June 27, 2022

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 positive results showing reduced agitation in patients with Alzheimer's dementia treated with brexpiprazole

- Results from a phase III clinical study for treatment of agitation in patients with Alzheimer's dementia showed that patients treated with brexpiprazole had a statistically significantly greater reduction in agitation compared to placebo
- Currently there are no FDA approved pharmacological treatments for agitation in Alzheimer's dementia

Otsuka Pharmaceutical Co., Ltd. (Otsuka) and H. Lundbeck A/S (Lundbeck) announce positive results of the phase III clinical trial of brexpiprazole in the treatment of agitation in patients with Alzheimer's dementia (NCT03548584). The analysis concluded that there is a statistically significant difference (p=0.0026) in the mean change from baseline to week 12 in the Cohen-Mansfield Agitation Inventory (CMAI) total score between brexpiprazole and placebo.

Full study results are not yet available. Further prespecified and exploratory analyses of the data set will be conducted to determine the full potential of brexpiprazole in the treatment of agitation in patients with Alzheimer's dementia.

Based on this outcome Otsuka and Lundbeck are planning a regulatory filing to the FDA later in 2022. The Supplemental New Drug Application will comprise this study as well as two earlier trials.[1] In February 2016, the FDA granted Fast Track designation for expedited review of brexpiprazole for treatment of agitation in patients with Alzheimer's dementia.

About the study

Trial 331-14-213 (NCT03548584; Trial 213) was designed to assess the safety, tolerability and efficacy of two fixed doses of brexpiprazole (2 mg/day or 3 mg/day) in the treatment of patients with agitation in Alzheimer's dementia. The trial consisted of a continuous, 12-week double-blind treatment period with a 30-day follow-up. The trial population included 345 male and female patients, aged 55–90 years (inclusive), with a diagnosis of probable Alzheimer's disease, and meeting criteria of agitation as defined by the International Psychogeriatric Association (IPA). The primary outcome was the change in the CMAI total score at week 12 for all patients treated with brexpiprazole vs those treated with placebo. The key secondary outcome was the change in the Clinical Global Impression – Severity of Illness (CGI-S) score, as related to symptoms of agitation.

In the study, the improvements from baseline on the primary endpoint of CMAI for patients receiving brexpiprazole or 2 mg/day or 3 mg/day were statistically greater than for those receiving placebo (p=0.0026). This result was supported by a statistically superior improvement on the key secondary endpoint of CGI-S, as related to agitation (p=0.0055).

Brexpiprazole was generally well tolerated, and no new safety signals were observed. The only treatment-emergent adverse event (TEAE) with more than 5% incidence in patients treated with brexpiprazole was headache (6.6% vs. 6.9% for placebo). The following TEAEs occurred at an incidence of at least 2% in the brexpiprazole treatment group and greater than that of placebo: somnolence, nasopharyngitis, dizziness, diarrhea, urinary tract infection, and asthenia. There was one death observed in the 3 mg/day treatment group, assessed as not related to treatment by the investigator.

About brexpiprazole

Brexpiprazole was approved in the U.S. in July 2015 as an adjunctive therapy to antidepressants in adults with major depressive disorder and as a treatment in adults with schizophrenia. Brexpiprazole was also approved in 2017 by Health Canada and by the EMA in Europe in 2018 for the treatment of schizophrenia. Brexpiprazole has also been approved in multiple other countries. Brexpiprazole is distributed and marketed under the brand name Rexulti®. In Europe, brexpiprazole is distributed and marketed under the brand name Rxulti®.

Brexpiprazole was discovered by Otsuka and is being co-developed by Otsuka and Lundbeck. The efficacy of brexpiprazole may be mediated through a combination of partial agonist activity at noradrenaline alpha1B/2C receptors, serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors, all at pharmacologically relevant potency.[2-3]

1. Grossberg GT et al. Efficacy and Safety of Brexpiprazole for the Treatment of Agitation in Alzheimer's Dementia: Two 12-Week, Randomized, Double-Blind, Placebo-Controlled Trials. Am J Geriatr Psychiatry. 2020;28(4):383-400
2. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: *in vitro* and *in vivo* characterization of a novel serotonin–dopamine activity modulator. *J Pharmacol Exp Ther.* 2014a; 350(3):589–604.
3. Maeda K, Lerdrup L, Sugino H, et al. Brexpiprazole II: antipsychotic-like and procognitive effects of a novel serotonin–dopamine activity modulator. *J Pharmacol Exp Ther*. 2014b;350(3):605–614.