

# OTSUKA PHARMACEUTICAL TO ACQUIRE AVANIR PHARMACEUTICALS

Full-scale entry to neurologic diseases area widens core business presence in CNS

**Tokyo, Japan – December 2, 2014** – Otsuka Pharmaceutical Co., Ltd. is pleased to announce an agreement with Avanir Pharmaceuticals, Inc. ("Avanir") in which Otsuka America, Inc., a US subsidiary, acquires Avanir for USD 3.5 billion in an all-cash tender offer. The contract was signed on December 2, Japan time.

#### **Avanir Pharmaceuticals**

Avanir is a biopharmaceutical company specializing in CNS diseases. It was founded in 1988 in Southern California and now employs approximately 500 people. Avanir developed and launched NUEDEXTA<sup>®</sup> (dextromethorphan hydrobromide/quinidine sulfate) 20mg/10mg capsules in the US in February 2011 as the world's first and only approved treatment for the neurologic disease pseudobulbar affect (PBA). Sales of NUEDEXTA in the twelve-month period from July 2013 through June 2014 were USD 94 million, a 50% increase over the prior-year period.

Avanir markets NUEDEXTA in the US through its own sales organization of over 300 sales representatives, 150 of whom were recently hired to accelerate the continued growth of NUEDEXTA for PBA. The company's pipeline includes programs in Alzheimer's disease, Parkinson's disease, migraine, and other CNS indications. The promising new chemical entity AVP-786, with a target indication for agitation associated with Alzheimer's disease, is being prepared to enter Phase III clinical trials.

## **Objectives of the acquisition**

The acquisition of Avanir will bring Otsuka three distinct values: 1) NUEDEXTA, created to treat the under-recognized, neurologic disease PBA; 2) the late-stage investigational compound AVP-786 in clinical development to treat agitation associated with Alzheimer's disease and; 3) Avanir's clinical development and commercial expertise in neurologic diseases, which complements Otsuka's capabilities in psychiatric diseases. These will accelerate Otsuka's existing expansion strategy in the neurologic area, widening the overall CNS portfolio, inclusive of the psychiatric and neurologic areas, supporting both short-and medium-term growth.

This acquisition is consistent with the Otsuka Group's investment philosophy: invest in companies and businesses with which we can share a common management philosophy, human resources, products and technology to enhance corporate value; and invest with long-term perspective. The acquisition is based on the concepts of creativity and *proof through execution* that Otsuka esteems.

## Creativity and proof through execution

Avanir has successfully taken on the challenge to create, develop and commercialize a drug in a new disease category PBA, for which no approved treatment existed. Avanir's approach to creativity is remarkably consistent with Otsuka's. The former has demonstrated strengths in neurologic diseases such as PBA whereas the latter has demonstrated strengths in psychiatric diseases such as schizophrenia, manic and mixed episodes of bipolar I disorder and adjunctive treatment of major depressive disorder. Furthermore, the October 2013 addition to the Otsuka Group of Astex Pharmaceuticals' Cambridge Research Institute, with its fragment-based drug discovery technology, will reinforce the integrated creative capacity of the three companies, accelerating and strengthening opportunities in the CNS field.

## NUEDEXTA, a treatment for PBA (pseudobulbar affect), a neurologic disease

PBA is a neurologic condition characterized by sudden and uncontrollable, disruptive laughing and/or crying outbursts that are often contrary or exaggerated in relation to the patient's inner mood state. As a result, many of those afflicted with PBA show significant impairment on standard measures of health status, and impairments in occupational and social function, often leading to social isolation. PBA occurs secondary to a variety of neurologic conditions such as traumatic brain injury (TBI), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease, stroke and Alzheimer's disease. When these disorders damage areas of the brain that regulate normal emotional expression, they can lead to uncontrollable, disruptive episodes of crying or laughing.<sup>i</sup>

In the US, the potential number of patients is estimated to be approximately two million people. The disease was neglected for many years in absence of an approved treatment. NUEDEXTA is an innovative combination of two well-characterized components; dextromethorphan hydrobromide (20mg), the ingredient active in the central nervous system, and quinidine sulfate (10mg), a metabolic inhibitor enabling therapeutic dextromethorphan concentrations. Dextromethorphan acts on the sigma-1 and NMDA receptors in the brain, although the mechanism by which NUEDEXTA exerts therapeutic effects in patients with PBA is unknown.

