypotension, dizziness, and syncope	21 **(3%)**	22 **(5%)**
Suicidality	4 **(0.6%)**	5 **(1%)**
Effect on glucose	3 **(0.5%)**	1 **(0.2%)**
Effect on lipids	2 **(0.3%)**	1 **(0.2%)**

*Mean change in weight from baseline to the last visit: +1.0 kg in Brex+Sert group versus -0.2 kg in sertraline alone group;

Combination Treatment of Brexpiprazole Plus Sertraline Was Well Tolerated in Patients with PTSD

1. Combination treatment of brexpiprazole plus sertraline when started concurrently was generally well tolerated with no added risk
2. AEs similar across both treatment groups with low frequency of SAEs
3. Safety profile consistent with prior approved indications of brexpiprazole in variety of psychiatric disorders and extensive post marketing experience

Clinical Perspective

Kathleen Brady, MD, PhD

Distinguished University Professor
Medical University of South Carolina
Director, South Carolina Clinical and Translational Research Institute

Where We Are Today

Substantial burden associated with PTSD[1]

↓

2 Approved pharmacotherapies in past 25 years with modest efficacy that do not consistently treat all 4 symptom clusters

↓

Trial and error with non-evidence-based therapies

1. American Psychological Association 2025; U.S. Department of Veterans Affairs 2017; Yehuda et al 2015

Patient Example: PTSD Is Chronic and Disabling

- 32-year-old woman with 2 children, developed PTSD following home intrusion/robbery 3 years ago
- Challenging treatment landscape
  - Started on SSRI with some benefit, but intrusive thoughts persisted
  - Some diminution of symptoms over time, but still easily triggered
  - Recent divorce reactivates symptoms – trouble sleeping, constant nervous/jittery
  - Lack of empirical data led to symptom specific management using non-evidence-based treatment

Brexpiprazole Plus Sertraline Is Exciting Option for PTSD

- > 1,200 individuals participated in 3 large-scale trials
- Statistically significant improvement vs sertraline alone in CAPS-5
- Remarkable reduction in patient's PTSD symptom severity
- Improvement across 4 CAPS-5 symptom clusters
- Positive benefits observed in CGI-S, B-IPF, and other important clinician and patient assessments

No New Safety Observations Identified in PTSD Population

- Incidence rates of adverse events similar to sertraline, including
  - Somnolence, dizziness, nausea, EPS, suicidality, metabolic effects
  - Except weight gain
- Well-tolerated

Safety profile of combination consistent with safety of approved indications of brexpiprazole and of sertraline alone

Substantial Evidence of Efficacy

Many RCTs in PTSD failed to separate from placebo

Rare to see positive results in RCTs with active comparator

2 positive trials with consistent and clinically meaningful results and favorable safety profile

Benefits far outweigh risks

Sponsor Q&A

Mary Hobart, PhD

Senior Vice President, Global Regulatory Affairs

Otsuka Pharmaceutical

Brexpiprazole in Combination with Sertraline for Treatment of Adults with Post-Traumatic Stress Disorder (PTSD)

July 18, 2025

Psychopharmacologic Drugs Advisory Committee

Otsuka Pharmaceutical Co.

Lundbeck Inc.

