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Amarantus Announces Positive Phase 2 Data for Eltoprazine in Alzheimer's Aggression

SAN FRANCISCO, December 8, 2015 /PRNewswire/ --

[Amarantus Bioscience Holdings, Inc.](#) (OTCQX: AMBS), a biotechnology company developing therapeutic and diagnostic product candidates in neurology and orphan indications, today announced positive data for Eltoprazine in a Phase 2 clinical trial of elderly patients with Alzheimer's dementia who are aggressive. Eltoprazine is a selective 5HT1a/1b partial agonist in development by Amaranthus for the treatment Parkinson's disease levodopa-induced dyskinesia, and is now poised for further clinical development as a symptomatic treatment in adult ADHD and Alzheimer's aggression.

"Verbal and physical agitation and aggression symptoms are commonly associated with Alzheimer's disease as the disease progresses into the dementia phase," commented - Paula T. Trzepacz, MD, Clinical Professor of Psychiatry, Indiana University School of Medicine and Scientific Advisory Board Member. Caregivers find these symptoms to be very distressing, leading to significant caregiver distress, health problems and burnout, as well as a high likelihood of patient institutionalization. There are currently no medications specifically indicated for these symptoms, though many types have been studied in clinical trials, including neuroleptics, antidepressants, anticonvulsants, anxiolytics, sedative/hypnotics, cholinesterase inhibitors, and glutamate system agents. Clinically, a variety of psychoactive medications are used off-label to attempt to manage these symptoms, but none have proven efficacy. Further, many carry problematic adverse effects such as excess sedation or even more serious ones such as stroke and death. Therefore, positive pilot data for a new drug that acts on the serotonin neurotransmitter system differently than marketed drugs offer hope. An adequately powered Phase 2 trial would be needed to further evaluate potential efficacy and safety of eltoprazine."

The data demonstrate a significant improvement in eltoprazine-treated patients in the severely aggressive eltoprazine-treated population (25.1 to 16.9) versus placebo (22.5 to 21.5), $p < 0.05$ as measured by the Social Dysfunction and Aggression Scale at the end of the four week treatment regimen, which followed a washout from previous psychoactive treatments and a 3-week placebo-lead-in period. Further evaluation of the complete data package is underway prior to submission for publication.

"Aggression associated with Alzheimer's disease, or dementia, represents a massive unmet medical need that disrupts the normal course of activity throughout the lifespan of nursing home facilities and the homes of Alzheimer's patients putting a tremendous strain on caregivers" said Gerald E. Commissiong, President & CEO of Amaranthus. "Amarantus

is committed to improving the lives of patients with Alzheimer's disease and their caregivers. Through our work in both the diagnostic and therapeutic arenas, we believe we believe we can ultimately have a meaningful positive impact on the management of this devastating international conundrum, which represents a looming \$2+ trillion cost to the world's healthcare systems by 2050. Amaranthus is uniquely positioned to improve both the diagnosis and treatment of Alzheimer's disease."

Eltoprazine & Aggression - Dementia IV

Eltoprazine in Demented Elderly Patients with Disruptive Behaviour. A Placebo and Baseline-Controlled Multi-Centre Study (Duphar study H.134.5012)

SDAS total scores upon treatment with Eltoprazine or Placebo

Patient group	Day -20	Day -1	Day 8	Day 15	Day 22	Day 29
Eltoprazine ³ 19 n=7	26.6	25.1	21.0	18.7	16.3	16.9
Placebo ³ 19 n=4	24.8	22.5	19.0	17.3	18.0	21.5
Eltoprazine <19 n=10	19.4	13.8	13.2	15.4	15.0	17.5
Placebo <19 n=4	19.3	13.8	13.8	20.3	17.8	19.3

Study Design

Study Objectives

There were four primary study objectives: 1. To collect data on safety on tolerability of multiple dose treatment of Eltoprazine in elderly subjects; 2. To evaluate the feasibility of the assessment methods; 3. To obtain information on the effects of Eltoprazine on hostile or disruptive behaviour in hospitalized demented elderly; 4. To obtain preliminary information on possible relations between plasma concentrations and eventual side-effects.

Methodology

The study was designed as a multi-centre (6) parallel-group study in demented elderly with aggressive behavior. Following screening subjects were directly randomized per block of 3 to receive eltoprazine or placebo (2:1) in the double-blind treatment phase.