## Drug development for agitation associated with Alzheimer's disease

Up to 50% of patients with Alzheimer's disease experience agitation, which can manifest as verbal abuse, confusion, and aggression.<sup>ii</sup> Dementia-related behavioral symptoms, including agitation, increase the burden on caregivers and can be extremely distressing to the individual, the family, and caregivers. These behavioral disturbances have been associated with more rapid cognitive decline, institutionalization and increased caregiver burden.

Avanir has continued to advance a clinical program for the treatment of agitation in Alzheimer's disease, a complication which currently lacks any effective and safe treatment. Avanir presented Phase II proofof-concept trial results at the American Neurological Association annual meeting in October 2014. Avanir expects to meet with the FDA in early 2015 to discuss advancement of the program.

## Medium-term management plan

In Otsuka's medium-term plan, the CNS therapy area, including global research and development, is one of the company's prioritized areas. The acquisition of Avanir will bolster Otsuka's business portfolio with NUEDEXTA and AVP-786. The psychiatric and neurologic areas will construct Otsuka's CNS business

which will exploit new synergies from research and development through to sales and marketing. These will serve as both a short-term and mid-term growth driver, with contributions to growth from NUEDEXTA revenues starting in 2015 and from Avanir's cash flow starting in 2016.

## Otsuka Pharmaceutical's strategy in CNS

Otsuka's pursuit of research and development in the CNS field for 25 years resulted in the introduction of ABILIFY<sup>®</sup> (aripiprazole) as the world's first dopamine  $D_2$  partial agonist in the United States in 2002 for the treatment of schizophrenia. In cooperation with Bristol-Myers Squibb, additional indications were developed in subsequent years in areas such as mixed and manic episodes of bipolar I disorder, and as adjunctive treatment of major depressive disorder. In 2011, Otsuka formed a far-reaching alliance with the Danish company Lundbeck in order to broaden CNS activities in Japan, the US, Europe and Asia. The alliance launched Abilify Maintena<sup>®</sup> (aripiprazole extended-release injectable suspension for intramuscular use), a once-monthly injectable schizophrenia treatment, in the US in 2013 and in the EU in 2014. Otsuka continues to expand its presence in the area of psychiatric diseases.

With this acquisition, Otsuka is expanding its therapeutic reach in the neurologic area which includes many diseases such as Alzheimer's-type dementia, multiple sclerosis, Parkinson's disease and amyotrophic lateral sclerosis, where there is large medical need for new therapeutic agents and where patients and healthcare providers are often unsatisfied with currently available therapeutic options.

There are many hurdles of research and development on CNS diseases. Mechanisms of action of drugs are often not completely understood, and animal testing models are not necessarily accurate predictors of efficacy in human diseases. Despite these hurdles, many new protein targets have been identified as targets for CNS diseases in recent years. The addition of Astex Pharmaceuticals to the Otsuka Group brought with it that company's Cambridge Research Institute. The institute's innovative fragment-based drug discovery technology is well suited to identify protein targets using techniques for low-molecular weight screening, enabling creation of candidate compounds in a short period of time.

By linking Avanir's clinical development and sales and marketing capabilities, Astex's Cambridge Research Institute, and Otsuka's Tokushima (Japan) Qs' Research Institute (for CNS drug discovery), an integrated drug development system in the CNS field can be constructed.

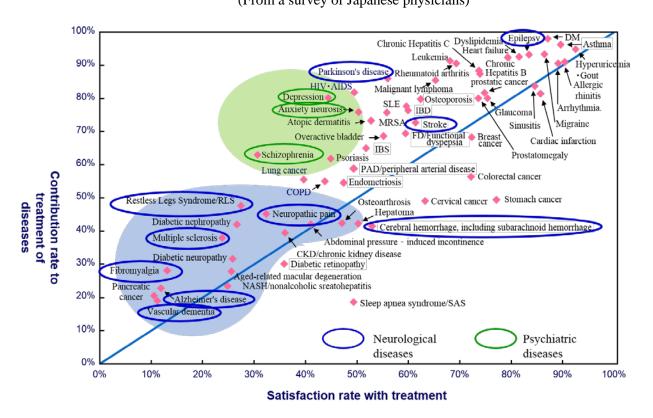
## Otsuka Pharmaceutical's engagement on Alzheimer's disease