Backup Slides Shown

Trial 072: Demographics Balanced Across Groups

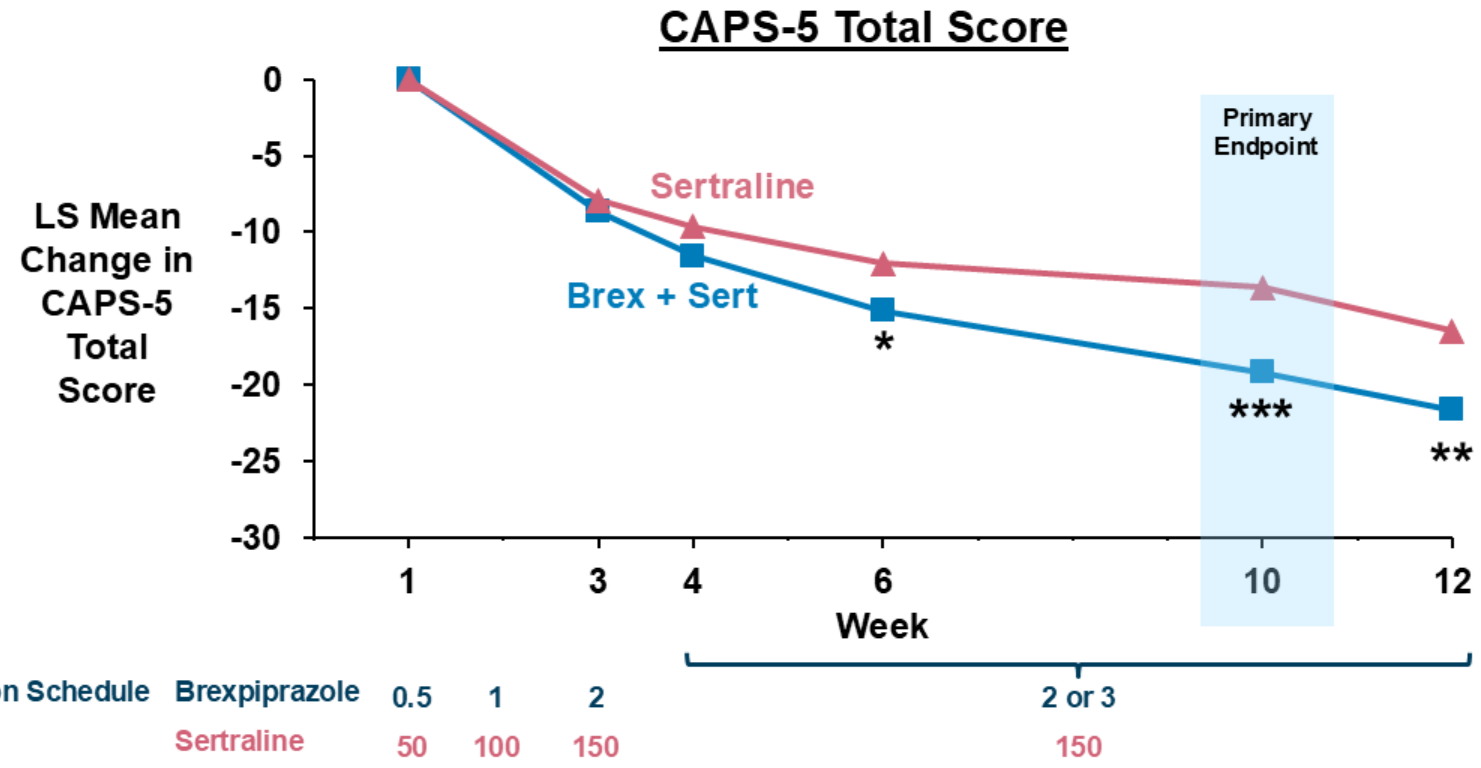
	Brex 2 mg + Sert N = 191	Brex 3 mg + Sert N = 185	Sert N = 177
Age (years), mean	37	36	38
Female	74%	76%	71%
BMI (kg/m^2), mean	30	29	28
Race, White	68%	67%	68%
Race, Black or African American	24%	24%	25%
Ethnicity, Hispanic or Latino	25%	20%	21%
Years since traumatic event, mean	4	4	4
Treatment history			
Previous psychotherapy	27%	34%	29%
Previous pharmacotherapy	20%	19%	20%

Trials 061 & 071: Prior Pharmacotherapy Treatments When Treated With Brexpiprazole + Sertraline (Efficacy)

Subgroup	Variable	Trials LSMD (LCL, UCL) Trial 061 Brex 1 -3 mg + Sert	Trials LSMD (LCL, UCL) Trial 071 Brex 2 – 3 mg + Sert
Pharmacotherapy	Previous Pharmacotherapy Yes	**-2.53** (-8.30, 3.23) **P = 0.3858** **N = 34, 37**	**-8.58** (-14.06, -3.10) **P = 0.0026** **N = 46, 34**
	Previous Pharmacotherapy No	**-6.98**(-12.31, -1.65) **P = 0.0106** **N = 43, 38**	**-4.53** (-8.52, -0.55) **p = 0.0260** **N = 102, 100**

