Update on CTD’s Clinical Program

European Task Force on Brain and Neurodegenerative Lysosomal Storage Diseases (LSDs)/Brains for Brain Symposium

Sharon H. Hrynkow, PhD
Frankfurt, Germany --- January 26, 2019
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For CTD: Sharon H Hrynkow, PhD, CTD Holdings Inc. and Bryan Hurst, MPhil, Boyd Consultants.

*Special thanks to Professor David Begley for critical review.*
CTD Holdings, Inc. (OTCQB “CTDH”), a clinical-stage biotechnology company, is developing cyclodextrin-based products for the treatment of diseases with unmet medical need.

**Trappsol® Cyclo™**

- Lead drug candidate, Trappsol® Cyclo™, being developed as treatment for orphan indication, Niemann-Pick Disease Type C (“NPC”), an orphan disease.
  - Rare Pediatric Disease Designation
  - Fast Track Designation
  - Orphan Disease Designation (US and EU)
- Founded in 1990
- Corporate headquarters in Alachua, FL
Multiple Manifestations of NPC

No two patients suffer in the same manner

**Systemic**
- Liver Disease and Failure
- Hepatomegaly
- Splenomegaly
- Respiratory Dysfunction

**Central Nervous System (CNS)**
- Impaired Motor Functions
- Behavioral Disturbance
- Loss of Cognition
- Vertical Supra-nuclear Gaze Palsy (VSGP)

**Impaired Quality of Life & Death**
CTD’s approach to its NPC clinical program is to focus on the systemic nature of the disease, inclusive of CNS, lung, liver, and spleen.

Our approach is therefore based on **Intravenous** administration of study drug, Trappsol ® Cyclo™.

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- low-risk compared to CNS-directed approaches

- potential for in-home infusions in extension protocols

- compassionate program characterized by safety, tolerability, physician reports of symptom improvement, including visceral and neurologic, behavioral benefits
Trappsol® Cyclo™

- HPβCD is a donut-shaped molecule comprised of seven glucopyranose units (see 2-CH(CH3)-O]n-H.
- Hydrophilic exterior, hydrophobic interior forms complexes with certain molecules.
- Exact mechanism by which Trappsol® Cyclo™ releases cholesterol from cells and how it causes improvements in NPC symptoms is not known.
- HPβCD is excipient in a number of products including Sporanox (broad-spectrum anti-fungal), eye drops, and mouthwash.
- Based on animal studies and compassionate use data with Trappsol® Cyclo™ since 2009, the CTD clinical program was launched with Trappsol® Cyclo™ as an active pharmaceutical drug ingredient.
- CTD has a Drug Master File Type II on file with FDA. CTD uses a proprietary manufacturing process.

β-Cyclodextrin, R=H
HPβCD, R=OCH₂CH(CH₃)OH or H

This schematic represents interaction of cylinder shaped cyclodextrins and cholesterol in a 1:1 or 1:2 ratio

Figure is courtesy of David Begley, Kings College
Trappsol® Cyclo™ Phase I Study to Evaluate Safety and Impact On Biomarkers of NPC Disease

Randomization 6:6 Between Dose Groups

Trappsol® Cyclo™: Bi-weekly 8 hour intravenous treatment for a period of 14 weeks

RANDOMIZE (N=12)

<table>
<thead>
<tr>
<th>Dose Group 1</th>
<th>Dose Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500 mg/kg</td>
<td>2500 mg/kg</td>
</tr>
</tbody>
</table>

- **Primary Endpoint**
  - Plasma levels of Trappsol® Cyclo™

- **Secondary Endpoint**
  - Markers of Cholesterol metabolism/synthesis
  - CSF Levels of Trappsol® Cyclo™
  - hepatic and splenic morphology
  - global impression of disease

- **Exploratory Endpoint**
  - CSF biomarkers of NPC Disease

- **Niemann-Pick Disease Type C**
  - Confirmed diagnosis of NPC – 1
  - NIH NPC Severity Score <30 and with no more then 4 individual domains with a score of > 3
  - Age range: 18 years upwards

- **Total Sites: 2 in United States**
  - UCSF Benioff Children’s Hospital Oakland, CA
  - Morristown Medical Center, NJ

