Assessment of cognitive executive function using CANTAB in a Phase 1/2 study of PTC923 in primary tetrahydrobiopterin-deficient subjects with hyperphenylalaninemia

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Introduction

• Primary tetrahydrobiopterin (BH₄) deficiencies (PBD) are caused by inherited defects in BH₄ biosynthesis or recycling.
• BH₄ is an essential cofactor for phenylalanine (Phe), tyrosine, and tryptophan hydroxylases.
• Phenotypically, PBD subjects present with hyperphenylalaninemia (HPA) and deficiency of the neurotransmitter precursors, L-dopa and 5-hydroxytryptophan, and thus may be detected through newborn screening programs, which measure Phe in order to detect phenylalanine hydroxylase deficiency (the exception being sepiapterin reductase deficient patients who have normal blood Phe concentrations).
• Untreated PBD patients present with severe neurological symptoms.
• Phe accumulation can cause impairments in psychomotor processing and executive functions.
• The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a highly sensitive set of cognitive assessments to detect impairments in executive cognitive functioning.
• CANTAB may offer a novel assessment tool for subjects with PBD who present with neurological symptoms early in life.

Objectives

• Explore neurocognition in subjects with PBD by assessing the change from baseline (pre-treatment) in CANTAB tests following treatment with PTC923 for 7 days. CANTAB assessments included:
  • Reaction Time (RTI)
  • Spatial Span (SPP)
  • Spatial Working Memory (SWM)
  • Rapid Visual Information Processing (RVI)
• Gain experience using CANTAB in this disease.

Subjects and Methods

• This was a Phase 1/2, multicenter, randomized, open-label, intra-patient dose escalation study designed to evaluate the safety, pharmacokinetics, and preliminary evidence of efficacy of PTC923 in male and female subjects with PBD (Figure 1).
• The study enrolled subjects 12 months and older with confirmed defects in de novo BH₄ biosynthesis due to 6-pyruvoyl-tetrahydropterin synthase (PTPS) or recessive guanosine triphosphate cyclohydrolase-1 (GTPCH) genes, abnormal enzyme activity of the PTPS or GTPCH enzymes, or a cerebrospinal fluid (CSF) biochemical profile indicative of PTPS or GTPCH deficiencies.
• Following a screening period of up to 14 days, subjects washed out of sapropterin therapy for 4 days and began treatment with PTC923 administered twice daily for a total of 14 days (ie, two 7-day treatment periods separated by a 2- to 4-day washout).
• Each subject received two dose levels of PTC923; doses tested were 2.5, 5, 10, and 20 mg/kg/day.
• Subjects maintained neurotransmitter supplementation of levodopa/carbidopa and 5-hydroxytryptophan throughout the study.
• CANTAB testing was administered at the Screening visit, Day 1 (pre-dose), and Day 7 of each treatment period.
CANTAB Assessments

- **Reaction Time**
  - The RTI assessment requires subjects to hold down a home button until another button lights upon the tablet screen.
  - At this point subjects were instructed to release the home button and touch the light button with the same hand and then return to hold the home button as quickly as possible.
  - This was repeated several times.
  - The mean and median measurements of reaction time, movement time, numbers of errors (ie, inaccurate, no response, premature) were assessed.

- **Spatial Span**
  - The SSP assesses working memory and requires subjects work through a growing sequence of flashing buttons.
  - The mean and median measurements of forward span of correct sequence selection (ie, length of sequence, number of attempts, span reached, errors) were assessed.

- **Spatial Working Memory**
  - The SWM assesses working memory and requires subjects match tokens in boxes.
  - The measurements of strategy and errors (ie, between errors, double errors, total errors) for increasing numbers of boxes (eg, from 4 to 6 to 8 boxes) were assessed.

- **Rapid Visual Information**
  - The RVI assesses executive function and requires subjects recognize a set sequence of numbers (ie, 3, 5, 7) in an otherwise random set of numbers flashing on the tablet screen.
  - Subjects are instructed to press a button every time they see the correct sequence of numbers.
  - The measurements of accuracy, response latency (both median and standard deviations), probabilities of false selection, hits, and total misses were assessed.

