# Trappsol®Cyclo™: Open Label Treatment in the TransportNPC™ Sub-Study in patients under the age of 3 diagnosed with Niemann Pick Disease Type C1

**Orna Staretz Chacham[1], Fatih Ezgu[2], Roberto Giugliani[3], Eugen Mengel[4], Sema Kalkan Ucar[5], Ronen Spiegel[6], Caroline Hastings[7], Bryan Hurst[8], Bryan Murray[8], Andreas Brecht[9], and Joseph Mejia[9]**

[1]Ben-Gurion University of the Negev, Beer Sheva, Israel, [2]Gazi University, Ankara, Turkey, [3]Hospital de Clínicas de Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil, [4]SphinCS GmbH, Hochheim, Germany, [5]Ege University Medical School, Izmir, Turkey, [6]Emek Medical Center, Afula, Israel, [7]UCSF Benioff Children's Hospital, Oakland, CA, USA, [8]Boyd Consultants Ltd, Crewe, Cheshire, UK, [9]Cyclo Therapeutics, Gainesville, FL USA

## Abstract

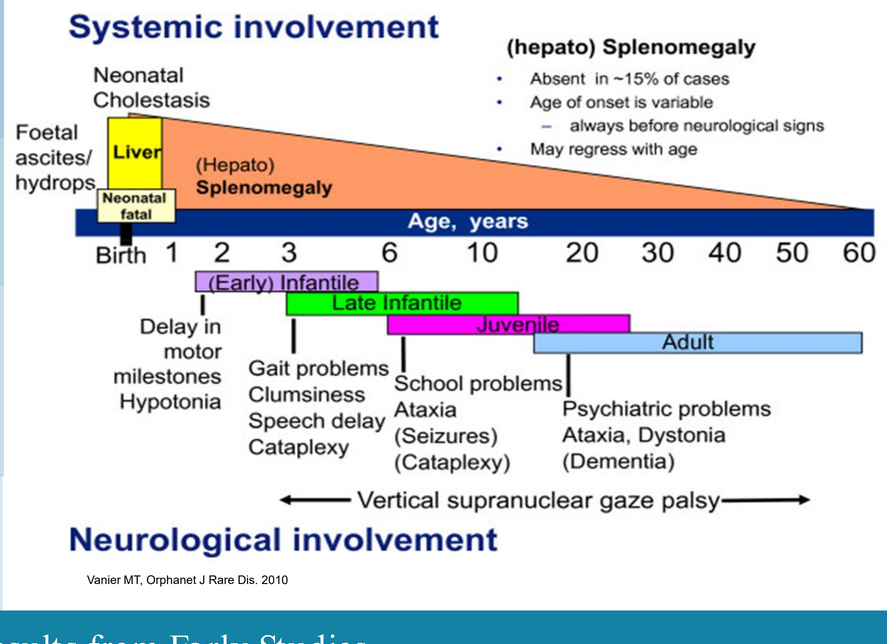
**Background:** Niemann Pick Disease Type C1 (NPC) is a highly heterogenous disease with very young children typically presenting rapid clinical deterioration. Visceral symptoms are predominant in the neonatal period (hepato-/splenomegaly, ascites, fetal hydrops, transient neonatal cholestasis which may lead to fatal outcome). Neurological symptoms may comprise developmental delays of motor milestones and progressive centrally-mediated hypotonia which results in unique rapid clinical decline. A safe and effective treatment addressing both CNS and systemic symptomatology is mandatory for this age cohort.

**Methods:** Two early phase clinical studies established the safety, tolerability and CNS penetration of intravenously administered Trappsol® Cyclo™ (HPβCD).
An ongoing pivotal, Phase 3, placebo-controlled study is evaluating the safety of biweekly IV HPβCD (2000 mg/kg) for 192 weeks and includes an open-label sub-study in symptomatic and asymptomatic patients (<3 years of age). The clinical global impression-severity (CGI-S) and clinical global impression-change (CGI-C) scales assess response to HPβCD on overall disease severity and disease change from baseline, respectively.

