



## **Transition Therapeutics Announces Results of Data Analysis from ELND005 Phase 2/3 Clinical Study in Agitation and Aggression in Alzheimer's Disease Patients**

- **Primary efficacy endpoint not achieved in overall study**
- **ELND005 significantly (p value < .05) improved agitation and aggression in a sub-population of Alzheimer's disease patients with severe agitation and aggression**
- **In this population, ELND005 demonstrated numerical improvement in 20 of 21 behavioral symptoms measured as part of primary efficacy endpoint**
- **ELND005 demonstrated acceptable safety and tolerability profile**
- **Company intends to meet with regulators to seek guidance on ELND005 Phase 3 program for AD patients with severe agitation and aggression**

**TORONTO, ON, October 15, 2015 – Transition Therapeutics Inc.** (“Transition” or the “Company”) (NASDAQ: TTHI, TSX: TTH) announced that its subsidiary, Transition Therapeutics Ireland Limited (“TTIL”), has completed a thorough review of the data related to the Phase 2/3 study of ELND005 in Alzheimer's disease (“AD”) patients with moderate or severe agitation and aggression. The analysis identified a significant clinical benefit of ELND005 in AD patients with severe agitation and aggression, and will serve as the basis for patient selection in a Phase 3 clinical study. The review was performed in consultation with a group of key opinion leaders in the field of neuropsychiatry.

“This study was originally designed as a Phase 2 study, and viewed from that perspective, it has provided TTIL with important data to select a patient population, effectively screen for these patients in a clinical setting and identify a dosing regimen with acceptable safety and tolerability. The next step will be to share these findings with regulators to discuss an ELND005 Phase 3 program in AD patients with severe agitation and aggression,” said Dr. Tony Cruz, Chairman and Chief Executive Officer of Transition. “We believe that the overall data generated in this Phase 2/3 study support the clinical advancement of ELND005 into a Phase 3 clinical study and will aid us in the identification of a target AD patient population with severe agitation and aggression.”

Anton P. Porsteinsson, M.D., Professor of Psychiatry at the University of Rochester School of Medicine and Dentistry and one of the investigators on the Phase 2/3 study commented, “Agitation and Aggression are a major cause of distress and disease burden in Alzheimer's Disease. It is critically important to find safe and well tolerated treatments for these behavioral disruptions. Whereas non-pharmacological interventions should always be first line treatments, they are less likely to be adequate for those with more severe agitation and aggression, thus necessitating the use of medications. Currently, there are no FDA approved pharmacological treatments for this indication and the medications used by default lack consistent evidence of benefit but are well known to cause dangerous and troublesome side effects in these patients. Finding safe and effective treatment options for those who need relief the most is a major public health need.”



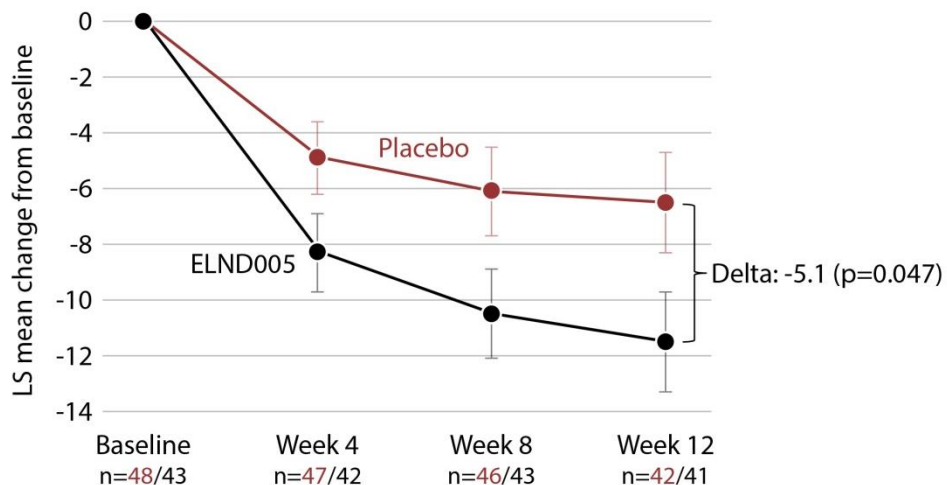
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### Efficacy Findings

As previously announced, the primary efficacy endpoint of the Phase 2/3 study (12 week change from baseline of the NPIC A+A scale) was not achieved in the overall study population of AD patients with moderate or severe agitation and aggression.

