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New data presented at the 2012 Annual Meeting of the American Psychiatric Association (APA) suggest that Lu AA21004 may have positive effect on cognitive dysfunction in patients with major depressive disorders

- *Study showed benefits of the investigational compound Lu AA21004 in the treatment of elderly patients (>65 years old) with recurrent Major Depressive Disorder (MDD)*
- *In this study, Lu AA21004 demonstrated positive impact on the cognitive symptoms associated with MDD*
- *In a 52-week open-label extension study, Lu AA21004 maintained improvement of depressive symptoms throughout the treatment period in subjects with MDD*
- *Lundbeck is committed to further investigate the effects of Lu AA21004 and its multimodal activity on cognitive dysfunction in depression*
- *Lu AA21004 is planned to be submitted for US and European approval during the second half of 2012*

H. Lundbeck A/S (Lundbeck) today announced the presentation of new data on Lu AA21004, an investigational compound for the treatment of major depressive disorder (MDD), at the 165th Annual Meeting of the American Psychiatric Association (APA) in Philadelphia, USA. The presentations included results from clinical phase III studies as well as non-clinical data.

"*The data from the phase III studies in adults further contribute to our understanding of Lu AA21004 as a multimodal antidepressant in our ongoing efforts to advance options that may address the multi-factorial symptoms faced by people with depression,* " says Executive Vice President Anders Gersel Pedersen, Head of Research & Development at Lundbeck, and continues: "*The data presented at APA support further investigation into how Lu AA21004 may address challenging symptoms of MDD such as difficulty concentrating, indecisiveness and forgetfulness.*"

Summary of clinical results presented at APA

Abstract no 8-44: *Efficacy and safety of Lu AA21004 in a randomised, double-blind, placebo-controlled, active-referenced, fixed-dose study in elderly depressed patients*
This study is a multi-national, randomised, double-blind, placebo-controlled, active-reference, fixed-dose study in elderly patients with recurrent MDD assessing the efficacy and tolerability of Lu AA21004 at doses of 5 mg/day.

452 MDD patients aged 65 years or older with a current major depressive episode (MDE) of at least 4-week duration, at least one previous episode before the age of 60 years, and a Montgomery–Åsberg Depression Rating Scale (MADRS) total score of 26 or more, were randomly assigned (1:1:1) to Lu AA21004 5 mg/day, duloxetine 60mg/day (active reference), or placebo for 8 weeks.

Study results:
In this study of elderly patients with recurrent MDD, Lu AA21004 was efficacious and well tolerated. The primary endpoint was mean change from baseline in the 24-item Hamilton Depression Rating Scale ($HAM\text{-}D_{24}$) total score, a measure of the severity of MDD. According to the study results, patients taking Lu AA21004 showed a significantly (p=0.0011) greater improvement on the primary efficacy endpoint versus placebo at Week 8 (mean difference to placebo of 3.3 $HAM\text{-}D_{24}$ points). $HAM\text{-}D_{24}$ response (53.2% versus 35.2%) and $HAM\text{-}D_{17}$ remission (29.2% versus 19.3%) rates at endpoint were higher for Lu AA21004 than for placebo. The active reference, duloxetine, also separated from placebo, demonstrating assay sensitivity.

The study also included secondary endpoints evaluating cognitive function. These neuropsychological tests were the Digit Symbol Substitution Test (DSST), a measure of executive function, working memory, processing speed and visuo-spatial attention, and the Rey Auditory Verbal Learning Task (RAVLT), a measure of verbal learning, including recall and recognition. Lu AA21004 showed superiority to placebo in both of these tests. Duloxetine showed superiority to placebo in the RAVLT, but not in the DSST, confirming previously published results[i].

Withdrawal rates due to adverse events were 5.8% (Lu AA21004) and 2.8% (placebo). Nausea was the only adverse event with a significantly higher incidence for Lu AA21004 (21.8%) versus placebo (8.3%). For duloxetine, discontinuation due to adverse events was 9.9%, and adverse events with significantly higher incidence than seen with placebo were: nausea (33.1%), constipation (13.9%), dry mouth (21.9%), hyperhidrosis (10.6%) and somnolence (10.6%).

Abstract no 4-45*: Long-term safety and tolerability of Lu AA21004 in subjects with major depressive disorder*
This was a 52-week open-label extension study of subjects who completed 1 of 2 previous short-term MDD efficacy studies of Lu AA21004. In this study, up to 10 mg/day of Lu AA21004 was well tolerated with no indication of safety concerns. Lu AA21004 maintained improvement of depressive symptoms throughout the treatment period in this population of subjects with MDD.

Abstract no 4-05*: Lu AA21004 in the prevention of relapse in adult patients with generalised anxiety disorder*
This study investigated the long-term maintenance of efficacy of Lu AA21004 at 5 or 10mg/day in the prevention of relapse in patients with generalised anxiety disorder (GAD) who had responded to acute treatment with Lu AA21004. In the study, Lu AA21004 was efficacious in preventing relapse and was well tolerated in the maintenance treatment of GAD.