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Figure 1. Study Schema

- **Treatment Period**
  - Period 1: 2.5 mg/kg/day X7 days
  - Period 2: 10 mg/kg/day X7 days
  - Period 1: 5 mg/kg/day X7 days
  - Period 2: 20 mg/kg/day X7 days

- **Washout**
  - End of study
  - Phone Follow-up Visits

- **Days**
  - Day-14 to Day-4
  - Day-3 to Day-1
  - Day 1
  - 3 (±1) days
  - ≤48 hrs after last dose
  - 7 to 10 days and 30 (±3) days after last dose
### Results – Demographics and Baseline Characteristics

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<th>Cohort 1 (N=4)</th>
<th>Cohort 2 (N=1)</th>
<th>Overall (N=5)</th>
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<td>7.0, 19.0</td>
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<td>Blood Phenylalanine Level (µmol/L)</td>
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<tr>
<td>Mean (SD)</td>
<td>884.21 (975.5)</td>
<td>1619.6</td>
<td>1031.3 906.6</td>
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</tbody>
</table>

Cohort 1: PTC923 2.5 mg/kg/day in Period 1 and 10 mg/kg/day in Period 2  
Cohort 2: PTC923 5 mg/kg/day in Period 1 and 20 mg/kg/day in Period 2  

**Abbreviations:** BMI, body mass index; CANTAB, Cambridge Neuropsychological Test Automated Battery; Phe, phenylalanine

- A total of 8 subjects were randomized, including 4 subjects in Cohort 1 (PTC923 2.5 mg/kg/day in Period 1 and 10 mg/kg/day in Period 2) and 4 subjects in Cohort 2 (PTC923 5 mg/kg/day in Period 1 and 20 mg/kg/day in Period 2).  
- All patients completed the study treatment.  
- All subjects completed the study.  
- Of the 8 subjects only 5 participated in CANTAB assessments (4 subjects from Cohort 1 and 1 subject from Cohort 2) due in part to the age of the subject (CANTAB assessments were only administered to subject ≥6 years) and/or physically not being able to complete the assessments secondary to the subject’s underlying disease (Table 1).  
- Blood Phe concentrations for all subjects and at all dose levels normalized by Day 2 and were maintained normal throughout the 7-day treatment period.

### Results: Reaction Time

**Figure 2: CANTAB RTI (SD) Five-Choice Movement Time Test Scores by Treatment Dose and Day**

CANTAB RTI (SD) Five-Choice Movement Time test scores are graphically represented by treatment dose and time point in Figure 2. The scale is milliseconds.  

**Abbreviations:** RTI, Reaction Time; SD, standard deviation; CANTAB, Cambridge Neuropsychological Test Automated Battery
Results: Spatial Span

Figure 3: CANTAB SSP Forward Span Reached Test Scores by Treatment Dose and Day

CANTAB SSP Forward Span Reached test scores are graphically represented by treatment dose and time point in Figure 3. Higher scores represent improved forward span reach.

Abbreviations: SSP, Spatial Span; CANTAB, Cambridge Neuropsychological Test Automated Battery

Spatial Working Memory

Figure 4: CANTAB SWM Between Errors 8 Boxes Test Scores by Treatment Dose and Day

CANTAB SWM between errors 8 boxes test scores are graphically represented by treatment dose and time point in Figure 4. Decrease in SWM between errors indicated improvement.

Abbreviations: SWM, Spatial Working Memory; CANTAB, Cambridge Neuropsychological Test Automated Battery
Rapid Visual Information Processing

Figure 5: CANTAB RVP Median Response Latency Test Scores by Treatment Dose and Day

CANTAB RVP median response latency test scores are graphically represented by treatment dose and time point in Figure 5. The scale is milliseconds.

Abbreviations: RVP, Rapid Visual Information Processing; CANTAB, Cambridge Neuropsychological Test Automated Battery

Conclusions

• Due to the small number of subjects, subject variability, and the short duration of treatment, assessment of executive function, memory, and cognition as measured by the CANTAB battery was limited.

• Individual improvements were demonstrated indicating potential trends towards improvement in working memory and pattern recognition, for example, but longer studies may be needed to better understand any potential effects of PTC923 on these domains (Figures 2 through 5).

• Of note, these exploratory assessments were included in the study to gain experience using these tools in this disease.

Acknowledgements

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Disclosures

• NL, TO, MM, CW perform clinical trials for PTC Therapeutics, Inc.

• NL, NB, and TO are consultants for PTC Therapeutics, Inc.

• NS is an employee and shareholder of PTC Therapeutics, Inc.