Abstract

Cyclo Therapeutics, Inc. (Gainesville, FL) is conducting a randomized (2:1), double-blind, placebo-controlled, multi-center Phase 3 trial to evaluate the efficacy and safety of Trappsol® Cyclo™ 2000 mg/kg administered intravenously biweekly in NPC1 patients age 3 years and older. Several design elements position the Phase 3 trial for success. Eligible subjects must have an Annual Severity Increment Score (ASIS) between 0.5-2.0 to predict more homogenous disease progression. Study endpoints were developed in collaboration with regulatory authorities, such that the primary endpoint is a modified 4-domain NPC-CCS for the US FDA and the 5-domain NPC-CSS for the EU EMA and other countries. Secondary endpoints quantitatively evaluate ataxia, adaptive behavior, and swallow. The 96-week study includes a formal interim analysis at 48 weeks to stop the study early for success. The sample size of 93 subjects, extensive rater training with calibration videos for NPC-CSS, and emphasis on objective assessments maximize trial sensitivity (clinicaltrials.gov NCT04860960).

NPC1 Background

Rare, Progressive, and Fatal Genetic Disorder

- Autosomal recessive with birth prevalence 1/100,000
- 95% cases caused by mutations in NPC1, 5% in NPC2
- NPC1 and NPC2 proteins are required to shuttle unesterified cholesterol from the late endosomal/lysosomal compartment to other cellular membranes
- Deficiency of NPC1 or NPC2 proteins leads to accumulation of cholesterol and other lipids primarily in brain and liver
- Juvenile-onset is most common form (80%) with death by age 20 from neurodegeneration (“Childhood Alzheimer’s”)
- Infantile-onset form often presents with severe liver and/or lung disease and is followed by late-infantile neurodegeneration and death by age 5
- Late-onset form is increasingly being diagnosed in late adulthood with neurological and often psychiatric symptoms

Neurovisceral Symptoms

- Enlarged liver and spleen (hepatosplenomegaly)
- Severe liver disease and dysfunction (cirrhosis)
- Respiratory infections and interstitial lung disease
- Loss of cognitive skills (dementia)
- Difficulty with speech (dysarthria)
- Difficulty with swallowing and feeding (dysphagia)
- Difficulty coordinating movement (ataxia)
- Seizures
- Abnormal eye movements (vertical supranuclear gaze palsy)
- Low muscle tone (hypotonia)

High Unmet Medical Need

- No FDA Approved NPC Therapies
- Zavesca® (miglustat) approved in EU for the treatment of neurological manifestations in NPC1
Trappsol Cyclo Background Data

Cyclo Therapeutics Scientific Rationale for NPC

**Mechanistic Attributes of Trappsol® Cyclo™**

Trappsol® Cyclo™ is a formulation of hydroxypropyl-β-cyclodextrin (HPβCD) and has an affinity for cholesterol. HPβCD replaces the function of NPC1, transporting accumulated cholesterol from the late endosomal/lysosomal compartment to other cell membranes, thereby restoring intracellular cholesterol flow and lipid trafficking.

**Mechanism of Action**

What distinguishes the Cyclo Therapeutics clinical program is the intravenous route of administration of HPβCD, which allows the drug to act peripherally, as evidenced by the clearance of cholesterol from the liver, and centrally, as evidenced by changes in CNS biomarkers that support the neurological effects observed in the ongoing and completed clinical trials.

**Cholesterol Clearance from Liver Cells**

Cholesterol as measured by Filipin staining at Baseline and after 14 weeks

**Reduction in Brain Cholesterol**

Reduction in Tau

24S-hydroxycholesterol, a cholesterol metabolite produced in the CNS and transported across the BBB, increases in serum following IV administration of Trappsol® Cyclo™. Shown here are serum levels after the 1st and 7th doses, suggesting removal of excess cholesterol from the brain.