A post-hoc analysis demonstrated that ELND005 provided a clinically meaningful 5.1 point improvement relative to placebo on the NPIC A+A scale ( $p=0.047$ ) in a severe agitation and aggression population. An evaluation of progressively severe patient subsets with baseline NPIC A+A scores greater than 22 showed a consistent and greater improvement over the 5.1 points observed in the overall severe population. Multiple analyses performed on the severe agitation and aggression dataset determined that outliers, baseline demographics, AD severity, and concomitant medications did not appear to contribute to the improvement observed in the ELND005 treatment group.

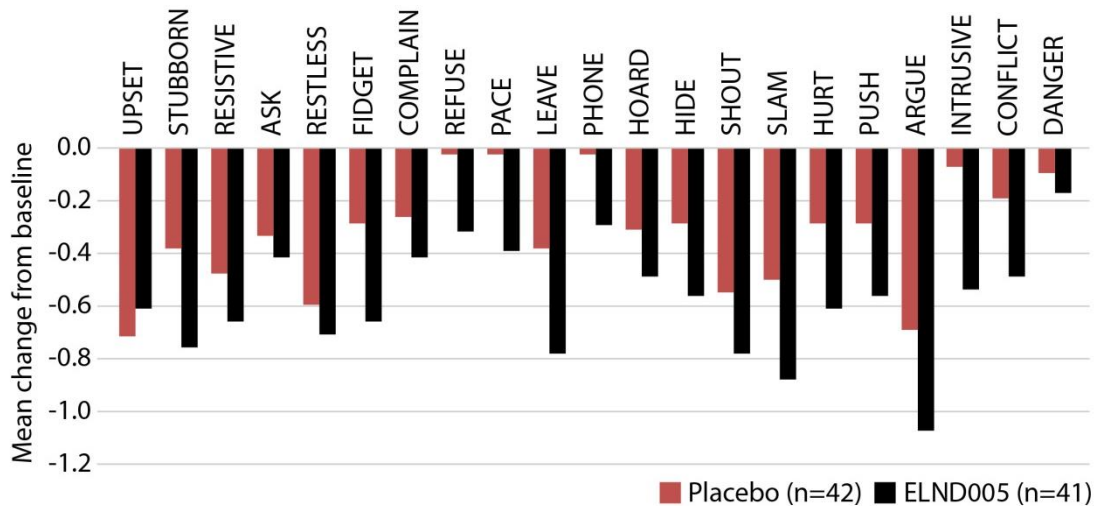
*NPI-C agitation and aggression combined score change from baseline for Alzheimer’s disease patients (baseline MMSE score  $\geq 8$ ) with severe agitation and aggression (baseline NPI-C agitation and aggression combined score  $\geq 22$ )*





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*NPI-C agitation and aggression 21 sub-item score change from baseline at week 12 for Placebo and ELND005 treated Alzheimer’s disease patients (baseline MMSE score  $\geq 8$ ) with severe agitation and aggression (baseline NPI-C agitation and aggression combined score  $\geq 22$ )*



The NPIC A+A scale is an aggregate score of severity related to 21 behavioral symptoms (13 agitation, 8 aggression behaviors). Analysis of the patient population with a baseline NPIC A+A < 22 showed that the major symptoms manifested were upset, stubborn, resistance, ask and shouting, and the remaining 16 behavioral symptoms were much less prevalent and had lower severity. As the baseline severity of NPIC A+A increased above 22 in AD patients, particularly above 26, many of the verbal and physical aggression items (hit, push, intrusive, argue, complain, danger, slam conflict), as well as the excessive motor activities (restless, fidget, pace), also increased in prevalence and severity. In this population of AD patients with severe agitation and aggression, 20 of the 21 symptoms measured by the NPIC A+A numerically favored ELND005 relative to placebo. These data demonstrated that ELND005 appeared to have a more pronounced effect on the verbal and physical aggression symptoms, as well as the excessive motor activities, that were more prevalent in AD patients with increasing agitation and aggression disease severity.