**Results:** As of September 2024, ten patients have been enrolled ranging from ages 7 to 31 months. Baseline CGI-S established mild to marked disease stage with the majority showing neurological symptoms at recruitment. 7 of 8 patients who have reached 24 weeks and 6 of 7 who have reached 48 weeks show stabilization or improvement in CGI-C. Of note, an infant enrolled at 7 months old diagnosed neonatally with abnormal liver enzymes has shown progressive improvement in liver function despite not being on any other disease modifying therapy.
Overall, AEs are limited, with 15 reported SAEs in 5 patients considered unrelated to treatment. Two patients withdrew due to family decision post 48 weeks.

**Conclusion:** Early use of Trappsol® Cyclo™ in very young children with NPC may provide an effective intervention for addressing long-term neurological and systemic damage, due to the direct action of reducing intracellular cholesterol accumulation.
Contact: Lori J McKenna; +1.508.410.0104; patients@cyclotherapeutics.com;
clinicaltrials.gov NCT04860960

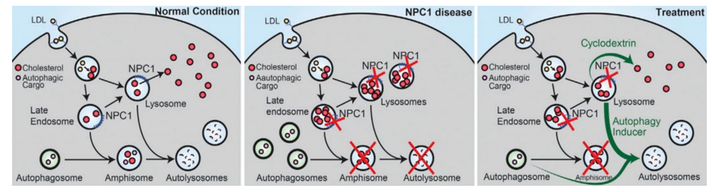
## Overview




Vanier MT, Orphanet J Rare Dis. 2010

TransportNPC™

## Mechanism of Action of HPßCD




Maetzel et al., 2014

- HPβCD is taken into cells via bulk phase endocytosis and into the late endosome/ lysosome (LE/L)
- Selectively allows trapped unesterified cholesterol to be released from the LE/L into the cytosol from where it enters cellular cholesterol processing
- Levels up to 1.0 mM mobilize stored cholesterol in LE/L
- Neurotoxicity/acute cell death at concentrations of > 10mM
- During infusion HPßCD reaches plasma concentration of about 1 mM
- Transfer over the BBB happens by micropinocytosis with a transfer rate of 0.1 – 0.2 µl / g tissue / minute
- Assumed peak concentration of HPßCD in brain tissue is 0.04 – 0.08 mM; confirmed by values obtained in lumbar CSF (0.02 – 0.03 mM)

Peake K. & Vance J., J. Biol. Chem. 2012; Hastings C. et al., Mol. Genet. Metab. 2022; Sharma R., Hastings C. et al., Mol. Genet. Metab. Rep. 2023
Abbreviations: mM - millimolar

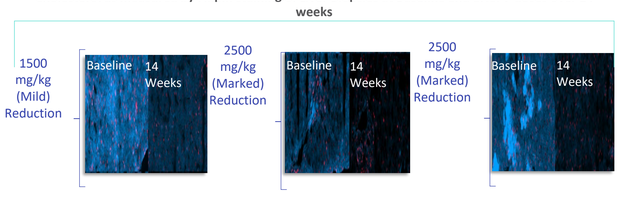
# Results from Early Studies

## Early Phase Study: Systemic & CNS Effect

**Systemic:**
Filipin-stained positive tissue area in liver tissue samples from 8 NPC1 subjects at Baseline and 2 weeks after the seventh HPβCD infusion.

HPβCD enables the effective transport of cholesterol out of cells

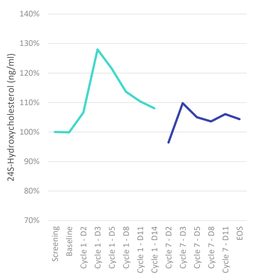
**Cholesterol as measured by Filipin staining of Liver Biopsies at Baseline and after 7 doses over 14 weeks**




The lack of light blue represents the clearing of cholesterol from cells

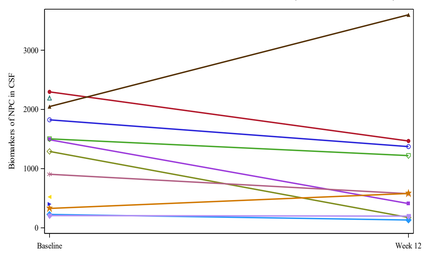
**Central nervous system:**

The mean serum **24S-hydroxycholesterol** (ng/ml) level increases in NPC patients following IV administration of HPβCD, signaling effect on CNS cholesterol metabolism. Shown here are data after 1st infusion cycle (week 1) and 7th infusion cycle (week 13)




**Central nervous system**

**Tau** levels as measured in the CSF are shown here for 10 NPC patients who had lumbar punctures prior to treatment with HPβCD and after seven doses. Seven of 10 patients showed a reduction in Tau levels, one remained stable, and two increased, no dose-response relationship.