Before entering the double-blind treatment phase all subjects were placed in a single-blind placebo run-in period over 3-weeks to establish a baseline of aggressive behavior. Other psychotropic medications were anticipated to have been washed-out before the on-drug portion of the study.

Number of subjects and demographics

29 subjects entered the study. 20 were randomized to receive Eltoprazine, with a mean age of 83.6 years (range 74-92); 14 were female, 6 were male. Nine subjects were randomised to receive placebo, with a mean age of 81.1 years (range 70-86); 6 were female, 3 were male.

Diagnosis and criteria for inclusion

All subjects had to have been diagnosed with Senile Dementia of Alzheimer's Type (SDAT) or mixed SDAT/Multi-Infarct Dementia according to DSM-III-R criteria. Subjects had to score less than 60 points on the CAMCOG, a test assessing cognitive functioning. All subjects had to have been hospitalized for at least 2 months and have shown a minimum of 4 episodes of hostile or disruptive behavior per week over the 4 weeks preceding entry to the study.

Test product, dose and mode of administration and catch number

Eltoprazine was provided in capsules containing either 1mg Eltoprazine or 5mg Eltoprazine for oral use. The maximum daily dose was 10mg b.i.d.

Reference Product, dose and mode of administration and batch number

Placebo was provided in identical capsules to be used during the washout period from non-permitted psychotropic medication (if applicable), during the 3 week placebo run-in period in all subjects and during the double-blind treatment phase in those patients randomised to receive placebo.

Duration of treatment

The double-blind treatment phase lasted 29 days including a 5 day taper-on period and a 6-8 day taper-off period depending on the final dose reached (5 or 10mg b.i.d.; at day 13 the dose could be optionally increased from 5 to 10mg b.i.d. in the course of 4 days).

Criteria for evaluation

The safety and tolerability were monitored by means of haematological and biochemical laboratory tests, urinalysis, assessment of vital signs, ECG recording and clinical observation to detect potential side-effects.

Potential influences on the demented state were evaluated by the Sandoz Clinical Assessment Geriatric Scale. The anti-aggressive properties of the study medication were evaluated by the Social Dysfunction and Aggression Scale and the Staff Observation Scale.

Statistical Analysis

In view of the small number of subjects only the most important efficacy variables were statistically tested for treatment using Wilcoxon test with adjustment for ties. Calculations were done, where possible, for absolute values and pre-treatment adjusted values. The

calculated p-values are two-sided. For all the other variables, where appropriate, the mean, standard deviation and number of subjects are given.

Results

Of the 20 subjects randomised to receive Eltoprazine, two dropped out during the placebo run-in phase, one because of fatal lung infection, the other subject refusing to eat or drink. One subject was prematurely withdrawn because of physical deterioration due to lung carcinoma. One subject had to be excluded from the efficacy analysis because of an erratic dosing regimen.

Of the 9 subjects randomised to receive placebo, one dropped out during the placebo run-in phase due to a heart failure. There were no worrying safety problems related to Eltoprazine treatment. In general, eltoprazine was reasonably well tolerated. Treatment emergent signs and symptoms were confusion (4 subjects), insomnia (2), somnolence (3) and anxiety (2). One male experienced delusions, which spontaneously disappeared within one week.

There was no influence of Eltoprazine on the demented state per se. The overall aggression level was modest and mainly of a verbal or mild physical nature. Clinically significant reductions in aggressive behavior in Eltoprazine-treated subjects were especially apparent from the descriptions in the case summaries, which were partly substantiated by the scorings on the Social Dysfunction and Aggression Scale.

Conclusions

Using a dosing regimen with phases of gradual dose increase followed by reduction eltoprazine appeared safe and reasonably well tolerated in a population of demented elderly subjects with aggressive behavior. There are clear hints of anti-aggressive efficacy in more severely aggressive subjects which merit further research. The study design proved feasible and useful.

Further research needs to be done into the correlation between overt aggressive events and basal aggression. Measurements of anti-aggressive efficacy should preferably address both components of aggressive behavior.

About Agitation and Aggression in Alzheimer's Disease

An estimated 6 million Americans have Alzheimer's disease, a number that has doubled since 1980 and is expected to be as high as 16 million by 2050. Alzheimer's disease is generally characterized by cognitive decline, impaired performance of daily activities, and behavioral disturbances. Behavioral and psychiatric symptoms develop in as many as 60% of community-dwelling dementia patients and in more than 80% of patients with dementia living in nursing homes. Dementia-related behavioral symptoms, including agitation and aggression, 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. There are currently no approved treatments for agitation in patients with dementia related to Alzheimer's disease.

