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Press release

Valby, 11 December 2014

Imaging (fMRI) study reveals Brintellix® (vortioxetine) affects the underlying brain systems involved in working memory in people remitted from depression

The findings show Brintellix® (vortioxetine) increases neural efficiency compared to placebo during a working memory challenge

New pharmacological data from people previously suffering from major depressive disorder (MDD, most commonly known as depression) demonstrated that Brintellix® increases neural efficiency during a working memory challenge, according to imaging (functional magnetic resonance imaging or fMRI is a technique for measuring and mapping brain activity) data presented as poster presentations at the 53rd Annual Meeting of the American College of Neuropsychopharmacology (ACNP) December 7–11 2014, Phoenix, Arizona.

Depression is associated with a range of cognitive difficulties, including deficits in attention, executive function and working memory[i]. Lundbeck has undertaken this pharmacological study to investigate the influence of Brintellix® on cognitive performance and its effects on brain activity during resting state in people remitted from depression and a never-depressed control group.

"Our goal is to enable a fundamental biologic understanding of how Brintellix® affects working memory. Using fMRI helps us to study the brain at a deeper level that could yield insights previously not possible in brain diseases" commented Anders Gersel Pedersen, Executive Vice President, Research and Development at Lundbeck.

The efficacy and tolerability profile of Brintellix® has been established in an extensive clinical development program comprising 16 large-scale short-term and 6 long-term clinical trials in MDD patients. Brintellix® demonstrated clinically relevant and broad efficacy in MDD, including, in some trials[ii], improvement of cognitive deficits as assessed using objective measures (neuropsychological tests such as the DSST and UPSA, a performance-based functional capacity assessment) complemented by subjective measures (patient-reported cognitive function outcomes and a patient-reported work-productivity questionnaire).

Normalization of brain activity

Previous studies have demonstrated that people suffering from depression over-activate their brain (neural) systems in order to perform on cognitive tasks[iii].

The present findings suggest that Brintellix® may be able to normalize such over-activity (improve neural efficiency) within neural circuits important for executive function and working memory. For the people remitted from depression who received Brintellix®, less effort was required (as measured by brain activity) to perform at the same level on cognitive tasks compared to the control group, who received placebo.

During resting state, Brintellix® was also found to alter brain activity in the opposite direction (normalizing) to that found in people with acute depression. Abnormal resting-state activity in brain regions involving the so-called default mode network has been linked to the cognitive dysfunction characteristic of depression[iv].

The default mode network is typically active when the mind wanders and is not active when an individual engages in a focused activity. Researchers have found the network is active in people who are depressed, even when they are concentrating on specific tasks.[v]

The findings of this fMRI study show a reversal of the changes in brain activity previously reported in people with depression, and suggest that Brintellix® may be able to normalize over-activity (improve neural efficiency) within neural circuits important for executive function in depression as well as normalizing brain activity during resting state.

About the fMRI study

Forty-eight persons remitted from depression (HAM-D_{17} ≤7) who reported subjective cognitive difficulties and who had received no treatment for at least 6 weeks and forty-eight healthy never-depressed controls participated in a 4-armed, multi-site, placebo-controlled, randomized, double-blind trial in the United Kingdom. Subjects were treated with once daily doses of vortioxetine (20 mg) or placebo for 12 – 13 consecutive days. Resting-state and task-related functional magnetic resonance imaging (fMRI) was assessed in a 3T magnetic resonance scanner during a baseline visit (pre-treatment), and again after 12-13 days of treatment (post-treatment).

- **Monday, 8 December 2014 from 5:30 -7:30pm**
  Poster Session I
  Poster #: M155
  Effects of vortioxetine on resting-state activity in subjects remitted from depression and healthy controls

- **Wednesday, 10 December 2014 from 5:30 -7:30pm**
  Poster Session III
  Poster #: W12
  Vortioxetine Reduces BOLD Signal during Performance of the N-Back Task in Subjects Remitted from Depression and Healthy Control Participants

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About Brintellix® (vortioxetine)
Brintellix® is an inhibitor of serotonin (5-HT) reuptake and is also an agonist at 5-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors and an antagonist at 5-HT_3, 5-HT_{1D} and 5-HT_7 receptors. Brintellix® is considered to be the first and only compound with this combination of pharmacodynamic activity, although the mechanism of the antidepressant effect of Brintellix® is not fully understood and has not been established.

Vortioxetine was discovered by Lundbeck researchers in Copenhagen, Denmark. The clinical trial program in the U.S. was conducted jointly by Lundbeck and Takeda, and Takeda holds marketing authorization for the U.S. Brintellix® is a trademark of H. Lundbeck A/S and is used under licence by Takeda Pharmaceuticals America, Inc.

The World Health Organization has issued an Anatomical Therapeutic Chemical (ATC) code for Brintellix® that places it in the category of "Other" antidepressants.

About Lundbeck
H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is a global pharmaceutical company specialized in brain diseases. For more than 50 years, we have been at the forefront of research within neuroscience. Our key areas of focus are alcohol dependence, Alzheimer's disease, bipolar disorder, depression/anxiety, epilepsy, Huntington's disease, Parkinson's disease, schizophrenia, stroke, and symptomatic neurogenic orthostatic hypotension (NOH).

An estimated 700 million people worldwide are living with brain disease and far too many suffer due to inadequate treatment, discrimination, a reduced number of working days, early retirement and other unnecessary consequences. Every day, we strive for improved treatment and a better life for people living with brain disease – we call this Progress in Mind.

Read more at www.lundbeck.com/global/about-us/progress-in-mind

Our approximately 6,000 employees in 57 countries are engaged in the entire value chain throughout research, development, production, marketing and sales. Our pipeline consists of several late-stage development programmes and our products are available in more 100 countries. We have research centres in China, Denmark and the United States and production facilities in China, Denmark, France and Italy. Lundbeck generated revenue of approximately DKK15.3 billion in 2013 (EUR2.1 billion; USD2.7 billion).

For additional information, we encourage you to visit our corporate site www.lundbeck.com

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[i] McIntyre RS, et al. (2013) Cognitive deficits and functional outcomes in major depressive disorder: determinants, substrates, and treatment interventions. Depress Anxiety 30:515-527
[ii] McIntyre RS, Lophaven S, Olsen CK International Journal of Neuropsychopharmacology 2014;17(10):1557-1567
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[iv] Sheline et al. (2008) The default mode network and self-referential processes in depression. Proc Natl Acad Sci USA 106:1942-1947
[v] http://news.wustl.edu/news/Pages/13649.aspx