### Safety and Tolerability Results

ELND005 was shown to have an acceptable safety and tolerability profile in the study. The overall incidence of treatment emergent adverse events (“TEAEs”) in the ELND005 group and the placebo group were similar (56.6% vs 54.3%), as was the incidence of study drug-related TEAEs (13.1% vs 14.9%). Most TEAEs were mild or moderate in severity. The most common TEAEs in the ELND005 group that



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were  $\geq 5\%$  in incidence were: agitation (8.0% vs. 7.4% in placebo), diarrhea (8.0% vs. 2.9% in placebo), urinary tract infection (6.9% vs. 4.0% in placebo), and falls (6.3% vs. 5.1% in placebo). Overall, the incidence of serious adverse events was higher in the ELND005 group (9.7%) compared with the placebo group (2.9%). There were no deaths reported in the study. The overall patient discontinuation rate was low (10.3%); 4.6% of patients discontinued the study due to an adverse event in the ELND005 group versus 4.0% in the placebo group. No clinically meaningful changes in electrocardiographic findings were observed. ELND005 was not associated with cognitive impairment or sedation in this study.

### **Insights from the Study on Agitation and Aggression Subjects, Symptoms and Assessment Tools for Future Clinical Development**

The ELND005 Phase 2/3 study is one of the largest completed agitation and aggression in AD clinical studies, and is the first study to utilize the NPIC A+A endpoint in a placebo-controlled drug trial. The study enrolled 350 AD subjects who were considered to have moderate or severe agitation and aggression. This study dataset provided unique insight into placebo changes with various agitation and aggression patient populations, as well as the prevalence of each of the 21 behavioral symptoms assessed in NPIC A+A scale in patient populations with increasing severity.

TTIL believes that these data support the use of the NPIC A+A scale as a tool to provide a global assessment of agitation and aggression as defined by a broad set of behaviors associated with excessive motor activity, and physical and verbal aggression.

### **Plans for Further ELND005 Clinical Development**

Over the next few months, TTIL intends to submit a request to the FDA to discuss the data from the completed Phase 2/3 study. The objective of the meeting will be to seek guidance on the design of Phase 3 clinical studies for the ELND005 program in severe agitation and aggression in AD patients. Since AD patients with severe agitation and aggression are in the most need for treatment and most likely candidates for institutionalization, ELND005 could provide significant benefit and impact to this patient population and their caregivers, as well as reduce overall costs in managing this patient population. In parallel, TTIL has prepared sufficient drug supply for future phase 3 studies and begun to identify potential clinical sites for enrolment.

The Phase 2/3 study data will be presented at the Clinical Trials in Alzheimer's Disease meeting in Barcelona, Spain, which will take place November 5-7, 2015.<sup>(1)</sup>



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### **About the Phase 2/3 Study (Harmony AD Study; AG201 Study)**

The Phase 2/3 clinical study evaluated the efficacy, safety and tolerability of ELND005 over 12 weeks of treatment in patients with mild to severe AD, who were experiencing at least moderate levels of agitation/aggression. The randomized, double-blind, placebo-controlled study enrolled 350 AD patients (175 subjects per study arm). Subjects received either placebo or a fixed dosing regimen of ELND005. The fixed dosing regimen consisted of a loading dose of 1000 mg twice daily (“BID”) for 4 weeks, followed by a maintenance dose of 250 mg BID for a subsequent 8 weeks. The primary efficacy endpoint of the study was the change from baseline in the Neuropsychiatric Inventory – Clinician (“NPIC”) scale of agitation and aggression at 12 weeks.

### **About Transition**

Transition is a biopharmaceutical development company, advancing novel therapeutics for CNS and metabolic disease indications. The Company's wholly-owned subsidiary, Transition Therapeutics Ireland Limited is developing CNS drug candidate ELND005 for the treatment of Alzheimer's disease and Down syndrome. Transition’s lead metabolic drug candidate is TT401 (LY2944876) for the treatment of type 2 diabetes and accompanying obesity. The Company's shares are listed on the NASDAQ under the symbol "TTHI" and the Toronto Stock Exchange under the symbol "TTH". For additional information about the Company, please visit [www.transitiontherapeutics.com](http://www.transitiontherapeutics.com).

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<sup>(1)</sup> For more information on the 8th Clinical Trials in Alzheimer’s disease Conference, refer to <http://www.ctad-alzheimer.com/>



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