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**ADAMAS PHARMACEUTICALS PRESENTS POSITIVE PHASE 2/3 RESULTS FOR ADS-5102 FOR THE TREATMENT OF LEVODOPA-INDUCED DYSKINESIA (LID) IN PARKINSON'S DISEASE**

**SYDNEY, AUSTRALIA AND EMERYVILLE, CALIF., JUNE 18, 2013** – Adamas Pharmaceuticals, Inc. presented final results today from a Phase 2/3 clinical trial of ADS-5102 (amantadine HCl extended release) capsules demonstrating a statistically significant improvement in levodopa-induced dyskinesia (LID) as measured by change from baseline at week 8 versus placebo in the Unified Dyskinesia Rating Scale (UDysRS). ADS-5102 is Adamas' investigational extended-release formulation of amantadine intended for once-nightly administration that is being studied for the treatment of LID in Parkinson's disease (PD) patients. Data from the Phase 2/3 EASED™ (Extended Release Amantadine Safety and Efficacy Study in Levodopa-Induced Dyskinesia) clinical trial were presented today at the 17<sup>th</sup> International Congress of Parkinson's Disease and Movement Disorders.

“For Parkinson's disease patients suffering from the dyskinesia side effects of levodopa treatment, reducing the time and severity of these effects has been a long-term goal in their treatment. ADS-5102 demonstrated a significant reduction in the duration and severity of troublesome dyskinesia among PD patients with levodopa-induced dyskinesia in this well-designed, controlled clinical study,” said Rajesh Pahwa, M.D., Professor of Neurology, University of Kansas Medical Center and an investigator for the EASED study. “The clinical results seen in this study of ADS-5102 are extremely encouraging and have the potential to make a difference in patients' lives,” Dr. Pahwa added.

The EASED study of ADS-5102 met its primary endpoint; both the 340 mg and 420 mg ADS-5102 dose levels significantly reduced LID as measured by the change in UDysRS Total Score over eight weeks versus placebo. The study enrolled 83 subjects who were randomized in a 1:1:1:1 ratio to the four treatment groups: placebo, 260 mg ADS-5102, 340 mg ADS-5102 and 420 mg ADS-5102. At the 340 mg dose of ADS-5102, a treatment difference of 11 points (reduction in LID) was observed ( $p=0.005$ ). The 420 mg dose of ADS-5102 also met statistical significance with a treatment difference of 10 points ( $p=0.013$ ). While the lowest dose tested of 260 mg ADS-5102 reduced UDysRS by 5.6 points, it did not achieve statistical significance at week 8 ( $p=0.159$ ). Consistent with the changes observed in the UDysRS, ADS-5102 also demonstrated statistically significant functional improvement in dyskinesia as assessed by the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS, item 4.2), a measure of the degree of impact that dyskinesia has on the patient's daily function in terms of activities and social interactions. In addition, subjects reported a statistically significant increase of approximately three hours in “ON Time without troublesome dyskinesia” compared to placebo at week 8 across all dose levels.

The adverse events (AEs) reported in this study were consistent with Parkinson's disease and the known amantadine safety profile. Treatment emergent AEs were common in all treatment groups, and most were mild to moderate in severity. The most commonly reported AEs were constipation, dizziness, dry mouth, hallucination, fall, confusional state, headache, nausea, and asthenia, each reported in two or more subjects in the active treatment groups. Sixteen subjects (19%) discontinued treatment. Two subjects withdrew from the placebo group due to non-study drug-related reasons. The remainder of the discontinuations from the study were attributed to adverse events (260 mg, three subjects, 340 mg three subjects and 420 mg, eight subjects).

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### **Additional EASED Study Results**

In addition to the results reported above, the EASED study also assessed the change from baseline in UDysRS Total Objective Score (III, IV); the dose response for the ADS-5102 treatment groups in UDysRS Total Score; MDS-UPDRS combined score (parts I, II and III); several parameters of dyskinesia as assessed by a PD diary including ON time without troublesome dyskinesia, ON time with troublesome dyskinesia, ON time with dyskinesia, OFF time; Clinician's Global Impression of Change in overall PD symptoms including dyskinesia; Fatigue Severity Scale (FSS); and Parkinson's Disease Questionnaire (PDQ-39), a quality of life measure.

- ADS-5102 significantly reduced the UDysRS Total Objective Score (III, IV), as compared to placebo at both the 340 mg and 420 mg dose levels ( $p=0.004$  and  $p=0.0004$ , respectively).
- A dose response was confirmed using the same statistical model used for the primary efficacy analysis of UDysRS Total Score for the treatment groups in mean change from baseline to week 8 ( $p<0.01$ ).
- Treatment with ADS-5102 did not result in clinical worsening of PD, as measured by the MDS-UPDRS combined score (parts I, II, and III).
- PD diary changes from baseline to week 8 relative to placebo were observed, and for the results for the 340 mg ADS-5102 dose group were:
  - Decrease in ON time with troublesome dyskinesia of 1.8 hours ( $p=0.055$ )
  - Decrease in ON time with dyskinesia of 2.1 hours ( $p=0.12$ )
  - Decrease in OFF time of 0.9 hours ( $p=0.199$ )
- The Clinician's Global Impression of Change demonstrated a statistically significant improvement for the 340 mg dose of ADS-5102, but not statistically significantly improved for either the 260 mg or 420 mg groups.
- No significant treatment group differences were noted in the Fatigue Severity Scale or the PDQ-39.