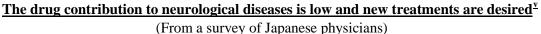
Alzheimer's-type dementia, one of the most pressing medical needs, is a neurologic disease in which nerve cells in the brain gradually die off, progressively destroying cognition and other mental faculties. Alzheimer's disease is the most frequently occurring type of dementia, accounting for 50-60% of dementia cases.<sup>iii</sup> There are estimated to be more than 30 million people with Alzheimer's disease worldwide.<sup>iv</sup>

As the disease progresses, typical symptoms including cognitive impairment, confusion, and agitation progress to the point that everyday functioning becomes difficult.

Otsuka views Alzheimer's disease as one of its core therapeutic focus areas with multiple programs in various stages of development, including two Phase III compounds targeting the symptoms of the disease. The addition of Avanir's AVP-786 is expected to further cement Otsuka's commitment to Alzheimer's

patients and address some of the critical medical needs such as reducing agitation and behavioral symptoms that arise from Alzheimer's-type dementia.





Otsuka Pharmaceutical president and representative director Taro Iwamoto commented, "As we bring together Otsuka's experience and business track record in the area of mental illnesses with Avanir's strengths in neurologic diseases, we believe that we can evolve into a truly global CNS pharmaceutical company. Avanir's creativity and proven execution on drug discovery and development for largely unexplored medical indications, typified by PBA, represents a hand-in-glove fit with Otsuka's culture. We admire and respect Avanir's innovative vision and execution, and want to continue to grow together."

Keith A. Katkin, president and chief executive officer of Avanir Pharmaceuticals, also noted, "I am extremely excited to see these two organizations come together to create a leading CNS company. Otsuka is a clear leader in psychiatry and Avanir in neurology; together I believe our organizations will be able to more rapidly develop and commercialize needed medications to potentially help millions of patients around the world."

## About NUEDEXTA

NUEDEXTA is an innovative combination of two well-characterized components; dextromethorphan hydrobromide (20 mg), the ingredient active in the central nervous system, and quinidine sulfate (10 mg), a metabolic inhibitor enabling therapeutic dextromethorphan concentrations. NUEDEXTA acts on sigma-

1 and NMDA receptors in the brain, although the mechanism by which NUEDEXTA exerts therapeutic effects in patients with PBA is unknown.

NUEDEXTA Important Safety Information:

NUEDEXTA is indicated for the treatment of pseudobulbar affect (PBA). PBA occurs secondary to a variety of otherwise unrelated neurologic conditions, and is characterized by involuntary, sudden, and frequent episodes of laughing and/or crying. PBA episodes typically occur out of proportion or incongruent to the underlying emotional state.

Studies to support the effectiveness of NUEDEXTA were performed in patients with amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). NUEDEXTA has not been shown to be safe and effective in other types of emotional lability that can commonly occur, for example, in Alzheimer's disease and other dementias.

NUEDEXTA and certain other medicines can interact, causing serious side effects. If you take certain drugs or have certain heart problems, NUEDEXTA may not be right for you.

NUEDEXTA causes dose-dependent QTc prolongation. When initiating NUEDEXTA in patients at risk for QT prolongation and torsades de pointes, electrocardiographic (ECG) evaluation should be conducted at baseline and 3-4 hours after the first dose.

The most common adverse reactions are diarrhea, dizziness, cough, vomiting, asthenia, peripheral edema, urinary tract infection, influenza, increased gamma-glutamyltransferase, and flatulence. NUEDEXTA may cause dizziness.

These are not all the risks from use of NUEDEXTA. Please refer to full Prescribing Information at <u>www.NUEDEXTA.com</u>.

# About Otsuka Pharmaceutical Co., Ltd.

Otsuka Pharmaceutical 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.

Numerous innovation seeds have been created through our horizontal alliances in the CNS field with other companies: Lundbeck and BMS on psychiatric therapies, and IBM and Proteus Digital Health on digital solutions for patients, their families, healthcare providers and other caregivers.

Otsuka Pharmaceutical Co., Ltd., which employs 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 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 Avanir Pharmaceuticals, Inc.