Hastings C. et al., Mol. Genet. Metab. 2022

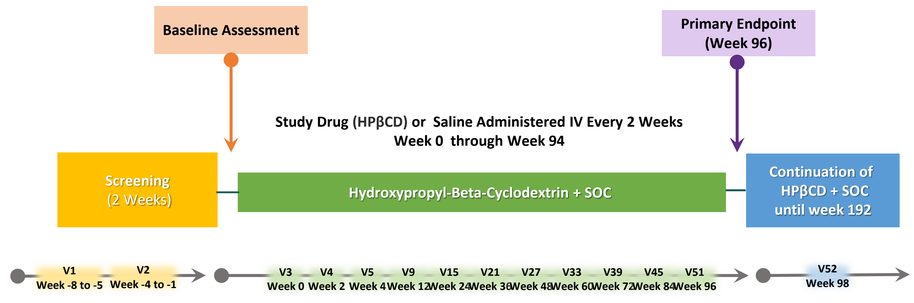
## Time Course of Effects of HPβCD

| Within hours | Over 14 Days | 14 Weeks | Longer time |
|---|---|---|---|
| • PK is well understood ($t_{1/2}$ visceral: 2h; $t_{1/2}$ CNS: 6h)<br>• Mobilization of lysosomal cholesterol | • Transient decrease in cholesterol biosynthesis (liver)<br>• Transient increase in cholesterol catabolism (liver)<br>• Transient increase in cholesterol catabolism (CNS neurons) | • Removal of excess cholesterol from liver lysosomes (biopsies, reduced response @14 weeks /precursors, metabolites)<br>• Removal of 24S(OH)cholesterol from CNS neurons (reduced response @14 weeks) | • Promising data from phase 1 / 2 study[1)]<br>• From earlier studies<br>– Apparent improved regulation of cholesterol metabolism: visceral and in CNS[2)]<br>• Phase 3 study (301) ongoing |

[1)]Sharma R., Hastings C. et al., Mol. Genet. Metab. Rep. 2023
[2)]Hastings C. et al., Mol. Genet. and Metab. 2022

# Study Design

## Trial Design: Sub-Study – Global Open Label Phase 3




**Study Drug Infusions Following Required Assessments every 2 weeks**

| | |
|---|---|
| **Number of Subjects** | **Up to 12 target, 10 included** |
| **Study Sites EOY** | **6 sites across 4 countries** |
| **Dose** | **2000 mg/kg via IV infusion** |

Abbreviations: HPβCD=Hydroxypropyl-beta-cyclodextrin; n=Number; OLE=Open-label Extension, SOC=Standard of Care; V=Visit

# Sub-Study Endpoints

## Sub-Study (EU and RoW) Endpoints and Outcome Measures

### Objectives

**For EU, EMA and RoW**

- To evaluate the safety and tolerability of HPβCD and SOC in patients with NPC1 aged newborn to <3 years of age
- To evaluate the improvement following treatment with HPβCD and SOC using the CGI-S, CGI-C, CaGI-S, CaGI-C, and CaGI C24 scales in patients aged newborn to <3 years of age
- To evaluate the PK of HPβCD in patients aged newborn to <3 years of age

### Efficacy Endpoints

- Mean change from Baseline in CGI-S scores at 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96 weeks
- Mean change from Baseline in CGI-C scores at 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96 weeks
- Mean change from Baseline in CaGI-S scores at 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96 weeks
- CaGI-C scores as assessed pre-infusion at 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96 weeks
- CaGI-C24 scores at 0, 2, 4, 12, 24, 36, 48, 60, 72, 84, and 96 weeks

### Safety Outcome Measures

- AEs
- AESI
  - infusion reactions
  - worsening of hearing
- Vital Signs
- ECGs and lab tests
- Weekly safety phone calls

Abbreviations: CGI-S: Clinical Global Impression – Severity; CGI-C: Clinical Global Impression – Change; CaGI-S: Caregiver Clinical Global Impression – Severity; CaGI C24: Caregiver Clinical Global Impression –Change 24 hours post-infusion; AEs: Adverse events; AESI: Adverse events of special interest; ECGs: Electrocardiograms