N = Brex + Sert, Sert + Placebo

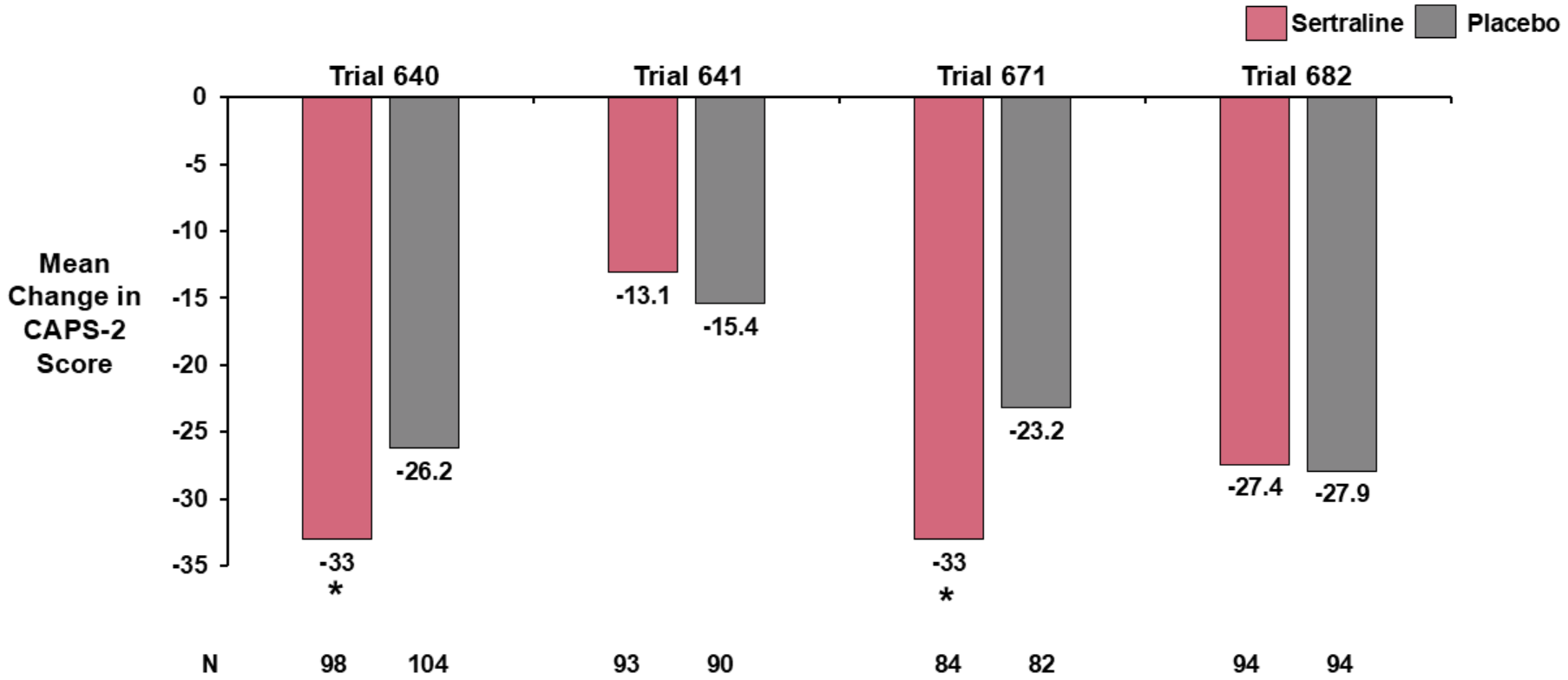
Trial 071: Met Primary Endpoint with Statistically Significant and Clinically Meaningful Reduction in CAPS-5



Nominal *p <0.05, **p <0.01, ***p <0.001

Baseline CAPS-5 Total Score: Brex + Sert = 38.35, n = 148; sertraline = 38.68, n = 134

