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Corporate Release

New study showed improvement in cognitive performance in adult patients treated with Brintellix® (vortioxetine) for acute episodes of major depression

- Outcome from the FOCUS study was presented at ACNP and Brintellix 10 mg and 20 mg demonstrated a statistically significant improvement in cognitive performance as assessed by DSST and RAVLT versus placebo
- Results from the FOCUS study showed improvement in measures of cognitive function in key domains such as executive function, attention, speed of processing and memory
- In the same study, Brintellix 10 mg and 20 mg significantly improved depressive symptoms as measured by the MADRS scale, with indication of dose response
- Major depression is among the leading causes of disability[i]. The WHO predicts depression will become the leading cause of disability by the year 2030[ii]
- Cognitive dysfunction is well-documented in the different phases of major depression, and plays an important role in functional recovery from major depression

Valby, Denmark, 10 December 2013 - H. Lundbeck A/S (Lundbeck) today announced results from FOCUS, a new study[iii] showing that Brintellix (vortioxetine) 10 mg and 20 mg, met its primary endpoint in demonstrating superiority versus placebo in a composite score of two tests, the Digit Symbol Substitution Test (DSST) and Rey Auditory Verbal Learning Test (RAVLT), that measure cognitive function in adults with major depression[iv]. In this study, Brintellix was shown to improve measures of cognitive domains such as executive function, speed of processing and attention. These data were presented at the 52nd Annual Meeting at the American College of Neuropsychopharmacology (ACNP) in Hollywood, Florida.

FOCUS, a global, eight-week, randomized, double-blind, parallel-group, placebo-controlled, fixed-dose study evaluated the efficacy of Brintellix on cognitive function and major depression across three arms in around 600 patients aged 18-65 with an acute episode of major depression. Cognitive function was measured in a series of validated tests that assessed changes from baseline to week 8 on specific cognitive domains known to be impaired in major depression, including executive function, speed of processing, attention and memory.

On the study's primary endpoint, Brintellix 10 mg and 20 mg demonstrated a statistically significant improvement in cognitive performance versus placebo (0.36 and 0.33 respectively, $p<0.0001$)[iv], as assessed by a composite score of two validated neuropsychological tests, DSST and RAVLT. The improvement in cognitive performance was shown to include a direct effect of Brintellix and was not solely due to improvement in depressive symptoms (MADRS score). The study also showed significant improvements in cognitive symptoms for both Brintellix 10 mg and 20 mg assessed with a patient-

reported outcome questionnaire (PDQ), which supports the clinical relevance of the findings in the neuropsychological tests.

The most commonly observed adverse events in patients treated with Brintellix (incidence ≥5%) were nausea (4.1%, 16.4%, and 20.8%) and headache (7.1%, 8.2%, and 12.6%) for placebo, Brintellix 10 mg and 20 mg, respectively. Overall, the most frequent primary reason for withdrawal was adverse events (AE) for placebo (4.1%), Brintellix 10 mg (3.6%) and Brintellix 20 mg (5.3%).[iv].

"*Neuropsychological tests are powerful indicators of cognitive function but are not routinely used in everyday, busy clinical practice, so it was equally important to understand how patients reported changes in cognitive symptoms that they experienced*," explained Dr. Roger McIntyre, Professor of Psychiatry and Pharmacology at the University of Toronto. "*We are encouraged that Brintellix not only showed benefits in cognitive function in patients with major depression based on the neuropsychological tests, but that patients themselves also reported noticeable improvements in their cognitive symptoms*."

"*In addition to the emotional symptoms of major depression, people with depression may also frequently experience a range of cognitive symptoms, including an impaired ability to think, concentrate or make decisions that can affect work, school and family life*," said Dr. McIntyre. "*Reducing highly prevalent symptoms beyond mood, including those related to cognition, remains a huge challenge to achieving full disease remission. While further studies are needed to confirm these findings, it is truly encouraging to have a new treatment option that may target a dimension of major depression that not only is a principal mediator of functional impairment (for example, workforce performance and attendance) but also a domain so highly related to patient reported quality of life and to feeling themselves again*."

