May 29, 2024

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Otsuka and Lundbeck Present Results from Three Clinical Trials of Brexpiprazole in Combination with Sertraline for the Treatment of Post-Traumatic Stress Disorder (PTSD) in Adults

Otsuka Pharmaceutical Co., Ltd. (Otsuka) announces that its US subsidiary Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Lundbeck Pharmaceuticals LLC (Lundbeck) presented results from the Phase II (Trial 061) and Phase III trials (Trial 071 and 072) evaluating the safety and efficacy of brexpiprazole in combination with sertraline for the treatment of adults with post-traumatic stress disorder (PTSD).[1,2] The findings were presented at the American Society of Clinical Psychopharmacology (ASCP) Annual Meeting in Miami.

The primary endpoint for all three trials was the change from Week 1 to Week 10 in the CAPS-5 total score for brexpiprazole and sertraline combination therapy versus sertraline plus placebo in patients diagnosed with PTSD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[1]

The trials were randomized, double blind, active-controlled, and Trial 061 and 071 were flexible dose trials, while Trial 072 was a fixed dose trial.[1] In Trial 061 and 071, brexpiprazole in combination with sertraline was associated with a statistically significant reduction ($p<0.05$) in PTSD symptoms compared to sertraline plus placebo, as measured by the change in the Clinician-Administered PTSD Scale (CAPS-5) total score from baseline to Week 10 (primary endpoint). In Trial 072, while the primary endpoint was not met, reductions in PTSD symptom severity with brexpiprazole in combination with sertraline were consistent with Trials 061 and 071. Improvements were consistently observed across the Clinical Global Impression Severity (CGI-S) scale and the four CAPS-5 clusters of re-experiencing, avoidance, negative cognition/mood and arousal/reactivity symptoms in Trials 061 and 071.[1,4]

"Only approximately half of people living with PTSD seek treatment, even though it is one of the most common mental health conditions in the United States," said Lori Davis, M.D., clinical professor of psychiatry in the Department of Psychiatry and Behavioral Neurobiology, University of Alabama School of Medicine. "For the first time, we now have data from a comprehensive clinical trial program that show a combination of medicines can help improve the four symptom clusters of PTSD as defined by the DSM-5."

Across the three randomized trials, the combination of brexpiprazole and sertraline in adult patients with PTSD were generally well-tolerated, and no new safety observations were identified. The safety and tolerability results were consistent with the known profile of brexpiprazole in its approved indications and what has been observed in other clinical trials. The overall incidence of treatment-emergent adverse events (TEAEs) across the three trials was 55.5 percent with brexpiprazole plus sertraline, and 56.2 percent with sertraline plus placebo.[2]

In Trial 061, the least squares mean change from randomization (Week 1) in CAPS-5 total score was -16.4 with brexpiprazole in combination with sertraline ($p=0.011$ versus sertraline plus placebo), -12.2 with brexpiprazole plus placebo, -11.4 with sertraline plus placebo, and -10.5 with placebo. In Trial 071, the least squares mean change was -19.2 with brexpiprazole in combination with sertraline ($p=0.0007$ versus sertraline plus placebo) and -13.6 with sertraline plus

placebo. In Trial 072, the least mean change was -16.5 with brexpiprazole 2 mg/day in combination with sertraline (p=0.52 versus sertraline plus placebo), -18.3 with brexpiprazole 3 mg/day in combination with sertraline (p=0.66 versus sertraline plus placebo), and -17.6 with sertraline plus placebo.[1]

"Lack of recognition and misdiagnosis of PTSD can result in ineffective management, with the average time from onset of symptoms to treatment being 12 years," said John Kraus, M.D., Ph.D., executive vice president and chief medical officer, Otsuka. "These findings represent a remarkable advancement in managing the PTSD symptoms of those affected by this chronically misunderstood and prevalent psychiatric disorder."

"With approximately 13 million people in the U.S. suffering from PTSD in a given year, these data are crucial to bringing forward a potential new treatment option," said Johan Luthman, Ph.D., executive vice president, Lundbeck research & development. "We're hopeful that brexpiprazole in combination with sertraline can become an approved treatment option for appropriate patients living with PTSD."

About CAPS-5

The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) is a structured interview designed to assess PTSD diagnostic status and symptoms severity as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). The interview consists of 30 items, with a higher score indicating a worse outcome.[4]

About Post-Traumatic Stress Disorder

PTSD is one of the most common mental health disorders in the United States, with approximately five percent of the population affected during a given year.[5,6,9-11] It may occur in people who have experienced or witnessed a traumatic event, series of events or set of circumstances. An individual may experience this as emotionally or physically harmful or life-threatening and may affect mental, physical, social, and/or spiritual well-being. Examples include physical/sexual assault, natural disasters, serious accidents, terrorist acts, war/combat, historical trauma, intimate partner violence and bullying.[7,12]

Symptoms of PTSD are generally grouped into four types: intrusion (re-experiencing), avoidance, negative cognitions and mood, and marked alterations in arousal and reactivity.[5,8] Symptoms can vary over time or vary from person to person.[7] Symptoms usually begin within 3 months of the traumatic incident, but they sometimes emerge later. To meet the criteria for PTSD diagnosis, symptoms must last longer than one month, and they must be severe enough to interfere with aspects of daily life, such as relationships or work. Symptoms also must not be due to medications, substance use, or a medical condition.[5] Guideline recommended first-line treatment includes psychotherapy (e.g., cognitive behavioral therapy) and first line pharmacotherapy options include certain antidepressants.[13]

About Brexpiprazole

Brexpiprazole was approved in the U.S. in 2015, as an adjunctive therapy to antidepressants in adults with MDD and as a treatment for schizophrenia in adults. Most recently, brexpiprazole was approved in the U.S. for the treatment of agitation associated with dementia due to Alzheimer's disease, in May 2023. Brexpiprazole was also approved by Health Canada for schizophrenia and adjunctive treatment of MDD in 2017 and 2019, respectively. It was approved by the Ministry of Health, Labour and Welfare in Japan and by the European Medicines Agency in 2018 for the treatment of schizophrenia.[3]

Brexpiprazole was discovered by Otsuka and is being co-developed by Otsuka and Lundbeck. The mechanism of action of brexpiprazole is unknown. Brexpiprazole has high receptor binding affinity to norepinephrine, serotonin and dopamine receptors. It is an antagonist at norepinephrine α1B and α2C receptors and serotonin 5-HT_{2A} receptors, as well as a partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors.[14,15]

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