Sertraline PTSD Registrational Trials Showed Varied CAPS-2 Change from Baseline



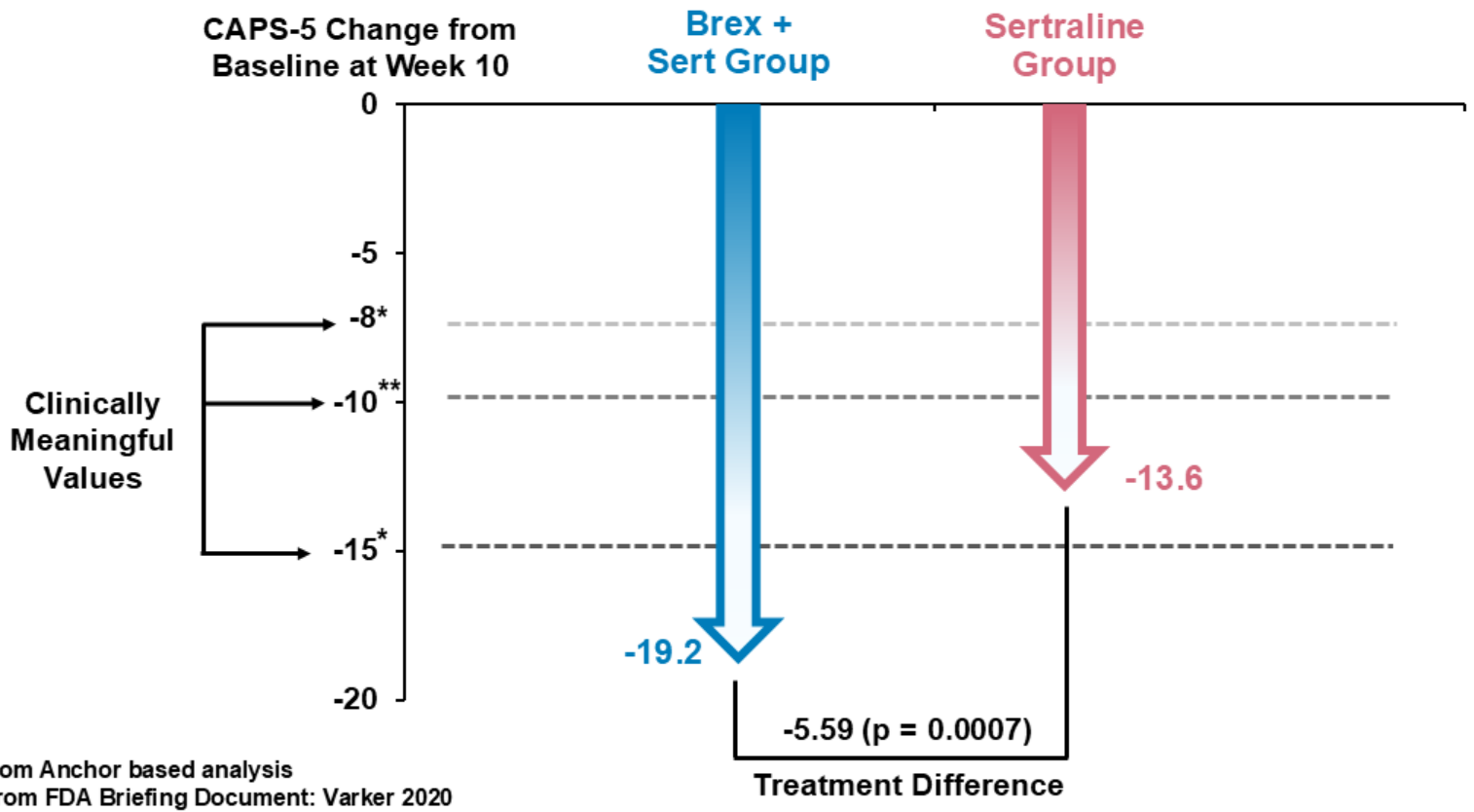
* $p < 0.05$

Means adjusted for treatment, site, treatment-by-site, and baseline values

Weight Increased Reported in Long-Term Trials Up To 52 Weeks for MDD & Schizophrenia

