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Prana Announces Successful Phase 2 Results in Huntington Disease Trial

Key Points:

- *Primary endpoints of safety and tolerability met.*
- *Secondary endpoint: Statistically significant improvement in a measure of executive function (cognition) in research participants administered 250mg PBT2 daily (p=0.042).*
- *PBT2 250mg was also associated with a favourable signal in functional capacity.*
- *Preliminary evidence suggests PBT2 250mg reduced atrophy of brain tissue in areas affected in Huntington disease, seen in a pilot imaging sub-study.*
- *Company plans to advance PBT2 to a confirmatory Phase 3 clinical trial.*

MELBOURNE, Australia and NEW YORK, USA February 18, 2014: Prana Biotechnology (ASX:PBT / NASDAQ:PRAN) has today announced the results of its Reach2HD Phase 2 clinical trial investigating PBT2 as a treatment for Huntington disease. The double-blind, placebo-controlled study was conducted by the Huntington Study Group at research sites in the United States and Australia. The study enrolled 109 individuals with Huntington disease who were randomly assigned to receive daily doses of either PBT2 250mg, PBT2 100mg, or placebo for 26 weeks.

Primary Objective: Safety and Tolerability

The primary endpoint of the study was met. In this study, PBT2 was safe and well tolerated. 95% (104 of 109) of participants completed the study on their assigned dose.

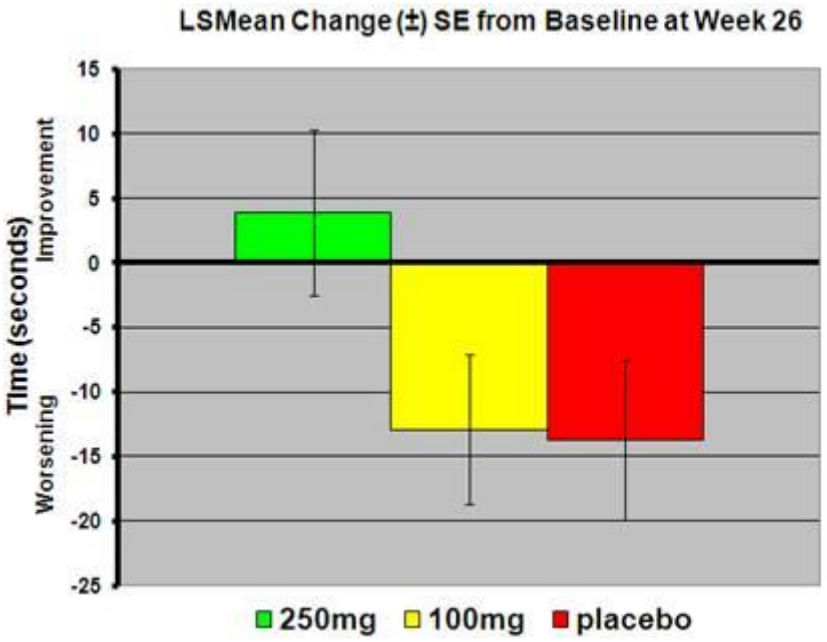
An independent Data Safety Monitoring Board met on five occasions over the course of the trial and on each occasion recommended that the trial continue as per the original protocol.

There were no substantial differences in adverse events across the two PBT2 dose groups and the placebo group. Only one of the ten reported serious adverse events was deemed by the clinical site investigator to be related to drug treatment. This occurred during the 4-week follow-up period (i.e. not on study drug) after completing the six month treatment.

Secondary Objective: Efficacy

The effects of PBT2 were tested on cognition, motor performance, behaviour and functional capacity, of which cognition was pre-specified as the main efficacy outcome.

There was a statistically significant improvement in performance on the Trail Making Test Part B (as illustrated in the graph), in the PBT2 250mg group compared to placebo at both 12 ($p<0.001$) and 26 weeks ($p=0.042$).



Trail Making Test Part B is a measure of executive function (e.g., ability to plan activities), which is impaired early in the course of Huntington disease and is also affected in Alzheimer's disease.

Given the evidence from an earlier trial that showed that PBT2 improved executive function in Alzheimer's disease patients, the Reach2HD trial included a plan to assess the effects of PBT2 on an Executive Function Composite z-score that included the Trail Making Test Part B. There was a statistically significant improvement in this z-score ($p=0.038$) in a pre-specified analysis of Reach2HD participants with early stage Huntington disease, as measured by their Total Functioning Capacity score. Across all participants, which comprised both early and mid-stage patients, there was a trend to improvement ($p=0.069$).