Brintellix was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults with Major Depressive Disorder (MDD) and in October 2013 recommended for approval by the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA) for treatment of adult patients with Major Depressive Episodes.

FOCUS study further builds upon established efficacy and tolerability profile of Brintellix

Brintellix 10 mg and 20 mg significantly improved depressive symptoms as measured by the traditional MADRS scale, with indication of dose response (-4.7 and -6.7 respectively, $p<0.0001$, MMRM ANCOVA)[iv]. The study confirmed Brintellix to have a good safety and tolerability profile and well tolerated overall.

These findings also add to previously reported clinical data suggesting Brintellix improved cognitive performance in elderly patients with major depression first presented at the 2012 American Psychiatric Association Annual Meeting[v]. In addition, these data build upon preclinical in-vivo evidence suggesting that the observed improvement in cognitive function in depressed patients of Brintellix may be supported by the pharmacological profile of Brintellix, which has shown positive effects on cognition in animal models through enhanced neurotransmission and synaptic plasticity in brain areas critical for cognitive function. However, the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to man.

IMPORTANT SAFETY INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend towards reduced risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

BRINTELLIX has not been evaluated for use in pediatric patients.

CONTRAINDICATIONS

Hypersensitivity: Hypersensitivity to vortioxetine or any components of the BRINTELLIX formulation. Angioedema has been reported in patients treated with BRINTELLIX.

Monoamine Oxidase Inhibitors (MAOIs): Due to an increased risk of serotonin syndrome, do not use MAOIs intended to treat psychiatric disorders with BRINTELLIX or within 21 days of stopping treatment with BRINTELLIX. Do not use BRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. Do not start BRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk: All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality (anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania), especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients daily.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants (SNRIs, SSRIs, and others), including BRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, delirium, and coma), autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination),

seizures, and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If such symptoms occur, discontinue BRINTELLIX and any concomitant serotonergic agents, and initiate supportive symptomatic treatment. If concomitant use of BRINTELLIX is clinically warranted, patients should be made aware of and monitored for potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Abnormal Bleeding: Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when BRINTELLIX is co-administered with NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of Mania/Hypomania: Activation of mania/hypomania can occur with antidepressant treatment. Prior to initiating treatment with an antidepressant, screen patients for bipolar disorder. As with all antidepressants, use BRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Hyponatremia: Hyponatremia has occurred as a result of serotonergic drugs and in many cases, appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted can be at greater risk. More severe or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. Discontinue BRINTELLIX in patients with symptomatic hyponatremia and initiate appropriate medical intervention.

Adverse Reactions: The most commonly observed adverse reactions for BRINTELLIX in 6- to 8-week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were by dose (5 mg, 10 mg, 15 mg, 20 mg) vs placebo: nausea (21%, 26%, 32%, 32% vs 9%), constipation (3%, 5%, 6%, 6% vs 3%) and vomiting (3%, 5%, 6%, 6% vs 1%).

Drug Interactions: Concomitant administration of BRINTELLIX and strong CYP2D6 inhibitors or strong CYP inducers may require a dose adjustment of BRINTELLIX.

Please see full Prescribing Information and Medication Guide for BRINTELLIX.

About cognitive function in major depression

Cognitive dysfunction is well-documented in the different phases of major depression, and plays an important role in functional recovery from major depression[vi]. A general assumption is that cognitive dysfunction is restored as mood symptoms of depression improve[vii]. This is also supported by studies that have shown that daily life functioning, including work and family life often remain impaired even in remission[viii].

Research suggests that different factors may explain why improvement in depression-related symptoms is not followed by improvement in daily life functioning[v]. These associated factors include residual symptoms, comorbidity, misdiagnosis and long-lasting cognitive impairment[ix].