About Alzheimer's Disease

According to the Alzheimer's Association, it is estimated that over 5.4 million people in the United States suffer from Alzheimer's disease. Over 500,000 patients are diagnosed annually, with nearly one in eight older Americans affected by the disease. Alzheimer's disease is the third leading cause of death in the United States. The cost of unpaid care in the United States is estimated at over \$210 billion annually. Total payments for care are estimated at over \$200 billion annually, including \$140 billion in cost to Medicare and Medicaid. Alzheimer's expenditures in the United States are expected to exceed \$1.2 trillion by 2050. There is no cure or effective treatment for Alzheimer's disease. Worldwide, about 35.6 million individuals have the disease and, according to the World Health Organization, the number will double every 20 years to 115.4 million people with Alzheimer's by 2050.

About Eltoprazine

Eltoprazine is a small molecule 5HT1A/1B partial agonist in clinical development for the treatment of Parkinson's disease levodopa-induced dyskinesia (PD-LID) at Amaranthus. Clinical studies have also been completed in adult attention deficit hyperactivity disorder (ADHD) and Alzheimer's aggression. Eltoprazine has been evaluated in over 680 human subjects to date, and has a well-established safety profile. Eltoprazine was originally developed by Solvay Pharmaceuticals for the treatment of aggression. Upon Solvay's merger with Abbott Pharmaceuticals, the eltoprazine program was out-licensed to PsychoGenics. PsychoGenics licensed eltoprazine to Amaranthus following successful proof-of-concept trials in PD-LID and adult ADHD.

About Amaranthus BioScience Holdings, Inc.

Amaranthus BioScience Holdings (OTCQX:AMBS) is a biotechnology company developing treatments and diagnostics for diseases in the areas of neurology and orphan diseases. The Company has an exclusive worldwide license to intellectual property rights associated to Engineered Skin Substitute (ESS), an orphan drug designated autologous full thickness skin replacement product in development for the treatment of adult severe burns currently preparing to enter Phase 2 clinical studies. The Company is currently evaluating human clinical data from previously conducted studies in pediatric severe burns and Congenital Giant Hairy Nevus to support clinical development expansion into those areas. AMBS also has development rights to eltoprazine, a small molecule currently in a Phase 2b clinical program for Parkinson's disease levodopa-induced dyskinesia with the potential to expand into adult ADHD and Alzheimer's aggression. AMBS owns the intellectual property rights to a therapeutic protein known as mesencephalic-astrocyte-derived neurotrophic factor (MANF) and is developing MANF as a treatment for orphan ophthalmic disorders, initially in retinitis pigmentosa (RP) and retinal artery occlusion (RAO). AMBS also owns the discovery of neurotrophic factors (PhenoGuard™) that led to MANF's discovery.

AMBS' Diagnostics division owns the rights to MSPrecise®, a proprietary next-generation DNA sequencing (NGS) assay for the identification of patients with relapsing-remitting multiple sclerosis (RRMS) at first clinical presentation, has an exclusive worldwide license to the Lymphocyte Proliferation test (LymPro Test®) for Alzheimer's disease, which was

developed by Prof. Thomas Arendt, Ph.D., from the University of Leipzig, and owns intellectual property for the diagnosis of Parkinson's disease (NuroPro).

For further information please visit <http://www.Amarantus.com>, or connect with the Company on [Facebook](#), [LinkedIn](#), [Twitter](#) and [Google+](#).

Forward-Looking Statements

Certain statements, other than purely historical information, including estimates, projections, statements relating to our business plans, objectives, and expected operating results, and the assumptions upon which those statements are based, are forward-looking statements. These forward-looking statements generally are identified by the words "believes," "project," "expects," "anticipates," "estimates," "intends," "strategy," "plan," "may," "will," "would," "will be," "will continue," "will likely result," and similar expressions. Forward-looking statements are based on current expectations and assumptions that are subject to risks and uncertainties which may cause actual results to differ materially from the forward-looking statements. Our ability to predict results or the actual effect of future plans or strategies is inherently uncertain. Factors which could have a material adverse effect on our operations and future prospects on a consolidated basis include, but are not limited to: changes in economic conditions, legislative/regulatory changes, availability of capital, interest rates, competition, and generally accepted accounting principles. These risks and uncertainties should also be considered in evaluating forward-looking statements and undue reliance should not be placed on such statements.

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