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Corporate Release

US FDA accepts Otsuka and Lundbeck's filing for review of brexpiprazole for the treatment of schizophrenia and as adjunctive therapy for the treatment of major depression

- *In the clinical program, brexpiprazole demonstrated improvement in symptoms in both schizophrenia and as adjunctive therapy in major depression (MDD)*
- *July 2015 is the anticipated completion timing of the FDA's review (based on PDUFA timeline)*
- *Brexpiprazole is a serotonin-dopamine activity modulator (SDAM) and is believed to possess a balanced combination of binding affinity and functional activities at multiple receptors in the brain*

Valby, Denmark, and Tokyo, Japan, 24 September 2014 - H. Lundbeck A/S (Lundbeck) and Otsuka Pharmaceutical Co., Ltd. (Otsuka) today announced that the US Food and Drug Administration (FDA) has determined that the New Drug Application (NDA) for brexpiprazole for monotherapy in adult patients with schizophrenia and for adjunctive treatment of major depressive disorder (MDD) in adult patients is sufficiently complete to allow for a substantive review and the NDA is considered filed as of 9 September 2014 (60 days after submission). The PDUFA date is July 11, 2015.

The NDA is supported by seven completed placebo-controlled clinical phase II or III studies in proposed indications – three studies in schizophrenia and four studies with brexpiprazole as adjunct therapy in MDD. The dossier included data from more than 6,000 participants of whom more than 5,000 received brexpiprazole.

"*We are proud to have completed an extensive clinical program studying the safety and efficacy of brexpiprazole in adults with schizophrenia and those with MDD*," said Anders Gersel Pedersen, EVP and head of R&D in Lundbeck. "*We believe in the potential of brexpiprazole to fulfill unmet patient needs and look forward to working with the FDA throughout the NDA review*."

"*We and our collaborator Lundbeck are proud to have reached this juncture in the development of brexpiprazole*," said William H. Carson, M.D., president and CEO of Otsuka Pharmaceutical Development & Commercialization, Inc. "*In view of the importance of good mental health and the projected impacts of mental health disorders on people affected, their families and society, future new treatment options will be indispensable*."

Brexpiprazole in adult patients with schizophrenia

One clinical phase II and two clinical phase III placebo-controlled studies have been finalized using brexpiprazole in adult patients suffering from schizophrenia. Across the three studies more than 1,700 patients have been randomized.

In the first pivotal phase III study randomizing approximately 625 patients, brexpiprazole 2 mg/day and 4 mg/day both demonstrated greater improvement of symptoms relative to placebo as measured by change from baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at week 6 ($p<0.05$). Results of the key secondary endpoint supported primary results.

In the second pivotal phase III study randomizing approximately 650 patients, brexpiprazole 4 mg/day again demonstrated greater improvement of symptoms relative to placebo ($p<0.05$) in change from baseline in the PANSS Total Score at week 6. Brexpiprazole 2 mg/day showed numerical improvement ($p>0.05$) over placebo at week 6.

The results from the clinical phase II study[i] were presented at the 24th Annual US Psychiatric and Mental Health Congress in November 2011. The study showed a clinically meaningful improvement from baseline measured by PANSS total score at week 6, although it did not achieve statistical separation from placebo[ii].

In the placebo-controlled phase II and III studies, the rates of discontinuation due to adverse events were 8.1% for patients receiving brexpiprazole compared to 12.7% of patients receiving placebo; the only adverse event that occurred in more than 5% of brexpiprazole patients and more frequently than placebo was akathisia (5.8% vs. 4.5%).

Brexpiprazole as adjunctive therapy in major depression (MDD)

Four studies have been included in the dossier using brexpiprazole as adjunctive therapy for adult patients suffering from MDD, who had demonstrated a consistent inadequate, response to at least two regimens of prior antidepressant treatment. Patients with MDD and an inadequate response to one to three antidepressants were enrolled and received antidepressants for 8 weeks, single blinded, in the two phase III studies. Patients with an inadequate response after this prospective phase were provided antidepressant therapy and randomized adjunctive treatment with either brexpiprazole or placebo for 6 weeks. The primary efficacy endpoint was the change in MADRS (Montgomery–Åsberg Depression Rating Scale) Total Score from baseline at week 6. MADRS is a commonly used scale to assess the range of symptoms in patients with MDD. Inadequate response prior to randomization was defined as having persistent symptoms without substantial improvement during eight weeks of antidepressant treatment. Across the four studies, over 3,900 patients entered the prospective phase of studies and over 1,800 patients were included in the randomized phase of the studies.

The first pivotal phase III results were presented in a poster session at the 22nd European Psychiatry Association Congress (EPA) in March 2014[iii]. This two-arm phase III study[iv] randomized approximately 380 patients and demonstrated an improvement of symptoms with an antidepressant plus 2 mg brexpiprazole that was greater than an antidepressant plus placebo ($p<0.001$).