Cognition is defined as the mental action or process of acquiring knowledge and understanding through thought, experience and the senses. It can be seen as comprised of several domains such as for example attention, memory, producing and understanding language, learning, reasoning, problem solving, and decision making. Cognition is generally impacted in major depression, and focus is often on four of the domains, executive function, attention, speed of processing and memory. Two tests that have been used in major depression studies to measure improvement in these key domains include DSST and RAVLT. The DSST is a test that evaluates executive function, attention and processing speed. RAVLT assesses verbal learning and memory, which evaluate proactive inhibition, retention, encoding versus retrieval, and subjective organization.

About Brintellix (vortioxetine)

The mechanism of action of vortioxetine is thought to be related to its direct modulation of serotonergic receptor activity and inhibition of the serotonin (5-HT) transporter. Nonclinical data indicate that vortioxetine is a 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the 5-HT transporter, leading to modulation of neurotransmission in several systems, including predominantly the serotonin but probably also the norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems. This multimodal activity is considered responsible for the antidepressant and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed with vortioxetine in animal studies. However, the precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly to man.

The World Health Organization has issued a new Anatomical Therapeutic Chemical (ATC) code for Brintellix to be implemented in 2014.

Brintellix was discovered by Lundbeck researchers in Copenhagen, Denmark.

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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 development and distribution of pioneering treatments continues to make a difference to people living with brain diseases. Our key areas of focus are alcohol dependence, Alzheimer's disease, depression/anxiety, epilepsy, Huntington's disease, Parkinson's disease, schizophrenia and stroke.

Our 5,800 employees in 57 countries are engaged in the entire value chain throughout research, development, production, marketing and sales, and are committed to improving the quality of life of people living with brain diseases. Our pipeline consists of several late-stage development programs and our products are available in more 100 countries. We have research centers in China, Denmark and the United States, and production facilities in China, Denmark, France, Italy and Mexico. Lundbeck generated revenue of approximately DKK 15 billion in 2012 (EUR 2 billion; USD 2.6 billion).

Lundbeck's shares are listed on the stock exchange in Copenhagen under the symbol "LUN". Lundbeck has a sponsored Level 1 ADR program listed in the US (OTC) under the symbol "HLUYY". For additional information, we encourage you to visit our corporate site www.lundbeck.com.

Safe Harbor/Forward-Looking Statements

The above information contains forward-looking statements that provide our expectations or forecasts of future events such as new product introductions, product approvals and financial performance.

Such forward-looking statements are subject to risks, uncertainties and inaccurate assumptions. This may cause actual results to differ materially from expectations and it may cause any or all of our forward-looking statements here or in other publications to be wrong. Factors that may affect future results include interest rate and currency exchange rate fluctuations, delay or failure of development projects, production problems, unexpected contract breaches or terminations, government-mandated or market-driven price decreases for Lundbeck's products, introduction of competing products, Lundbeck's ability to successfully market both new and existing products, exposure to product liability and other lawsuits, changes in reimbursement rules and governmental laws and related interpretation thereof, and unexpected growth in costs and expenses.

Certain assumptions made by Lundbeck are required by Danish Securities Law for full disclosure of material corporate information. Some assumptions, including assumptions relating to sales associated with product that is prescribed for unapproved uses, are made taking into account past performances of other similar drugs for similar disease states or past performance of the same drug in other regions where the product is currently marketed. It is important to note that although physicians may, as part of their freedom to practice medicine in the US, prescribe approved drugs for any use they deem appropriate, including unapproved uses, at Lundbeck, promotion of unapproved uses is strictly prohibited.

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[i] World Health Organisation; http://www.who.int/mental_health/management/depression/definition/en/

[ii] Murray CJL, Lopez AD: "The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020". Geneva, Switzerland; World Health Organization, 1996.

[iii] ClinicalTrials.gov Identifier: NCT01422213

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[v] Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. Int Clin Psychopharmacol. 2012 Jul;27(4):215-23.

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