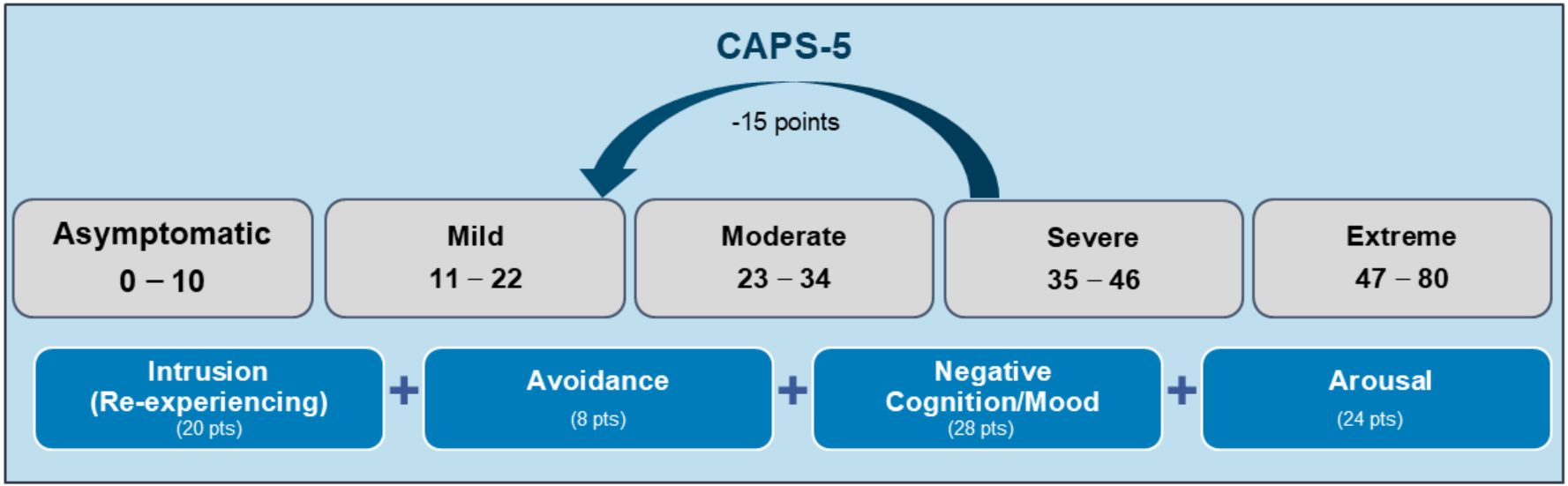
n (%)	MDD Long-Term Trials N = 2084	Schizophrenia Long-Term Trials N = 813
AEs of weight increased	515 **(25%)**	60 **(7%)**
Discontinuation due to AE of weight increased	74 **(4%)**	5 **(1%)**
Mean change in body weight from baseline to Week 52	**+3.1 kg**	**+2 kg**
PCR weight increase of ≥ 7% at any visit	612 **(30%)**	158 **(20%)**

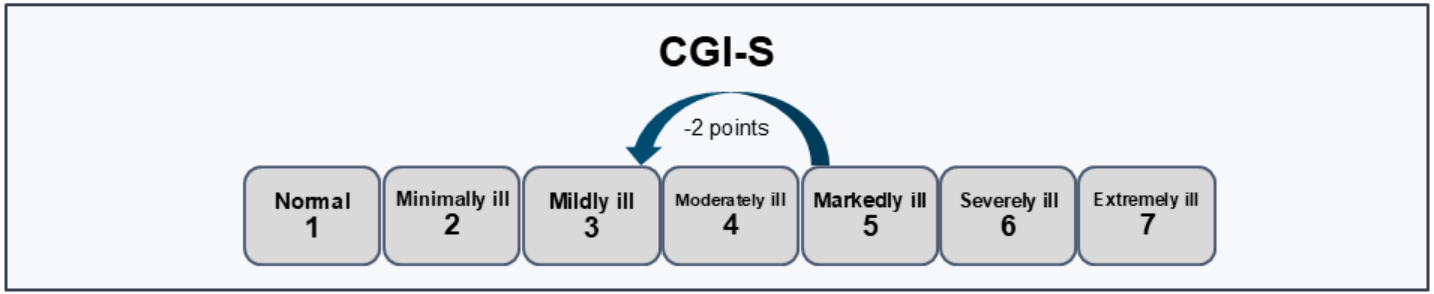
Trial 071: Treatment Difference and Clinically Meaningful Thresholds



* From Anchor based analysis
**From FDA Briefing Document: Varker 2020

Patient Improvement Vignette – CAPS-5 & CGI-S





Prazosin Taken During Double Blind Treatment (Safety Sample)

Drug Class	Trial 061 N = 316	Trial 071 N = 401	Trial 072 N = 536
Prazosin	3 **(1%)**	2 **(0.5%)**	5 **(1%)**

Trial 061: Primary Model for 061 with Prior SSRI Use in Model

- Pre-specified model
  - CAPS-5 primary endpoint week 10 effect size: -5.08, (95% CI: -8.96, -1.20)
  - p = 0.0106
- Model with prior SSRI use
  - CAPS-5 primary endpoint week 10 effect size: -5.28 (95% CI: -9.18, -1.38)
  - p = 0.0081