The results from the Phase 2/3 study were presented today by Dr. Pahwa during the "Parkinson's Disease: Clinical Trials" session in a poster entitled Randomized Trial of Extended Release Amantadine in Parkinson's Disease Patients with Levodopa-induced Dyskinesia (EASED Study) (abstract #443) at 12:30 pm AEST.

### **About the EASED™ Study**

The EASED study was a randomized, double-blind, placebo-controlled clinical trial that enrolled 83 Parkinson's disease subjects at 31 study sites in the US (NCT 01397422). The study's primary efficacy analysis compared ADS-5102 to placebo for reduction in LID over eight weeks as assessed by the Unified Dyskinesia Rating Scale (UDysRS). Secondary efficacy outcome measures included changes in a standardized PD diary, including: ON time without troublesome dyskinesia; overall PD clinical status as assessed by the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS); and fatigue measured using the Fatigue Severity Scale. The EASED trial also included an assessment of dose response for ADS-5102. The study enrolled male and female subjects aged 30 to 85 years who had Parkinson's disease and were experiencing troublesome LID. Study participants were randomized to receive 260 mg, 340 mg, or 420 mg doses of ADS-5102 or placebo once-nightly for eight weeks with a two-week safety follow-up. In order to participate in the study, subjects had to have a score of at least 2 on Part IV, item 4.2 (functional impact of dyskinesia) of the MDS-UPDRS at screening and Day 1, and be experiencing at least two 30 minute intervals of ON time with troublesome dyskinesia between the hours of 9 am-4 pm. Safety measures included adverse events and routine safety laboratory tests that were reviewed during the study by an independent data monitoring committee.

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### **About ADS-5102 (Nurelin™)**

ADS-5102 is a proprietary, investigational, extended-release formulation of amantadine HCl in development for the treatment of central nervous system (CNS) disorders, including LID in Parkinson's disease. Designed for once-nightly administration, ADS-5102's unique "chronotherapeutic" pharmacokinetic profile is characterized by a slow increase in initial amantadine plasma concentrations, high plasma concentrations during the daytime hours when LID can be troublesome and low plasma concentrations overnight. Adamas is investigating whether the low overnight amantadine plasma concentration may reduce the insomnia, sleep disturbances, and vivid dreams occasionally associated with amantadine. Due to its altered pharmacokinetic profile, ADS-5102 is being investigated in clinical studies at daily dose strengths 1.3 to 2.1 fold greater than the 100 mg twice-daily dose typically used with immediate-release amantadine.

### **About Levodopa-Induced Dyskinesia**

Levodopa (also known as L-dopa) remains the gold standard for the treatment of the debilitating motor symptoms of Parkinson's disease. An unfortunate side effect of prolonged treatment with levodopa is the occurrence of levodopa-induced dyskinesia (LID). LID is characterized by involuntary non-purposeful movements of the head and neck, arms, legs or trunk. With continued levodopa treatment, and as PD progresses, LID can become severely disabling and has been associated with a decrease in the quality of life for Parkinson's patients.<sup>1</sup> LID affects approximately 30% of patients taking levodopa<sup>2</sup>, and is particularly problematic among young-onset Parkinson's disease patients. There are currently no medications approved for the treatment of LID. Reducing LID and improving "ON time" without troublesome dyskinesia are among the greatest patient unmet medical needs in the treatment of advanced Parkinson's disease.<sup>3</sup>

### **About Adamas Pharmaceuticals, Inc.**

Adamas Pharmaceuticals is dedicated to improving the lives of those affected by central nervous system (CNS) disorders by optimizing the pharmacokinetic profiles of approved drugs to create novel treatments for use alone and as components of fixed-dose combination products. The Company is currently advancing a pipeline of aminoadamantane-based drug candidates for the treatment of Parkinson's disease, Alzheimer's disease, and other CNS disorders. The Phase 2/3 EASED study investigating ADS-5102 (amantadine HCl extended release) for the treatment of levodopa-induced dyskinesia in Parkinson's disease has recently been completed. MDX-8704 (memantine HCl ER/donepezil, US) and ADS-8704 (memantine HCl ER/donepezil, ex-US) are fixed-dose combination products in late-stage investigation for the treatment of dementia associated with Alzheimer's disease. In November 2012, Adamas entered into an agreement with Forest Laboratories, Inc. for the development and commercialization of MDX-8704 in the United States. Adamas plans to advance its product candidates through approval and commercialize products in the United States through a specialty CNS sales force. For more information about Adamas, please visit [www.adamaspharma.com](http://www.adamaspharma.com).

- 1) Encarnacion, E. V., Hauser, R. A., "Levodopa-induced dyskinesias in Parkinson's disease: etiology, impact on quality of life, and treatments." *Eur Neurol*, 2008. 60(2): 57-66
- 2) DATATOP: A Multicenter Controlled Clinical Trial in Early Parkinson's Disease. *Archives of Neurology*, 1989. 46(10): p. 1052-60
- 3) The Michael J. Fox Foundation ([www.michaeljfox.org](http://www.michaeljfox.org))

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