Niemann-Pick disease type C: Clinical experience in 11 patients with intravenous hydroxypropyl-β-cyclodextrin

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• Janssen R&D, LLC
A little history...

• 2007: HP-β-CD prolongs lifespan in NPC mouse model

• 2008-9: First supply by CTD of Trappsol® Cyclo™ for clinical use
  – iIND protocol developed (C Hastings) and submitted to FDA

• 2009: FDA approves iIND application, treatment of 1st 2 patients initiated

• 2010: Expansion of HP-β-CD use under research protocols
  – ‘Oakland protocol’ adopted in Brazil (C. Vieira), Trappsol® Cyclo™ supplied by CTD
  – Additional iIND holders in USA using Trappsol® Cyclo™
  – NPC Severity Score model published
  – Intrathecal administration introduced

• 2013: Janssen R&D, LLC offer HP-β-CD (Kleptose®) via a Donation Program
  – Some US iIND holders transition to Kleptose®, no further FDA approvals needed

Formalized clinical development of Trappsol® Cyclo™

• 2014: CTD Holdings board and management expansion
  – Considers options to build upon learning from compassionate use program
  – Initiates discussions with clinicians and patient representatives about the potential for formal clinical development

• 2015
  – CTDH announces donation of Trappsol® Cyclo™ to NPC families in need at NNPDF meeting, Chicago
  – Trappsol® Cyclo™ clinical development team meet with UK regulators to discuss program

• 2016
  – CTDH holds pre-IND meeting with FDA, plans for IND submission
  – Expected launch of phase I/II clinical studies of IV Trappsol® Cyclo™
NPC has multiple manifestations

- **CNS**
  - Impaired motor function
  - Behavioral disturbance
  - Loss of cognition
  - Vertical Supra-nuclear Gaze Palsy (VSGP)

- **Systemic**
  - Liver disease and failure
  - Hepatomegaly
  - Splenomegaly
  - Respiratory dysfunction

No two sufferers are the same: No single outcome applies to all.
IV and/or IT treatment: The debate

• Treatment with HP-β-CD has used 4 different paradigms
  – IV only
  – IV followed by the addition of IT (SEQ*)
  – IV and IT initiated concurrently
  – IT only

• Rationale for IT Rx is that cyclodextrins do not cross the blood brain barrier

• However in the mouse and cat models systemic HP-β-CD positively affects CNS disease
  – CNS penetration may not be essential for neurologic efficacy

* Sequential
NPC mouse model:
Peripheral HP-β-CD administration: Understanding effects on cholesterol burden and severity of disease

Clinical experience with Trappsol® Cyclo™

Trappsol® Cyclo™ Treatment
Clinicians: n=11, Patients n=23*

- No contact established
  Clinicians: n=1, Patients n=3

Responded to CTD enquiry
Clinicians: n=10, Patients n=20

- Comprehensive Reports
  Clinicians: n=7, Patients n=12
  - IV use only n=2
  - IV then IV+IT use n=9*
  - IT use only n=1

- Partial Information
  Clinicians: n=3, Patients 3
  - IV use only n=1
  - IV+IT use n=2

- No consent for disclosure
  Clinicians: n=4, Patients n=5
  - IV use only n=2†
  - IV then IV+IT use n=3†
## Demographics of treated patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at diagnosis, years</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.9 (5.6)</td>
</tr>
<tr>
<td>Median</td>
<td>5</td>
</tr>
<tr>
<td>Range</td>
<td>1–16</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td><strong>Received miglustat (n=8)</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
</tbody>
</table>
Natural History of NPC: Expectation of disease progression without intervention
NPC severity scores: Pre- and post-treatment

* This patient received only Kleptose ® (Janssen R&D LLC)
Post treatment NPC severity scale scores

Solid lines represent IV Rx only, dotted lines IV and IT

Years since initiation of IV Cyclodextrin

NPC Clinical Severity Scale Score

* This patient received only Kleptose® (Janssen R&D LLC)
Adverse events associated with treatment

<table>
<thead>
<tr>
<th>AEs associated with administration</th>
<th>AEs recognized as features of NPC</th>
<th>Other AEs of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Seizures</td>
<td>Port-a-Cath Infection</td>
</tr>
<tr>
<td>Generalized rash (trunk, elbow)</td>
<td>Pneumonia</td>
<td>Removal of Ommaya Reservoir</td>
</tr>
<tr>
<td>Tremor/chills/vomiting/fever</td>
<td>Thrombocytopenia</td>
<td>Post-operative delayed</td>
</tr>
<tr>
<td>Headache</td>
<td>Viral Illnesses</td>
<td>Parenchymal hemorrhage</td>
</tr>
<tr>
<td>Nausea</td>
<td>Viral Syndrome</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Stomach pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reduction in hepatomegaly

A 1 year old asian female who presented with severe dysphagia, hepatomegaly, and splenomegaly

Liver size according to MRI (cm³)
Improvement in language skills

• Male diagnosed at 2 years: liver disease at birth, lung disease, loss of developmental milestones

• Initiated IV Trappsol ® Cyclo ™ for 3 months prior to a 6 month interruption (FDA mandated)
  – While off treatment he lost the ability to sit as well as all language skills

• Re-initiation of IV treatment was associated with a recovery of some verbal skills in addition to improved wakefulness and decreased dystonia

• IT treatment was added to the regimen shortly afterwards

* Initially Trappsol® Cyclo ™ subsequently Kleptose® (Janssen R&D LLC)
Respiratory outcomes of treatment

• Following re-initiation of IV Trappsol ® Cyclo ™
  – Patient had immediate significant improvement in his respiratory status
  – Ability to wean off ventilator and to RA

• Multiple follow up chest x-rays and CT scans showed resolution of interstitial lung disease

• Current respiratory status is complicated by chronic respiratory failure requiring BiPAP use again secondary to restrictive/chronic lung disease from neuromuscular weakness and recurrent pneumonia
CT Chest Findings

Age 2 y 11 m before re-starting HPBCD: Diffuse marked confluent interstitial and alveolar process involving both lungs

Age 3 y 8 m after 9 months of HPBCD treatment: Dramatic improvement in interstitial and alveolar opacities
Improvements in fine motor control

Before IV Trappsol

After IV Trappsol
Conclusions

• IV HP-β-CD has been administered to >20 patients worldwide
  – Favorable tolerability profile amongst patients treated to date
  – Safety profile enabling physicians to continue treatment >6 years

• Individual patients exhibit objective CNS/Systemic responses
  – Reduction in hepatic size and improvement in transaminases
  – Restoration of language skills
  – Resolution of interstitial lung disease
  – Improvement in fine and gross motor skills
  – Improvement of quality of life

• Clinical experience warrants further investigation of intravenous HP-β-CD in the management of NPC
  – Treatment of clinical manifestations, systemic and neurologic
  – Halting or slowing the rate of disease progression
Special Thanks

All the patients and their families who agreed to provide their data and consented to its presentation today