- **Trial Timeline**
  - First patient enrollment: Q’3 17
  - First patient dosed Q’3 17
Trappsol® Cyclo™
Phase I/II Study to Evaluate Safety and Efficacy

## Randomization 4:4:4 Between Dose Groups

<table>
<thead>
<tr>
<th>Dose Group 1</th>
<th>Dose Group 2</th>
<th>Dose Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500 mg/kg</td>
<td>2000 mg/kg</td>
<td>2500 mg/kg</td>
</tr>
</tbody>
</table>

- **Trappsol® Cyclo™**: Bi-weekly 8 hour intravenous treatment for a period of 48 weeks
  - **Primary Endpoint**: Plasma levels of Trappsol® Cyclo™
  - **Secondary Endpoint**: Markers of Cholesterol metabolism/synthesis, CSF Levels of Trappsol® Cyclo™, Clinical Outcomes (motor Skills, cognition, eye movements, liver morphology et al), global impression of disease
  - **Exploratory Endpoint**: CSF biomarkers of NPC Disease

- **Niemann-Pick Disease Type C**
  - Confirmed diagnosis of NPC – 1
  - NIH NPC Severity Score <30 and with no more then 4 individual domains with a score of > 3
  - Age range: 2 years upwards

- **Total Sites: 5-6 in 4 Countries**
  - UK, Sweden, Italy, Israel
  - Aptus/Syneract is supporting Trappsol® Cyclo™ by doing site setup and monitoring

- **Trial Timeline**
  - First patient enrollment: Q’2 17
  - First patient dosed Q’3 17
Today’s Presentation – Blinded data

101/US
Primary
• To compare the plasma pharmacokinetics of HP-β-CD following 2 different dose levels of intravenous Trappsol® in patients with NPC-1 disease following single and multiple doses

Secondary
• To evaluate HP-β-CD concentrations in CSF following 2 different dose levels of intravenous Trappsol® in patients with NPC-1 disease following single and multiple doses

201/EU-Israel
Primary
• To compare the plasma pharmacokinetics of HP-β-CD following 3 different single doses of intravenous Trappsol® in patients with NPC-1

Secondary
• To evaluate HP-β-CD concentrations in CSF following intravenous administration of Trappsol® in patients with NPC-1

PK sample timings SOI Start of Infusion EOI End of infusion

<table>
<thead>
<tr>
<th>NominalTime h</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>8.5</th>
<th>9</th>
<th>10</th>
<th>12</th>
<th>16</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>SOI+4</td>
<td>EOI</td>
<td>EOI 1+</td>
<td>EOI 1</td>
<td>EOI +2</td>
<td>EOI =4</td>
<td>EOI =8</td>
<td>EOI =12</td>
</tr>
</tbody>
</table>

CTD Holdings, Inc.
Demography

Data is presented on first four patients in each trial

Subjects in 101 trial: 3 male, 1 female
   Ages range from 21 to 37
   All subjects Caucasian

Subjects in 201 trial: 4 female
   Ages range from 15 to 39
   All subjects Caucasian
Plasma Levels of Trappsol after a Single 8h Infusion
Single v Multiple Infusions

- Pt 1 Single
- Pt 1 Multiple
- Pt 2 Single
- Pt 2 Multiple
- Pt 3 Single
- Pt 4 Single
- Pt 4 Multiple