Avanir Pharmaceuticals, Inc. is a biopharmaceutical company focused on bringing innovative medicines to patients with central nervous system disorders of high unmet medical need. As part of our commitment, we have extensively invested in our pipeline and are dedicated to advancing medicines that can substantially improve the lives of patients and their loved ones. For more information about Avanir, please visit <u>www.avanir.com</u>. Avanir® and NUEDEXTA® are registered trademarks owned by Avanir Pharmaceuticals, Inc. All other trademarks are the property of their respective owners.

#### Note to Investors

The tender offer to purchase shares of Avanir common stock referenced in this press release has not yet commenced, and this press release is neither an offer to purchase, nor a solicitation of an offer to sell, any securities. The tender offer to purchase shares of Avanir common stock will be made only pursuant to a Tender Offer Statement on Schedule TO containing an offer to purchase, forms of letters of transmittal and other documents relating to the tender offer (the "Tender Offer Statement"), which Bigarade Corporation, a wholly-owned indirect subsidiary of Otsuka, will file with the Securities and Exchange Commission (the "SEC"). Avanir will file with the SEC a Solicitation/Recommendation Statement with respect to the tender offer (the "Recommendation Statement"). THE TENDER OFFER STATEMENT AND THE RECOMMENDATION STATEMENT WILL CONTAIN IMPORTANT INFORMATION THAT SHOULD BE READ CAREFULLY AND CONSIDERED BEFORE ANY DECISION IS MADE WITH RESPECT TO THE TENDER OFFER. Both the Tender Offer Statement and the Recommendation Statement will be mailed to Avanir stockholders free of charge. Investors and security holders of Avanir also are advised that they may also obtain free copies of the Tender Offer Statement and other documents filed by Bigarade Corporation with the SEC (when these documents become available) and the Recommendation Statement and other documents filed by Avanir (when these documents become available) on the SEC's website at www.sec.gov.

## Forward-looking Statements

Certain statements contained in this press release, including without limitation expectations as to future sales and operating results, constitute forward-looking statements. Forward-looking statements in this press release include statements regarding the anticipated benefits of the transaction; statements regarding the anticipated timing of filings and approvals relating to the transaction; statements regarding the expected timing of the completion of the transaction; and any statements of assumptions underlying any of the foregoing. Words such as "expects," "anticipates," "believes," "plans," "intends," "estimates," "projects," "forecasts," "outlook," and similar expressions are also intended to identify forward-looking statements. The statements involve known and unknown risks, uncertainties, and other factors which may cause the company's actual results, earnings, performance, or achievements to be materially different

from any future results, performance, or achievements expressed or implied by such forward-looking statements. Such factors include, but are not limited to, the following: general industry and market conditions, general domestic and international economic conditions such as interest rate and currency exchange fluctuations, technological advances and patents attained by competitors, challenges inherent in new product development and clinical trials, claims and concerns about product safety and efficacy, obtaining regulatory approvals, domestic and foreign healthcare reforms, and healthcare cost containment, laws and regulations affecting domestic and foreign operations, and failure to gain market acceptance or third-party consents. Risks and uncertainties that could cause results to differ from expectations also include: uncertainties as to the timing of the tender offer and merger; uncertainties as to how many Avanir stockholders will tender their stock in the offer; the risk that competing offers will be made; and the possibility that various closing conditions for the transaction may not be satisfied or waived, including that a governmental entity may prohibit, delay or refuse to grant approval for the consummation of the transaction. We will not undertake and specifically decline any obligation to update or correct any forward-looking statements to reflect events or circumstances after the date of such statements or to reflect the occurrence of anticipated or unanticipated events.

<sup>ii</sup> *Agitation in the elderly*. Psychiatric Times. 1999; XVI, Issue 1 http://www.psychiatrictimes.com/dementia/agitation-elderly

<sup>&</sup>lt;sup>1</sup> King R, Reiss J: *The epidemiology and pathophysiology of pseudobulbar affect and its association*. Degenerative Neurological and Neuromuscular Disease. 2013; 3: 23-31.

iii http://www.alz.co.uk/media/quick-facts. Accessed November 17, 2014

<sup>&</sup>lt;sup>iv</sup> <u>http://www.alzheimers.net/resources/alzheimers-statistics/</u>. Accessed November 17, 2014

<sup>&</sup>lt;sup>v</sup> *Outlook of medical needs in 2020*. Domestic Foundation Survey. Human Science Promotion Foundation (Japan), 2010