# Status of Global Open Label Sub-Study

## Sub-Study Population Update*

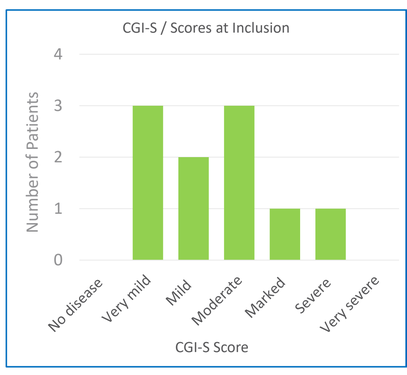
| Sub-study (0-3 years of age) | |
|---|---|
| **Age Range (Mean age at screening)** | 0 – 2 (1.4 yrs) |
| **Male** | 8 |
| **Female** | 2 |
| **Enrolled** | 10 |
| **Ongoing** | 8 |
| **End of Treatment** | 2 |
| **Reached Wk 48** | 8 |
| **Reached Wk 96** | 2 |
| **Sub-study (0-3 years of age)** | |
| **Reaching Wk 48 by 1 H 2025** | 2 |

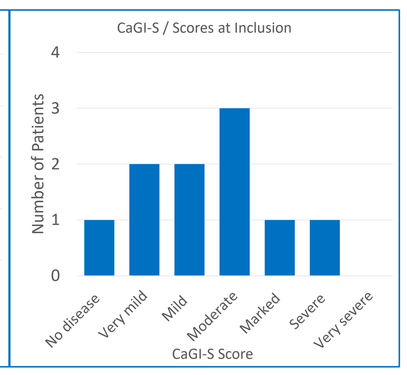
| Subject | Age/Sex (M or F) | Baseline | Current Disposition |
|---|---|---|---|
| **SubSt_001** | 2y 7m / M | 10-Mar-22 | Week 138 |
| **SubSt_002** | 0y 11m / M | 24-Apr-22 | Week 68, ET* |
| **SubSt_003** | 2y 3m / M | 09-Mar-22 | Week 48, ET* |
| **SubSt_004** | 1y 9m / F | 16-Nov-22 | Week 108 |
| **SubSt_005** | 2y 6m / F | 21-Jun-23 | Week 80 |
| **SubSt_006** | 1y 8 m / M | 14-Sep-23 | Week 66 |
| **SubSt_007** | 1y 1m / M | 27-Sep-23 | Week 66 |
| **SubSt_008** | 2y 2m / M | 07-Dec-23 | Week 52 |
| **SubSt_009** | 0y 7m / M | 16-May-24 | Week 30 |
| **SubSt_010** | 1y 0m / M | 22-May-24 | Week 28 |

* ET: early termination of treatment due to caregiver decision

Abbreviations: Wk= week; Yrs= years; Y= year; 1 H= first half; M= male; F= female; ET= Early termination;
*Data on file; cut-off date: December 2024

## Preliminary Sub-Study Outcomes*



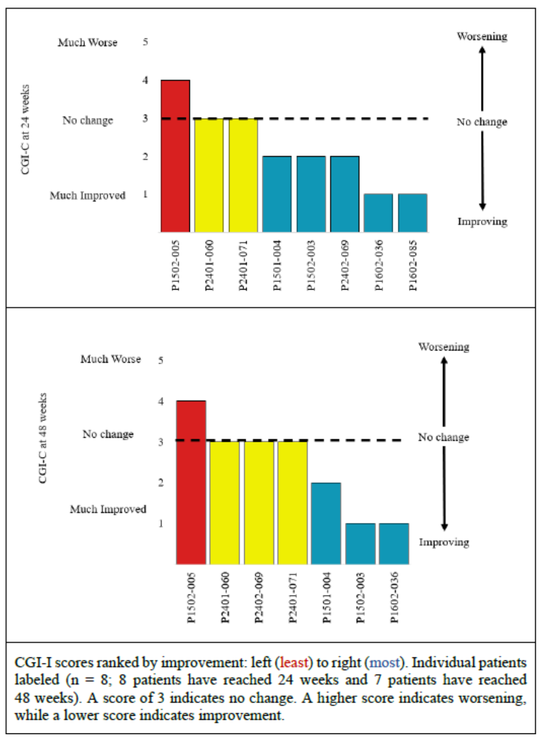

The severity scores as established by treating physician and caregivers give an overall picture of the disease stage. The evolution of both parameters will indicate how rapid disease progression is under treatment in the sub-study patient cohort