Non-clinical results presented at APA

Separate presentations at the 2012 APA meeting also included results from pre-clinical research to investigate the pharmacology of Lu AA21004:

- ***Abstract no 4-30****:* Lu AA21004, a multimodal antidepressant, is demonstrated to be active in a fluoxetine-insensitive rat model of depression and enhanced cognitive function in rats
- ***Abstract no 9-32****:* Effect of the multimodality-depressant Lu AA21004 on recognition, memory and hippocampal plasticity in rats

- ***Abstract no 4-34****:* The multimodal antidepressant Lu AA21004 but not escitalopram reversed cognitive dysfunction produced by serotonin depletion in rats
- ***Abstract no 4-31****:* Lu AA21004 effects on attention and vigilance measured as EEG activity in the rat
- ***Abstract no 4-36****:* Differential regulation of 5-HT_{1B} receptors by escitalopram and the multimodal antidepressant Lu AA21004
- ***Abstract no 4-26****:* Impact of the multimodal antidepressant Lu AA21004 on serotonin transmission in the rat hippocampus

Lundbeck and Takeda are committed to further investigate the effects of Lu AA21004 on cognitive function in depression and have initiated two studies in adult patients with MDD featuring neuropsychological tests as a primary endpoint.

About Lu AA21004

Lu AA21004 is a multimodal anti-depressant that is thought to work through a combination of two complementary mechanisms of action: receptor activity modulation and reuptake inhibition.

In vitro studies indicate that Lu AA21004 is a 5-HT_3 and 5-HT_7 receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist and inhibitor of the serotonin transporter (SERT). In vivo non-clinical studies have demonstrated that Lu AA21004 modulates neuronal firing and neurotransmitter release in multiple systems, resulting in enhanced levels of serotonin, noradrenaline, dopamine, acetylcholine and histamine in specific areas of the brain.

About major depression (MDD)

Major depressive disorder (MDD) - commonly referred to as major depression – is a highly prevalent, serious and debilitating medical condition. The disease can be described as a complex syndrome of emotional, psychological and somatic symptoms.

The significant clinical heterogeneity of the disease is frequently cited as a reason for the limited efficacy of currently available antidepressants. While several treatments are available, around 50% of patients remain symptomatic following first-line treatment, and a third fail to achieve full resolution of depressive symptoms after four established treatments.

MDD is the leading cause of years lost due to disability in the world, and projected to be the biggest contributor to the worldwide burden of disease by 2030. It is estimated that between a quarter and a third of the population will develop at least one episode of major depression during life-time and of these as many as two thirds will have recurrent episodes, and one third will develop a chronic condition.

Depression is associated with significant functional impairment and reduced quality of life[ii] . Many patients experience a range of symptoms of the disease that include cognitive symptoms such as the ability to think, concentrate, learn, remember and make decisions. Persistence of cognitive symptoms in patients with MDD can contribute to impaired work function and predict poor occupational outcome. Additional treatment strategies are needed to prevent and treat these common and debilitating symptoms of depression.

The tolerability of antidepressants and patients' concerns about side effects negatively affect patient outcomes. Patients with MDD who experience at least one severe side effect are twice as likely to discontinue treatment prematurely. Common reasons for premature treatment discontinuation include weight gain, and gastrointestinal and sexual side effects.

Financial guidance

The content of this release will have no influence on the Lundbeck Group's financial guidance for 2012 which was provided on 8 February 2012 in connection with the release of the financial results for 2011.

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About Lundbeck

H. Lundbeck A/S (LUN.CO, LUN DC, HLUKY) is an international pharmaceutical company highly committed to improving the quality of life for people suffering from brain disorders. For this purpose, Lundbeck is engaged in the research, development, production, marketing and sale of pharmaceuticals across the world. The company's products are targeted at disorders such as depression and anxiety, psychotic disorders, epilepsy and Huntington's, Alzheimer's and Parkinson's diseases.

Lundbeck was founded in 1915 by Hans Lundbeck in Copenhagen, Denmark. Today Lundbeck employs approximately 6,000 people worldwide. Lundbeck is one of the world's leading pharmaceutical companies working with brain disorders. In 2011, the company's revenue was DKK 16.0 billion (approximately EUR 2.2 billion or USD 3.0 billion). For more information, please visit www.lundbeck.com.

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[i] Joel Raskin et al.: " Efficacy of Duloxetine on Cognition, Depression, and Pain in Elderly Patients With Major Depressive Disorder: An 8-Week, Bouble-Blind, Placebo-Controlled Trial"; Am J Psychiatry 164:6, June 2007

[ii] Tracy L. Greer et al.: "Defining and Measuring Functional Recovery from depression"; CNS Drugs 2010; 24 (4): 264-284