Reach2HD Phase 2 Clinical Trial
Top Line Results
Investor Conference Call 19th February 2014
Safe Harbour

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Introduction

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Mr Geoffrey Kempler, Chairman and Chief Executive Officer
Dr Ray Dorsey, Professor of Neurology, University of Rochester; Principal Investigator
Outline

- Huntington disease and cognition
- Reach2HD study
- Results
Huntington disease (HD) is a rare, inherited neurodegenerative disorder

- **Who**
  - Approximately 30,000 Americans and over 80,000 individuals globally
  - Affects both sexes equally

- **What**
  - Inherited disorder that causes involuntary movements (chorea), behavior changes, and cognition decline
  - Only one FDA-approved treatment for chorea (tetrabenazine) is available

- **When**
  - Disease onset is typically between 30 to 50 years of age
  - Rarer, childhood onset forms occur

- **Where**
  - Higher prevalence in Europe and North America
  - Lower prevalence in Japan and Africa

- **Why**
  - Disease is caused by a trinucleotide (CAG) expansion in *huntingtin* gene
  - The huntingtin protein is expressed in higher concentrations in the brain; its exact function remains unclear, but it is involved in regulation of gene expression

Preclinical and clinical data supported the study of PBT2 in HD

Study rationale

Mechanism

• In Huntington disease, copper concentrations are elevated in the brain (basal ganglia) where they could promote aggregation of mutant huntingtin
• PBT2 belongs to a class of metal-protein attenuating compounds that reduce metal-induced toxicity of mutant huntingtin

Preclinical study

• In the R6/2 mouse model of Huntington disease, PBT2 improved motor performance, increased body and brain weight, and increased lifespan by 26%
• PBT2 also delayed the onset of paralysis in C. elegans worm model of HD

Clinical study

• In a 12-week, phase 2, randomized controlled study in 78 individuals with Alzheimer disease, PBT2 was well tolerated and safe
• Individuals receiving PBT2 250 mg performed significantly better on two executive function tests – Category Fluency and Trail Making Test Part B – and on the Executive Factor composite z-score

Trail Making Test Part B is a test of executive function, which is impaired in HD

Executive function and Trail Making Test Part B

Cognitive decline is universal in Huntington disease
- Cognitive decline begins before diagnosis and is progressive
- Cognitive decline predicts impairments in everyday function

Executive cognitive decline in HD
- Refers to cognitive control processes, such as planning, problem solving, flexibility of behaviour when situational demands change.

Trail Making Test Part B
- Timed executive function measure (flexibility), impaired in HD
- Patients ‘Connect the dots’ alternating numbers and letters (1→A→2→B→3…)
- Slowing indicates impaired flexibility

The Reach2HD: Phase 2, randomized, double-blind placebo-controlled study

Study design

- **109 individuals** with early to mid-stage Huntington disease
- **Treatment duration:** 26 weeks

- 36 randomized to PBT2 250mg once daily
- 38 randomized to PBT2 100mg once daily
- 35 randomized to placebo

**Study Objectives**

Primary: To evaluate the tolerability and safety of PBT2

Secondary: To evaluate the effect of PBT2 on the following:
- Primary efficacy variables were cognition
- Secondary efficacy variables were motor, behavior, function, and global outcomes
- Additional biomarker and imaging outcomes
Baseline characteristics of participants were well balanced across groups