Dr Rudy Tanzi, Professor of Neurology at Harvard Medical School and Prana's Chief Scientific Advisor, commented that "the observation of significant improvement in executive function with PBT2 in this clinical trial for Huntington disease and the previously reported Alzheimer's trial, suggests a common mechanism for neurodegeneration in these diseases based on metal interactions. In my opinion, these findings significantly elevate the potential for PBT2 as an effective therapy for both Huntington disease and Alzheimer's disease."

The improvement in executive function was accompanied by a small but favourable signal in a key measure of functional capacity. No significant improvements were seen on other secondary efficacy measures in the study.

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Dr Ira Shoulson, Professor of Neurology at Georgetown University and Chair of the Huntington Study Group, who was not involved in the trial and acts as an advisor to Prana, added: "In the Reach2HD trial, the improvement in executive function performance was also accompanied by a favourable signal of a slowing of functional decline, as measured by the Total Functional Capacity score. This is the first time we have observed dose-related slowing in functional decline over a six month period of treatment – which taken together with the safety reassurance – will provide genuine optimism for the Huntington disease community to support a larger confirmatory trial of PBT2 in Huntington disease."

Exploratory Finding

As Huntington disease and other neurodegenerative disorders progress, there is a gradual loss of brain tissue or atrophy. In Reach2HD, brain imaging using magnetic resonance imaging (MRI) was performed in a small subset of patients (n=6) to map anatomical changes in brain structure. In the combined PBT2 groups (n=4) a reduction in atrophy of brain tissue in regions of the brain known to be affected by Huntington disease was observed compared to the placebo group.

Dr Diana Rosas, Associate Professor of Neurology at Harvard Medical School and the study's co-Principal Investigator who conducted the imaging sub-study commented: "Despite the very small number of patients in the sub-study, the data are suggestive of a beneficial effect of PBT2 in regions of the brain that are known to be vulnerable to Huntington disease."

Dr Ray Dorsey, Professor of Neurology at the University of Rochester and the Principal Investigator on the trial added: "We are very pleased that the results of the Reach2HD study have shown that PBT2 is well tolerated and generally safe over six months in individuals with early to mid-stage Huntington disease."

"In addition, the results indicated a significant benefit on cognition that is consistent with the previous trial in Alzheimer's disease and is accompanied by an encouraging finding in functional capacity. We are very thankful for the involvement of the research participants and investigators in this study and look forward to future trials of this promising therapy for one of the cardinal features of Huntington disease."

Prana plans to advance PBT2 into a confirmatory Phase 3 clinical trial that could allow PBT2 to be approved for the treatment of Huntington disease.

A clinical appendix accompanies this announcement.

For further information please visit the Company's web site at www.pranabio.com.
For patient enquiries please contact huntingtons@pranabio.com or call 1300 13 90 33.

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Contacts:

Global Investor Relations Lead

Rebecca Wilson

T: +61 3 8866 1216

E: rwilson@buchanwe.com.au

Investor Relations (USA)

Josh Drumm

T: +1 (347) 327-2863

E: jdrumm@tiberend.com

Media Relations (Australia)

Ben Oliver

T: +61 3 8866 1233

E: boliver@buchanwe.com.au

Media Relations (US)

Jason Rando

T: +1 (347) 327-2863

E: jrando@tiberend.com

Clinical Appendix

PBT2-203 "Reach2HD" Study Design and Results

Number of patients	109 patients randomized; 104 patients completed study.
Key patient selection criteria	▪ Men and women with clinical features of Huntington disease (HD) and a CAG repeat number ≥ 36 ▪ Total Functional Capacity (TFC) 6-13, inclusive. 'Early-stage' HD defined as TFC of 11-13 and 'mid-stage HD' defined as TFC 6-10 ▪ ≥ 25 years of age ▪ Montreal Cognitive Assessment (MoCA) score ≥ 12 ▪ If taking tetrabenazine, on a stable dose for at least 3 months
Rationale	PBT2 is a moderate affinity metal ligand that inhibits metal mediated toxic gain of function of disease proteins such as mutant Huntingtin. In addition, the ionophore capability of PBT2 facilitates the redistribution of copper and zinc to their correct brain tissue compartments. Collectively, PBT2 has been shown to reduce toxic protein accumulation, support synaptic plasticity and promote neuronal growth and function in animal models. Based on these mechanisms of action and the reported success of PBT2 in a Phase 2a study in Alzheimer's disease, on both measures of cognition (executive function) and biomarkers, the Reach2HD trial investigated a range of efficacy outcomes, in particular, cognition (executive function).
Blinding	Double-blind
Placebo controlled	Yes
Route of administration	Oral (capsules)