The second pivotal phase III study[v] was a three-arm study in which approximately 675 patients were randomized to treatment with an antidepressant plus either placebo, 1 mg brexpiprazole or 3 mg brexpiprazole. Patients in both brexpiprazole treatment groups showed greater improvement in symptoms as measured by the MADRS compared to placebo (1 mg $p>0.05$, 3 mg $p<0.05$). Results of the second pivotal phase III study in MDD have not yet been published.

The first clinical phase II study[vi] randomized approximately 425 patients in four arms and was presented at the 164th Annual Meeting of the American Psychiatric Association in May 2011. Patients exhibited greater improvements than adjunctive placebo in MADRS Total score with the 1.5 (±0.5) mg/day dose of brexpiprazole after six weeks of treatment ($p<0.05$ vs. placebo)[vii]. The second phase II study in MDD including randomizing approximately 372 patients has not yet been published but supports the findings in the other studies.

Across the four placebo-controlled phase II and III studies, over 90% of patients completed the studies. The rates of discontinuation due to adverse events was 2.9% for patients receiving brexpiprazole compared to 0.8% of patients receiving placebo; the only adverse events that occurred in more than 5% of brexpiprazole patients and more frequently than placebo were akathisia (8.6% vs. 2.8%) and increased (7.3% vs. 1.9%).

Full data from the four clinical phase III studies in the two indications will be made available through scientific disclosure at upcoming medical congresses and in scientific publications. Data from the clinical phase III program in schizophrenia and adjunctive therapy in MDD has been submitted to the 53rd Congress of American College of Neuropsychopharmacology (ACNP) on 7-11 December 2014 in Phoenix, Arizona.

About brexpiprazole (OPC-34712)

Brexpiprazole is a novel investigational psychotropic compound discovered by Otsuka and under co-development with Lundbeck. Brexpiprazole is a serotonin-dopamine activity modulator (SDAM) that acts as a partial agonist at 5-HT_{1A} and dopamine D_2 receptors at similar potency, and an antagonist at 5-HT_{2A} and noradrenaline $alpha_{1B/2C}$ receptors.

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About Otsuka Pharmaceuticals Co., Ltd.

Otsuka Pharmaceutical Co., Ltd. is a global healthcare company with the corporate philosophy: 'Otsuka-people creating new products for better health worldwide.' Otsuka researches, develops, manufactures and markets innovative and original products, with a focus on pharmaceutical products for the treatment of diseases and nutraceutical products for the maintenance of everyday health.

In pharmaceuticals, Otsuka is a leading firm in the challenging area of mental health and also has research programs on several under-addressed diseases including tuberculosis, a significant global public health issue. These commitments illustrate more powerfully than words how Otsuka is a “big venture” company at heart, applying a youthful spirit of creativity in everything it does.

Otsuka Pharmaceutical Co., Ltd., which employees approximately 28,700 people worldwide, is a wholly owned subsidiary of Otsuka Holdings Co., Ltd., the holding company for the Otsuka Group that is headquartered in Tokyo, Japan. The chairman Akihiko Otsuka is the third generation of Otsuka family members to lead the business, whose origins date from 1921. The Otsuka Group has business operations in 25 countries and regions around the world, with consolidated sales of approximately USD 14.1 billion for fiscal year 2013 (4/1/2013-3/31/2014.) Otsuka Pharmaceutical welcomes you to visit its global website at https://www.otsuka.co.jp/en.

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 than 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 DKK 15.3 billion in 2013 (EUR 2.1 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] Clinicaltrials.gov ID: NCT00905307

[ii] McQuade, R., Hobart, M., Forbes, R.A., Pfister, S., L.B. Duncan, S. Wu, J. Ouyang, Skuban, A., Sanchez, R.: "*A Phase II trial assessing the efficacy and safety of OPC-34712 in the acute treatment of adult schizophrenia (Study 331-07-203)*"; presented at 24th Annual US Psychiatric and Mental Health Congress,
7-11 November 2011, Las Vegas, NV, USA

[iii] Thase, M.E., Hobart, M, Augustine, C., Youakim, J.M., Zhang, P., Hefting, N., et al: "*Efficacy and Safety of Adjunctive Brexpiprazole (OPC-34712) in Major Depressive Disorder (MDD): A Phase 3, Randomized, Placebo-Controlled Study*"

[iv] Clinicaltrials.gov ID: NCT01360645

[v] Clinicaltrials.gov ID: NCT01360632

[vi] Clinicaltrials.gov ID: NCT00797966

[vii] Thase, M.E., Fava, M., Hobart, M., Skuban, A., Zhang, P., McQuade, R.D., et al: "*Efficacy and Safety of Adjunctive OPC-34712 in Major Depressive Disorder: A Phase II, Randomized, Placebo-Controlled Study*"