Baseline characteristics of the Reach2HD study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo  (N=35)</th>
<th>PBT2 100mg (N=38)</th>
<th>PBT2 250mg (N=36)</th>
<th>All (N=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age in years (range)</strong></td>
<td>51.2 (30-66)</td>
<td>54.1 (31-79)</td>
<td>50.3 (28-70)</td>
<td>51.9 (28–79)</td>
</tr>
<tr>
<td>Percent men</td>
<td>45.7%</td>
<td>50.0%</td>
<td>52.8%</td>
<td>49.5%</td>
</tr>
<tr>
<td><strong>Mean CAG repeat length</strong> (of the expanded allele)</td>
<td>44.1</td>
<td>43.2</td>
<td>44.4</td>
<td>43.9</td>
</tr>
<tr>
<td><strong>Mean score on Montreal Cognitive Assessment</strong></td>
<td>22.5</td>
<td>23.5</td>
<td>22.9</td>
<td>23.0</td>
</tr>
<tr>
<td>(range is 0-30)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Mean Total Functional Capacity</strong> (range is 0-13)</td>
<td>9.0</td>
<td>9.3</td>
<td>9.3</td>
<td>9.2</td>
</tr>
</tbody>
</table>
Tolerability

- **PBT2 250mg daily**
  - 32 (88.9%) of the 36 individuals randomized to PBT2 250mg completed the study

- **PBT2 100mg daily**
  - 38 (100%) of the 38 individuals randomized to PBT2 100mg completed the study

- **Placebo**
  - 34 (97.1%) of the 35 individuals randomized to placebo completed the study

**Overall, 95% of participants completed the 26-week study**
Safety of PBT2

- Ten serious adverse events occurred during the study
- Nine were in the PBT2 groups (6 in PBT2 250mg and 3 in PBT2 100 mg)
- Only one (on PBT2 250mg) was deemed related to study drug by the site investigator

- Frequency of adverse events did not differ significantly across the three study groups
- Most common adverse event was diarrhea, and the rate was similar across groups
PBT2 250mg significantly improved performance on Trail Making Test Part B

Change in Trail Making Test Part B

Improvement in Trail Making Test Part B was significant at 12 weeks (p<0.001) and 26 weeks (p=0.042)
Trend toward improvement on the executive function composite z-score

Other cognitive outcomes

Among all participants, there was a trend toward improvement in the composite executive function for those randomized to PBT2 250mg (p=0.069) that was significant among those with mild Huntington disease (p=0.038)

No other significant differences were observed at 26 weeks on the other cognitive measures
Cognitive improvement was also accompanied by a trend toward improvement on functional capacity

Other efficacy outcomes

- Total Functional Capacity is a key measure of function in occupation, finances, domestic chores, activities of daily living, and care level that is used in almost all clinical studies in Huntington disease
  - Score ranges from 0 (most impaired) to 13 (normal)
  - In Reach2HD, individuals randomized to PBT2 had a favorable signal on slowing functional decline over 6 months

No other statistically significant differences were observed on other efficacy measures

Small, exploratory neuroimaging study suggested decreased atrophy among those exposed to PBT2

Exploratory outcome

- In a small (n=6), pilot sub-study, individuals randomized to PBT2 (n=4) had reduced brain atrophy compared to those randomized to placebo

Context

- Brain atrophy is known to begin in the prodromal phase of Huntington disease and progresses along with the disease
- Brain atrophy and cortical thinning are associated with cognitive decline in Huntington disease
- A recent Huntington disease clinical trial suggested that pharmacological treatment could reduce cortical thinning relative to placebo

PBT2 is a promising therapy for a cardinal feature of HD

Summary

Tolerability and safety

• PBT2 was well tolerated and generally safe over 26 weeks in individuals with early to mid-stage Huntington disease

Efficacy

• PBT2 250mg daily significantly improved cognition on a key measure of executive function
  • Trails Making Test B significantly improved from Baseline to Week 26 in PBT2 250 mg treatment group
  • Improvement in executive function has never been previously demonstrated in a Huntington disease clinical trial
  • Results observed are consistent with that seen in the prior phase 2 trial of PBT2 in Alzheimer disease
• Cognitive improvement was accompanied by a favorable signal in functional capacity

Imaging

• Small sub-study suggested reduced brain atrophy among those exposed to PBT2

These promising results require confirmation in a larger phase 3 clinical trial
Dr Ira Shoulson, Professor of Neurology, Georgetown University; Chair, Huntington Study Group
Q&A

Reach2HD
A Huntington Disease Research Trial