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Study design	Randomized, double-blind, placebo-controlled, parallel three-group study to assess the safety and tolerability, and efficacy of PBT2 in patients with early- to mid-stage HD. An independent Data Safety Monitoring Board (DSMB) provided patient safety monitoring at regular intervals throughout the study.
Dose groups	0mg (placebo capsules of identical appearance), 100mg and 250mg
Duration	34 weeks: Four week Screening period, 6 month (26 week) treatment period and Follow-up 4 weeks post treatment.
Primary Objective: Safety and Tolerability	**Endpoints:** Adverse events, vital signs, clinical laboratory parameters, 12-lead ECG; physical examination; neurological examination; ophthalmological examination; Visual Evoked Response; Neuropsychiatric Inventory; Columbia Suicide Severity Rating Scale.
Secondary Objectives: Efficacy	**Endpoints:** • Primary/Main Efficacy Endpoint: Cognition Category Fluency Test, Trail Making Test Parts A and B, Map Search, Symbol Digit Modalities Test, Stroop Word Reading Test, Speeded Tapping Task, MoCA. **Main Composite Cognition z-score**: comprised of the mean of individual z-scores from the following tests: Category Fluency, Trail Making Part B, Map Search, Symbol Digit Modalities, Stroop Word Reading. **Exploratory Composite Cognition z-score**: as per Composite Cognition z-score with the addition of the Speeded Tapping component. **Executive Function Composite z-score**: comprised of the mean of z-scores from Category Fluency Test and Trail Making Test Part B. • Secondary Efficacy Endpoints: ○ Motor Function: United Huntington Disease Rating Scale (UHDRS) motor component ○ Behaviour: UHDRS Behavioural component ○ Functional Abilities: TFC and UHDRS Independence Scale ○ Global Assessments: Clinician's Global Impression Severity Scale and HD Patient Reported Outcomes ○ Biomarkers: *Urine*: 8 hydroxy 2'deoxyguanosine; creatinine *Blood*: soluble total Huntingtin protein (Htt) and mutant Htt
Exploratory Sub Study	Brain Volumes and Function: MRI

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Trial sites	20 clinical trial sites across USA (15) and Australia (5)
Efficacy Analysis populations	All efficacy analyses were conducted on the Intention-to-Treat (ITT) population. Efficacy analysis on the Per Protocol (PP) population was to be performed if the PP population comprised more than 95% or less than 50% of the ITT population.

Patient Demographics

	Placebo (N=35)	PBT2 100mg (N=38)	PBT2 250mg (N=36)	All (N=109)
Age (years) Mean: Range:	 51.2 30-66	 54.1 31-79	 50.3 28-70	 51.9 28–79
Male (%)	45.7	50.0	52.8	49.5
Mean CAG repeat no:	44.1	43.2	44.4	43.9
Mean MoCA score	22.5	23.5	22.9	23.0
Mean TFC score:	9.0	9.3	9.3	9.2

All baseline characteristics similar across dose groups

Primary Objective: Safety and Tolerability

PBT2, in this study of early- to mid-stage HD patients, was safe and well tolerated, with no significant findings or trends in any of the safety parameters measured.

Tolerability: PBT2 was well tolerated during this study as demonstrated by no difference in the Kaplan-Meier estimates of time-to-withdrawal between the 100mg dose and placebo groups (p=0.297) or between the PBT2 250mg and placebo groups (p=0.173). Of the 109 patients randomized, 104 patients completed the study (95.4% retention rate). Of the five participants who withdrew from the study, one participant in the placebo group and 3 participants in the 250mg group withdrew due to adverse events. One participant did not return for their follow up visit.

Safety: Of the 10 SAEs reported, one was in the placebo group, 3 in the 100mg PBT2 group and 6 in the 250mg group. With the exception of one SAE in the 250mg group, all SAEs were deemed to be not related to Study Drug by the site investigators. The participant who had an SAE deemed related to Study Drug reported a worsening of their HD symptoms during the 4 week follow up period (i.e. no Study Drug administered), after completing the 6 month treatment.

