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Company Name	Otsuka Holdings Co., Ltd.
Name of Representative	Tatsuo Higuchi President and Representative Director, CEO
Code Number	4578, Prime market of the Tokyo Stock Exchange
Contact	Yuji Kogure Director, Investor Relations Department (Phone: +81-3-6361-7411)

Otsuka Pharmaceutical and Lundbeck Announce Topline Results from Two Phase 3 Trials of Brexpiprazole as Combination Therapy with Sertraline for the Treatment of Post-Traumatic Stress Disorder in Adults

- The flexible dose phase 3 trial met its primary endpoint, while the fixed dose phase 3 trial missed its primary endpoint
- Otsuka and Lundbeck will discuss these results with FDA to determine next steps

Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) today announced results from two Phase 3 clinical trials of brexpiprazole as combination therapy with sertraline for the treatment of post-traumatic stress disorder (PTSD).

The first trial (NCT04124614) was a Phase 3, randomized, double-blind, 2-arm, flexible dose trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (2 - 3 mg/day) as combination therapy with sertraline in 416 randomized adult subjects with PTSD.

The second trial (NCT04174170) was a Phase 3, randomized, double-blind, 3-arm, fixed dose trial to evaluate the efficacy, safety, and tolerability of brexpiprazole (2 or 3 mg/day) as combination therapy with sertraline in 553 randomized adult subjects with PTSD.

The primary endpoint for both trials was the change in the Clinician-Administered PTSD Scale (CAPS-5) total score for brexpiprazole + sertraline combination therapy versus sertraline + placebo at week 10 in patients diagnosed with PTSD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).
The first trial met its primary endpoint by demonstrating improvements from baseline on the primary endpoint of CAPS-5 for patients receiving brexpiprazole 2-3 mg/day + sertraline combination therapy being statistically significantly greater than for those receiving sertraline + placebo ($p<0.05$). The second phase 3 trial missed its primary endpoint ($p>0.05$).

Overall, the safety and tolerability results were consistent with the profile of brexpiprazole as observed in the clinical trials for schizophrenia, agitation associated with dementia due to Alzheimer's disease (AADAD), and adjunctive treatment of major depressive disorder (MDD). The most common treatment-emergent adverse events in patients receiving combination therapy of brexpiprazole + sertraline versus sertraline + placebo (incidence at least 2% and greater than sertraline + placebo) were dyspepsia, fatigue, weight increased, akathisia and somnolence. Discontinuations due to adverse events occurred in 3.7% of patients treated with brexpiprazole + sertraline combination therapy and 7.6% of patients receiving sertraline + placebo.

Full trial results are not yet available. Further prespecified and exploratory analyses of this data set will be

conducted to further assess brexpiprazole as combination therapy with sertraline for the treatment of PTSD. The trial results are planned to be submitted for scientific publication.

"The results from the first trial indicate that brexpiprazole in combination with sertraline provides improvement of symptoms for people living with PTSD, whereas the second trial did not meet its primary endpoint," said John Kraus, M.D., Ph.D., executive vice president and chief medical officer, Otsuka Pharmaceutical Development & Commercialization, Inc. "We will fully analyze these results and will discuss our findings with the FDA to determine next steps."
"PTSD is a serious mental health disorder with a wide range of symptoms with no new therapeutic options in more than 20 years," Dr. Johan Luthman, executive vice president and head of Research & Development at Lundbeck. "The two trials constitute one of the largest clinical development programs ever conducted in PTSD. We will analyze the dataset to further determine the potential of brexpiprazole as combination therapy with sertraline in comprehensively addressing symptoms across the PTSD core domains."
Otsuka and Lundbeck are incredibly appreciative to all the patients with PTSD, their families, and the investigators who participated in the trials and contributed greatly to this research.

About the Trials
Trials 331-201-00071 (NCT04124614) and 331-201-00072 (NCT04174170) were designed to evaluate the efficacy, safety and tolerability of brexpiprazole and sertraline combination treatment in adults with PTSD. The trial populations included male and female patients, aged 18-65 years (inclusive), with a diagnosis of PTSD according to the DSM-5 and confirmed by the Mini International Neuropsychiatric Interview (MINI). The trials consisted of a 1-week double-blind placebo run-in period followed by 11-weeks of double-blind randomized treatment for a continuous 12-week double-blind treatment period with a 21-day follow-up]. Trial 331-201-00071 was a 2-arm, double-blind, flexible-dose trial in which patients were randomized to receive either flexible-dose brexpiprazole 2-3 mg/day plus sertraline 150 mg/day or sertraline 150 mg/day plus placebo during the 11-week randomized treatment period. Trial 331-201-00072 was a 3-arm, double-blind, fixed-dose trial in which patients were randomized to receive either fixed-dose brexpiprazole 2 mg/day plus sertraline 150 mg/day, brexpiprazole 3 mg/day plus sertraline 150 mg/day, or sertraline 150 mg/day plus placebo during the 11-week randomized treatment period. The primary outcome in both trials was the change from randomization to week 10 in the CAPS-5 total score in those patients that met blinded criteria at the week 1 visit of the trial.

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.

About Post-Traumatic Stress Disorder
PTSD is a psychiatric disorder that 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.[1] Examples include natural disasters, serious accidents, terrorist acts, war/combat, rape/sexual assault, historical trauma, intimate partner violence and bullying.[1]

PTSD can occur in all people, of any ethnicity, nationality or culture, and at any age. It affects more than 13 million people in the U.S. and nearly 6 in 100 people will be diagnosed with PTSD in their lifetime.[2] Women are twice as likely as men to have PTSD.[1]

Symptoms of PTSD are generally grouped into four types: intrusive memories, avoidance, negative changes in

thinking and mood, and changes in physical and emotional reactions. Symptoms can vary over time or vary from person to person.[3] Symptoms usually begin within 3 months of the traumatic incident, but they sometimes emerge later.[4] To meet the criteria for PTSD, symptoms must last longer than 1 month, and they must be severe enough to interfere with aspects of daily life, such as relationships or work.[4]

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 AADAD 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.
Brexpiprazole was discovered by Otsuka and is being co-developed by Otsuka and Lundbeck. The mechanism of action of brexpiprazole is unknown, however the efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors, antagonist activity at serotonin 5-HT_{2A} receptors, as well as antagonism of alpha 1B/2C receptors.

Citations

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