Update on CTD’s Clinical Trials using Trappsol® Cyclo™ by Intravenous Administration in NPC Patients

NNPDF Family Support & Medical Conference
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Bloomington, MN
Presenter: Caroline Hastings MD

- Pediatric hematologist/oncologist, UCSF Benioff Children’s Hospital Oakland
- Co-Principal Investigator for Phase I CTD trial using IV administration of Trappsol® Cyclo™ in NPC patients
- Senior Clinical Advisor for Phase I/II CTD trial in Europe and Israel using IV administration of Trappsol® Cyclo™ in NPC patients
- Conflict of Interest statement:
  
  -- Member, CTD Scientific Advisory Board, uncompensated

  -- Senior Clinical Advisor and Member of the Safety Review Committee for CTD Phase I/II clinical trial in the EU/Israel, uncompensated
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Dr. Benny Liu showed in 2006 (and published in 2007) that one type of cyclodextrins, hydroxypropyl beta cyclodextrins, could release cholesterol from cells in a mouse model of Niemann-Pick Disease Type C (NPC).

This discovery led directly to CTD providing cyclodextrins to NPC families for use in compassionate programs. Dr. Caroline Hastings wrote the first compassionate use protocol with the Hempel family and a team, and was first to administer CTD’s beta cyclodextrin product to NPC patients. This was in 2009. The route of administration was intravenous.

The Hempel family posted the protocol to the web, and the protocol was picked up and used by other physicians in the US and internationally, especially in Brazil.

As CTD gathered data from as many families and physicians as possible, this led directly to CTD’s decision to develop its version of hydroxypropyl beta cyclodextrin, Trappsol® Cyclo™, using an intravenous route of administration, as a treatment for Niemann-Pick Disease Type C.
Trappsol® Cyclo™ is CTD’s proprietary formulation of hydroxypropyl beta cyclodextrin. HPβCD = 7 glucose molecules in a ring, modified by adding hydroxypropyl groups, to enhance solubility. The inner core of HPBCDs can make complexes with cholesterol and other molecules. HPβCDs widely used as excipient in products including Sporanox (broad-spectrum anti-fungal), eye drops, and mouthwash.
Niemann-Pick Disease Type C: Overview of a Systemic Disease

An autosomal recessive lysosomal storage disease

1/80,000 - 1/120,000
Live Birth Incidence

The disease is associated with accumulation of cholesterol in late endosomes and lysosomes due to loss of normal function of the NPC protein (NPC1 in 95% of cases, NPC2 in 5% of cases).

NPC is highly variable, presenting usually in young children, who often do not survive into adulthood, and also has a later onset presentation which leads to longer term disability. The disease is difficult to diagnose and, therefore, under-diagnosed.

NPC damage can be found in the brain, liver, and other body tissues. Depending on severity of the disease, cognitive impairment, movement disorders, swallowing, lung, liver and other normal functions are affected.
What did CTD learn in 2015 from its Compassionate Use Program with Intravenous Trappsol® Cyclo™

<table>
<thead>
<tr>
<th>IV Trappsol® Cyclo™ had been administered to &gt; 20 NPC patients worldwide</th>
</tr>
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<tbody>
<tr>
<td>• Favorable tolerability profile among patients treated to date.</td>
</tr>
<tr>
<td>• Safety profile has enabled physicians to continue treatment &gt; 6 years.</td>
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<table>
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<tr>
<th>Individual patients exhibited objective Systemic/CNS responses</th>
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<tbody>
<tr>
<td>• Reduction in hepatic volume and improvement in transaminases.</td>
</tr>
<tr>
<td>• Restoration of language skills.</td>
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<tr>
<td>• Resolution of interstitial lung disease.</td>
</tr>
<tr>
<td>• Improvement in fine and gross motor skills.</td>
</tr>
<tr>
<td>• Improvement in quality of life.</td>
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</table>

Point 1. Clinical data had allowed treating physicians to use the drug compassionately for more than 6 years in some cases.
Point 2. Compassionate use with IT adds only limited benefit when added to IV regimen in this sub-set of patients.

In a set of patients for which CTD has years of data, IV Trappsol® Cyclo™ either stabilizes NPC disease (lowermost line and upper right lines) or is associated with clinical improvements, as exhibited by lowering of NPC Severity Scores following IV Trappsol® Cyclo™ administration over time. Note: all patients added intrathecal administration to IV within 1 year to 2 years, with limited additional benefit observed.
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

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
<th>SECONDARY ENDPOINT</th>
<th>EXPLORATORY ENDPOINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma levels of Trappsol® Cyclo™</td>
<td>Markers of Cholesterol metabolism/synthesis</td>
<td>CSF biomarkers of NPC Disease</td>
</tr>
</tbody>
</table>

Dose Group 1: 1500 mg/kg
Dose Group 2: 2500 mg/kg

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

- **Total Sites: 2 in United States**
  - Emmes is supporting the study with site management and monitoring
  - UCSF Benioff Children’s Hospital Oakland, CA; and, Morristown Medical Center, Morristown, 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

Trappsol® Cyclo™: Bi-weekly 8 hour intravenous treatment for a period of 48 weeks

<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>

Randomize (N=12)

- **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 than 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/Synteract is supporting the trial with site management and monitoring