The safety and tolerability profile of either dose of PBT2 was similar to placebo. There were no significant differences in the numbers of participants reporting any particular AE between PBT2 and placebo groups. The most common AE was diarrhea, with 16 participants reporting a total of 20 events. The frequency of this AE was similar across PBT2 and placebo groups.

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Secondary Objectives: Efficacy Main/Primary Efficacy Endpoint: Cognition	**Main Composite Cognition z-score and Exploratory Composite Cognition z-score.** No statistically significant changes. **Executive Function Composite z-score:** PBT2 250mg showed a significant improvement at 12 weeks (p=0.005) and trend at 26 weeks (p=0.069) compared with placebo. On a pre-specified subgroup analysis of early-stage HD (TFC 11-13), the change in Executive Function Composite z-score from baseline at 26 weeks was significantly improved in participants receiving 250mg PBT2 compared with placebo (p=0.038). Of the two tests within the Executive Function Composite, there was a statistically significant improvement in the Trail Making Test Part B after 12 weeks of treatment compared with placebo (p<0.001) and at 26 weeks (p=0.042). The effect of PBT2 at 26 weeks was dose-dependent (p=0.035). There were no statistically significant differences between either dose of PBT2 and placebo in other individual tests of cognition over 26 weeks.
Secondary Objective: Efficacy **Motor, Behaviour, Function, Global Endpoints**	No significant changes were seen in motor, functional, behavioural or global assessments in either PBT2 treatment group compared to placebo over the 26 week treatment period. A small but positive signal in TFC was observed on the 13 point scale across the PBT2 groups relative to placebo (mean changes from baseline: 250mg PBT2 = -0.3; 100mg PBT2 = -0.5; placebo= -0.6.
Secondary Objective: Efficacy–Biomarker Endpoint	There were no significant changes in the urine or blood biomarkers assessed at week 26 with PBT2 treatment compared to placebo.
Secondary Objective: **MRI brain volumes and function**	Changes in cortical thickness (mm) were mapped at week 26 for the combined treatment group (n=2 250mg and n=2 100mg) compared to placebo (n=2). The rate of thinning in the placebo group was faster than in the treated groups; however the effects did not reach statistical significance.

About Prana Biotechnology Limited

Prana Biotechnology was established to commercialise research into Alzheimer's disease and other major age-related neurodegenerative disorders. The Company was incorporated in 1997 and listed on the Australian Stock Exchange in March 2000 and listed on NASDAQ in September 2002. Researchers at prominent international institutions including The University of Melbourne, The Mental Health Research Institute (Melbourne) and Massachusetts General Hospital, a teaching hospital of Harvard Medical School, contributed to the discovery of Prana's technology.

Forward Looking Statements

This press release contains "forward-looking statements" within the meaning of section 27A of the Securities Act of 1933 and section 21E of the Securities Exchange Act of 1934. The Company has tried to identify such forward-looking statements by use of such words as "expects," "intends," "hopes," "anticipates," "believes," "could," "may," "evidences" and "estimates," and other similar expressions, but these words are not the exclusive means of identifying such statements. Such statements include, but are not limited to any statements

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relating to the Company's drug development program, including, but not limited to the initiation, progress and outcomes of clinical trials of the Company's drug development program, including, but not limited to, PBT2, and any other statements that are not historical facts. Such statements involve risks and uncertainties, including, but not limited to, those risks and uncertainties relating to the difficulties or delays in financing, development, testing, regulatory approval, production and marketing of the Company's drug components, including, but not limited to, PBT2, the ability of the Company to procure additional future sources of financing, unexpected adverse side effects or inadequate therapeutic efficacy of the Company's drug compounds, including, but not limited to, PBT2, that could slow or prevent products coming to market, the uncertainty of patent protection for the Company's intellectual property or trade secrets, including, but not limited to, the intellectual property relating to PBT2, and other risks detailed from time to time in the filings the Company makes with Securities and Exchange Commission including its annual reports on Form 20-F and its reports on Form 6-K. Such statements are based on management's current expectations, but actual results may differ materially due to various factions including those risks and uncertainties mentioned or referred to in this press release. Accordingly, you should not rely on those forward-looking statements as a prediction of actual future results.