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Corporate Release

New study shows that Brintellix® (vortioxetine) improves cognitive performance and function in adult patients with major depression

- *Late-breaking study results will be presented at the International College of Neuropsychopharmacology (CINP) World Congress in Vancouver, Canada, on 24 June 2014*
- *Brintellix 10-20 mg/day met the primary study endpoint in adult patients with major depression and showed a statistically significant improvement in cognitive performance as assessed by DSST versus placebo*
- *The study also met several secondary endpoints measuring symptoms of depression and patient outcomes; Brintellix was generally well tolerated.*
- *The study results are consistent with results from previous studies of Brintellix that demonstrated an improvement in cognitive performance in adult and in elderly patients with major depression*
- *Impairment in cognition (i.e., diminished ability to think or concentrate or indecisiveness) is a criterion item in the diagnosis of a major depression. Cognitive dysfunction affects functional impairment (i.e., workplace performance), and improvement in cognitive function significantly influences functional recovery from depression*

Valby, Denmark, 16 June 2014 - H. Lundbeck A/S (Lundbeck) today announced results from the *CONNECT* study showing that Brintellix (vortioxetine) 10 mg/day to 20 mg/day in adults with major depressive disorder (MDD) met the primary study endpoint of demonstrating superiority versus placebo in cognitive function as measured by the Digit Symbol Substitution Test (DSST). These findings will be presented as a late-breaking poster at the 29th International College of Neuropsychopharmacology (CINP) World Congress in Vancouver, Canada on 24 June 2014[i].

The objectives of this randomized, double-blind, placebo-controlled study were to evaluate the effects of Brintellix on cognitive function using objective neuropsychological tests associated with executive function, processing speed and attention after eight weeks of treatment in adults with major depression (MDD), while also confirming efficacy on overall symptoms of depression.

In the *CONNECT* study (NCT01564862), a total of 602 subjects were randomized (198 on Brintellix, 210 on duloxetine, and 194 on placebo). Adults (18-65 years) with MDD, MADRS≥26 and self-reported cognitive dysfunction were enrolled. The primary endpoint was change from baseline to Week 8 on the Digit Symbol Substitution Test (DSST). Key secondary endpoints, patient-reported Perceived Deficits Questionnaire (PDQ) and Clinical Global Impression – Global Improvement (CGI–I) Scale at Week 8 were analyzed in a pre-specified testing sequence using the full-analysis set (FAS). Additional endpoints included the objective performance-based University of San Diego Performance-Based Skills Assessment (UPSA) to measure functionality, the Montgomery–Åsberg Depression Rating Scale

(MADRS) to assess efficacy in depression, and a pre-specified path-analysis to detect direct vs indirect effects of Brintellix on cognitive function.

Brintellix was statistically superior to placebo on the primary endpoint (the Digit Symbol Substitution Test or DSST) ($p<0.05$) and two key secondary endpoints – patient-reported Perceived Deficits Questionnaire (PDQ) and CGI-I. Brintellix was statistically superior to placebo on the MADRS ($p<0.05$) and UPSA ($p<0.001$) change from baseline at Week 8. A pre-specified path-analysis to detect direct vs. indirect effects of treatment on cognition supported that the beneficial impact of Brintellix on cognitive performance is mostly a direct effect and not only due to alleviation of overall depressive symptoms.

Duloxetine was included in the study as an active reference to demonstrate assay sensitivity for depression. Duloxetine was not statistically significantly different from placebo on the primary study endpoint (DSST) or UPSA, but was significant on the PDQ, MADRS and CGI-I secondary endpoints.

Common adverse events (>5%) for Brintellix were nausea, headache, and diarrhea.

Brintellix was approved by the U.S. Food and Drug Administration (FDA) for the treatment of Major Depressive Disorders in adults and by the European Commission for the treatment of adults with Major Depressive Episodes. More recently, the Australian Therapeutic Goods Administration (TGA) approved vortioxetine for the treatment Major Depressive Disorders in April 2014.

***CONNECT* study further builds upon established efficacy and tolerability profile of Brintellix**

The findings add to previously reported clinical data showing that Brintellix improved cognitive performance in elderly patients with major depression[ii] and the placebo-controlled *FOCUS* study in adult patients with major depression[iii]. In addition, these data build upon pre-clinical 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.

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[iv]. A general assumption is that cognitive dysfunction is restored as mood symptoms of depression improve[v]. This is also supported by studies that have shown that daily life functioning, including work and family life often remain impaired even in remission[vi].

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[vii].

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.

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.

Brintellix (vortioxetine) was discovered by Lundbeck researchers in Copenhagen, Denmark. The clinical trial program in the US was conducted jointly by Lundbeck and Takeda, and Takeda holds marketing authorization for the US market. Brintellix is a trademark of H. Lundbeck A/S and is used under license 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.

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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 approximately 6,000 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 DKK 15.3 billion in 2013 (EUR 2.0 billion; USD 2.7 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] Atul R. Mahableshwarkar et al.: Efficacy of Vortioxetine on Cognitive Function in Adult Patients with Major Depressive Disorder: Results of a Randomized, Double-Blind, Active-Referenced, Placebo-Controlled Trial. CINP 2014 abstract

[ii] 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.

[iii] McIntyre RS, Lophaven S, Olsen CK. Randomized, double-blind, placebo-controlled study of the efficacy of vortioxetine on cognitive dysfunction in adult patients with major depressive disorder (MDD). Neuropsychopharmacology 2013;38:S380-S381. [Conference abstract] Abstract T160.

[iv] Jaeger J., Berns S., Uzelac S., Davis-Conway S. (2006). Neurocognitive deficits and disability in major depressive disorder, Psychiatry Research; 145(1):39-48.

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