**Trial Timeline**
- First patient enrollment: Q’2 17
- First patient dosed Q’3 17
## Global Investigators

<table>
<thead>
<tr>
<th>Name</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caroline Hastings, MD</td>
<td>Pediatric hematologist/oncologist, Co-PI, UCSF Benioff Children's Hospital Oakland</td>
</tr>
<tr>
<td>Benny Liu, MD</td>
<td>Gastroenterologist, Alamada Health System and UCSF Benioff Children's Hospital Oakland, Co-PI</td>
</tr>
<tr>
<td>Darius Adams, MD</td>
<td>Clinical geneticist and pediatric metabolic disease expert, PI, Morristown, NJ</td>
</tr>
<tr>
<td>Robin Lachmann, MD</td>
<td>Metabolic disease expert and PI, University College London</td>
</tr>
<tr>
<td>Reena Sharma, MD</td>
<td>Metabolic disease expert, and coordinating lead for Phase I/II trial, PI for Salford Royal Trust site, UK</td>
</tr>
<tr>
<td>Ronen Spiegel, MD</td>
<td>Clinical geneticist and Chair, Pediatrics, PI, Emek Medical Center, Israel</td>
</tr>
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<td>Orna Staretz, MD</td>
<td>Neonatologist, PI, Soroka Medical Center, Israel</td>
</tr>
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<td>Martin Paucar Arce, MD, PhD</td>
<td>Neurologist, PI, Karolinska Institute, Sweden</td>
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<td>Julian Raiman, MD</td>
<td>Pediatric metabolic disease expert, PI, Birmingham Children's, UK</td>
</tr>
<tr>
<td>Maurizio Scarpa, MD</td>
<td>Metabolic disease expert and Coordinator, European Reference Network for Hereditary Metabolic Diseases, PI for site at Udine University Hospital, Italy</td>
</tr>
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Initial Data from CTD’s Formal U.S. and E.U./Israel trials

- Safety data show positive profile.
  - Adverse events are minor and as expected based on knowledge from compassionate use programs.
  - Hearing losses have been noted, but all have been transient. No permanent hearing losses.
- **Trappsol® Cyclo™** releases cholesterol from cells of NPC patients, allowing for cells to normalize.
- Trappsol® Cyclo™ crosses the blood-brain-barrier following IV administration.
- One marker for NPC disease severity, lysosphingomyelin-509, shows a downward trend with successive administration of IV Trappsol® Cyclo™. Another biomarker of neurodegeneration, tau, trends downward in the cerebrospinal fluid. This tells us that as Trappsol® Cyclo™ clears cholesterol from cells, there are downstream effects on markers of NPC disease severity.
- Clinical efficacy data are limited but encouraging. Disease specific features, including fine motor, gait, and cognition improve in some subjects. Most patients for which data are available either stabilized or improved in disease specific features.
# Cholesterol Precursors

**Individual Serum levels of Lathosterol at each visit from 4 subjects in the 101 study and 4 subjects in 201 study**

<table>
<thead>
<tr>
<th>Time</th>
<th>ug/ml</th>
</tr>
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<tbody>
<tr>
<td>Screen 1 Screen 2 Pre infusion D2 Post D3 D4 D5 D8 D15</td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>1.50</td>
</tr>
</tbody>
</table>

Each colored line represents a unique patient.

**Mean Serum levels of Lathosterol**

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**Individual Serum Levels of Desmosterol at each visit from 4 patients in the 101 study and 4 subjects in 201 study**

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<td></td>
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<tr>
<td>0.540</td>
<td>0.560</td>
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Cholesterol Metabolites

Individual Patient Values for Serum 4B-hydroxy cholesterol

Mean values for Serum 4B-hydroxy cholesterol

Each colored line represents a unique patient.

Individual Patient Values for Serum 27-hydroxycholesterol

Mean values for serum 27-hydroxy cholesterol

Each colored line represents a unique patient.
Liver tissue from NPC patient in the US trial. Left panels, no filipin, control. Upper right, baseline, filipin. Lower right, after 7 doses of Trappsol® Cyclo™ over 14 weeks, filipin.
Initial Data from CTD’s U.S. and E.U./Israel trials

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Trappsol® Cyclo™ in cerebrospinal fluid

Each colored line represents a unique patient.

HPBCD ug/ml

H after start of infusion

United States
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Levels of Tau in cerebrospinal fluid

Baseline
End of Infusion Dose 1
End of Infusion Dose 7

ng/ml
Units

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NPC Clinical Severity Score

- Widely used tool in clinical research community starting in 2010

- Based on 9 major domains, or features of NPC disease: eye movement, ambulation, speech, swallow, fine motor skills, cognition, hearing, memory, and seizures.

- And 8 modifying domains: Gelastic cataplexy, narcolepsy, behavior, psychiatric, hyperreflexia, incontinence, auditory brainstem response, and respiratory.

- Each major domain is scored 0 – 5, modifying domains 0 – 2 with 0 being normal or no history of the disease manifestation. Most severe patients are scored 61 with this tool.
For patient 1 (yellow): The improvement in total score of 3 points (compared with baseline) is due to reductions in severity in the eye movement (1 to 0), fine motor skills (2 to 1) and psychiatric modifier (1 to 0). For patient 2 (green): The improvement in total score (compared with baseline) is due to reductions in severity in eye movement (1 to 0), cognition (5 to 3), gelastic cataplexy (2 to 1) and incontinence (1 to 0). However, ambulation worsened (1 to 2) as did speech (3 to 4). Total score change reflects an improvement of 3 points. \(N=2\)
Following completion of the 14 week/7 dose treatment protocol:

1 patient was withdrawn from the trial due to hypersensitivity.
2 patients remain clinically stable.

4 of 6 patients report increased alertness, focus, enhanced communication and speech fluency.
3 of 6 patients note increased strength and motivation leading to increase in movement or ambulation.

Global Impression of Disease scores, standardized tool, to be analyzed.
A Special Thank You

to all of the patients, families and physicians who support CTD’s ongoing clinical trials and who provided their data from compassionate use programs early on, making our trials possible.
Thank You!