Abbreviations: CGI-S: Clinical Global Impression – Severity; CaGI-S: Caregiver Clinical Global Impression – Severity
*Data on file

# Preliminary Outcomes

## Clinical Global Impression–Change (CGI-C) at 24 Weeks and 48 Weeks*

- Graphs show individual patients (N=9)
- Age at recruitment below 3 years of age
- The majority of this highly progressive cohort (early pediatric onset of neurodegeneration) shows stabilization or improvement under treatment
- At 24 weeks of study 7 out of 8 subjects (87%) show stabilization or improvement with 4 patients being rated by the clinician as minimally or much improved
- At 48 weeks, 6 out of 7 subjects (86%) show stabilization or improvement.




CGI-I scores ranked by improvement: left (least) to right (most). Individual patients labeled (n = 8; 8 patients have reached 24 weeks and 7 patients have reached 48 weeks). A score of 3 indicates no change. A higher score indicates worsening, while a lower score indicates improvement.

Abbreviations: CGI-I= Clinical Global Impression – Improvement also referred as CGI-C
*Data on file; cut-off date: Sept 2024

# Safety Profile

## Summary of AE/SAE for Sub-Study Only*

| Adverse Event Summary | Total | Mild / Grade 1 | Moderate / Grade 2 | Severe / Grade 3 |
|---|---|---|---|---|
| Total Number AEs | 107 | 82 | 24 | 1 |
| Considered Possibly Related or Related by the Investigator | 1[1] | 1 | 0 | 0 |
| Serious (SAE) | 19[2] | 11 | 8 | 0 |
| Considered Possibly Related or Related by the Investigator | 0 | 0 | 0 | 0 |

[1]-Just 1 AE considered as being Possibly Related; i.e., vomiting
[2]-19 non-study treatment related SAE's

| Serious Adverse Events (SAE) | | |
|---|---|---|
| **Mild** | **N = 11** | RSV bronchiolitis; Gastroenteritis / rotavirus x 2/ campylobacter, Fever x 3; Post surgical bleed (tonsillectomy), Seizure exacerbation; |
| **Moderate** | **N = 8** | Fever; Lymphadenitis; Gastroenteritis, UTI; URI; Malnutrition x 2 ; Parainfluenza infection |
| **Severe** | **N = 0** | |

Abbreviations: AESI= adverse events of special interest; UTI= urinary tract infection; URI= upper respiratory infection
*Cut-off date: Dec 2024

# Conclusions – HPβCD for the Treatment of NPC

- **IV administration of hydroxypropyl-beta-cyclodextrin reaches both central and peripheral compartments**
- Clearance of lipids centrally and systemically were consistently demonstrated in a completed 14-week phase 1 study in adult patients with NPC
- Slowing down disease progression through cholesterol mobilization is an important consideration for patients with established disease, who can expect to experience neurodegeneration without treatment
- The open-label sub-study in patients (< 3 years old), with or without neurological symptoms will establish the effect of HPßCD on progress of NPC in this age cohort
- Progress in patients with neurological symptoms from the early pediatric stage is expected to be more rapid
- Ten patients were recruited, of which two terminated the study after 48 weeks (caregiver decision)
- At baseline, sub-study patients had a mixture of very mild to severe disease based on CGI-S. Clinical improvements seem to be best in patients with clinically mild to moderate disease
- 7 of 8 patients who have reached 24 weeks and 6 of 7 who have reached 48 weeks show stabilization or improvement in CGI-C
- AE profile is in line with prior findings from earlier studies, and from a double-blind phase 3 study running in parallel irrespective of age and disease severity
- As of Dec 2024, AEs are limited (107), majority are mild (77%) or moderate (22%) and 1 AE severe; with only 1 (mild grade) considered possibly related or related to study drug.
- Of all 107 AEs, 19 were reported as SAEs. No SAEs were considered as related to or possibly related to study drug
- By the first half of 2025, all currently enrolled patients will have completed at least 48 weeks of treatment; Three patients will likely have completed 96 weeks of treatment
- This will be the first data in NPC1 on treatment in this age group over a period of 48 weeks