HPBCD ug/ml vs H after Start of Infusion
Mean Plasma HPBCD

HPBCD ug/ml

H after start of infusion

Infusion

HPBCD Mean after Single Infusion

HPBCD Mean after Multiple Infusions
Trappsol in CSF ug/ml

- Pt101
- Pt102
- Pt20101
- Pt3102
- Pt101-01
- Pt101-02
- Pt101-03
- Pt101-04

H after start of infusion

HPBCD ug/ml

0h 4h 8h 12h
### pK CSF – Example 1

<table>
<thead>
<tr>
<th>Patient A (pt101)</th>
<th>Plasma 0hr</th>
<th>Plasma 2hr</th>
<th>Plasma 4hr</th>
<th>Plasma 6hr</th>
<th>Plasma 8hr</th>
<th>Plasma 8.5hr</th>
<th>Plasma 9hr</th>
<th>Plasma 10hr</th>
<th>Plasma 12hr</th>
<th>Plasma 16hr</th>
<th>Plasma 20hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure time minutes</td>
<td>0</td>
<td>120</td>
<td>240</td>
<td>360</td>
<td>480</td>
<td>510</td>
<td>540</td>
<td>600</td>
<td>720</td>
<td>960</td>
<td>1200</td>
</tr>
<tr>
<td>Plasma [C] ug/ml</td>
<td>0</td>
<td>947</td>
<td>1470</td>
<td>1900</td>
<td>1930</td>
<td>1800</td>
<td>1630</td>
<td>1070</td>
<td>573</td>
<td>163</td>
<td>57.5</td>
</tr>
<tr>
<td>CSF [C] ug/ml</td>
<td>0</td>
<td>6.89</td>
<td>22.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure time minutes</td>
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<td></td>
<td>480</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>720</td>
</tr>
<tr>
<td>[C]csf/[C]p</td>
<td>0</td>
<td></td>
<td></td>
<td>0.004687</td>
<td></td>
<td></td>
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<td></td>
<td>0.064049</td>
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</tbody>
</table>

![Graph 1: [C]csf/[C]p (ul/ml) vs Time (mins)](image1)

![Graph 2: [C]p (ug/ml) vs Time (mins)](image2)
## pK CSF – Example 2

<table>
<thead>
<tr>
<th>Patient D (pt301-02)</th>
<th>Plasma 0hr</th>
<th>Plasma 2hr</th>
<th>Plasma 4hr</th>
<th>Plasma 6hr</th>
<th>Plasma 8hr</th>
<th>Plasma 8.5hr</th>
<th>Plasma 9hr</th>
<th>Plasma 10hr</th>
<th>Plasma 12hr</th>
<th>Plasma 16hr</th>
<th>Plasma 20hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure time minutes</td>
<td>0</td>
<td>120</td>
<td>240</td>
<td>360</td>
<td>480</td>
<td>540</td>
<td>600</td>
<td>720</td>
<td>960</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>Plasma [C] ug/ml</td>
<td>0</td>
<td>1030</td>
<td>1590</td>
<td>1590</td>
<td>1370</td>
<td>995</td>
<td>765</td>
<td>482</td>
<td>184</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>CSF [C] ug/ml</td>
<td>0</td>
<td>307</td>
<td>352</td>
<td>732</td>
<td>147</td>
<td>720</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure time minutes</td>
<td>0</td>
<td>240</td>
<td>480</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C)\text{csf}/(C)p</td>
<td>0</td>
<td>0.193082</td>
<td>0.256934</td>
<td>0</td>
<td>0.798913</td>
<td></td>
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</tr>
</tbody>
</table>

### Graphs

1. **[C]_{\text{csf}}/[C]_p (\text{ul/ml}) vs Time (min)**
2. **[C]_p (\text{ul/ml}) vs Time (min)**

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**CTD Holdings, Inc.**
Summary

Cmax of Trappsol® Cyclo™ in plasma occurs 6 – 8 hrs after start of infusion, consistent with expectations from pre-clinical studies and named patient use experience.

Half-life of Trappsol® Cyclo™ in plasma is between 1 -2 hours, consistent with expectations from other studies.

Multiple dose pK in plasma is consistent with single dose pK.

Trappsol® Cylco™ crosses the blood-brain-barrier at low but significant levels, while CSF albumin levels decrease slightly pre- and post-infusion 1.

The kinetics of drug crossing the BBB can be measured at steady rates which continue after cessation of IV infusion for at least 4 hours.
The collection point for CSF in the lumbar spine does not relay information about where or how the drug crosses the BBB.

The 10-fold range in amounts of drug detected in the CSF could be due to dose levels, potential bleed at the collection site, changes in the BBB in individual patients, or other factors.

Once the 101 and 201 studies are unblinded, we will compare pK data with clinical outcomes.

Initial clinical data (blinded) will be presented at WORLD, Orlando, on Wed. Feb 6, 4:30 pm to 6:30 pm, late-breaking posters.
Our thanks to

All of the patients and their families who are participating in our clinical trials today, and also those who provided data early on from the compassionate use of our product.
Thank You

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