24S-hydroxycholesterol (ng/l)

Clinical treatment benefits observed in completed Phase 1 and Phase 2/1 study in pediatric and adult patients with NPC

A Phase 1 study: Randomized, double-blind, uncontrolled trial evaluating the safety, tolerability, PK, and preliminary efficacy of 2 doses of Trappsol® Cyclo™ (1500 mg/kg and 2500 mg/kg) administered IV every 2 weeks for 14 weeks. Twelve adults were enrolled (18 – 69 years), and 10 completed the trial. The safety and tolerability profile was favorable. Three drug-related SAEs of transient hearing loss, all subclinical and detected by audiometry, were reported with the 2500 mg/kg dose. The half-life of the drug in plasma was ~2 hrs. The drug was detectable in CSF at 4 hr post-infusion. Subjects and caregivers reported improvements in speech, swallow, gait, social interactions, and quality of life. A long-term extension study is ongoing in which subjects are being administered study drug at home. After 1-2 years of treatment, individual subjects have demonstrated improvement, disease stability, or less worsening than expected on the 5-Domain NPC Clinical Severity Scale (5D-NPC-CSS) based on natural history data from the literature.

A Phase 1/2 study: Randomized, double-blind, uncontrolled trial evaluating the safety, tolerability, PK and efficacy of 3 doses of Trappsol® Cyclo™ (1500, 2000, or 2500 mg/kg) administered IV every 2 weeks for 48 weeks. Twelve subjects were enrolled (2 – 34 years) with 9 completing the trial and 3 discontinuing early for reasons not related to study drug. The safety and tolerability profile was favorable. The PK was similar to the Phase 1 trial. Of the 9 completers, 8 (88%) met the first efficacy outcome measure of a ≥ 1 point improvement in ≥ 2 domains of the 17-domain NPC-CSS. In addition, all 9 completers were assessed as clinically stable or improved by their study site physicians.
Trial Design for Double-blind Period

- **Randomization (2:1) Baseline Assessment**

- **Study Drug (Trappsol® Cyclo™ or ½ NS Administered Every 2 Weeks**
  (Week 0 through Week 94)

- **Trappsol® Cyclo™ + SOC (n=62)**

- **Placebo (Saline) + SOC (n=31)**

- **Two-week Follow-up or Transition to OLE**

- **Primary Endpoint (Week 96)**

- **Interim Analysis at Week 48**

- **Study Drug Infusions Following Required Assessments at**
  Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, and 94

- **Screening (2 Weeks)**

- **Abbreviations:** 1/2 NS= Half-normal Saline; n=Number; OLE=Open-label Extension, SOC=Standard of Care; V=Visit

TransportNPC is the largest (N=93) and longest (up to 2 years) controlled Phase 3 to be conducted in subjects with NPC1. The study design provides the best opportunity to demonstrate clinical benefit and the potential for disease modification, given the central and systemic effects of the study drug.

Once all subjects have completed the Week 48 clinic visit assessments, an interim analysis will be performed and reviewed by an independent DMC, which will determine whether the primary endpoint has reached statistical significance and the study can be stopped prematurely, or will continue until all subjects have completed the Week 96 visit.

**Rescue Criterion:** Subjects who experience a substantial clinical decline (≥ 2 levels on the Clinician Global Impression of Severity [CGI-S]) for at least 12 weeks beginning at Week 36 may enter the open-label extension and receive Trappsol Cyclo after Week 48.

Trial Design for Extension Period

- **Trappsol Cyclo Administered Every 2 Weeks**
  (Week 96 through Week 190)

- **Trappsol® Cyclo™ + SOC**

- **Study Drug Infusions Following Required Assessments at**

- **Interim Analysis at Week 98**

- **Abbreviations:** 1/2 NS= Half-normal Saline; n=Number; OLE=Open-label Extension, SOC=Standard of Care; V=Visit

All subjects who successfully complete the double-blind period are eligible to receive Trappsol® Cyclo™ in a 2-year open label extension study.

Trial Design for Sub-study

- **Up to 12 subjects <3 years of age with confirmed NPC1, who may be symptomatic or asymptomatic, are eligible to receive open-label Trappsol® Cyclo™ for up to 4 years.** The objective of the sub-study is to evaluate the safety, tolerability, and preliminary efficacy of Trappsol® Cyclo™. This sub-study was requested by EMA to evaluate Trappsol® Cyclo™ as a potential preventative treatment and is being conducted in the ex-US only. The safety and efficacy results from the sub-study will be analyzed separately from the main study cohort.
Phase 3 Study Entry Criteria

**Key Inclusion Criteria**

1. Confirmed diagnosis of NPC1
2. Annual Severity Increment Score between 0.5 and 2.0 using the 17-domain NPC Severity Scale
3. Treated or not treated with miglustat (patients must be on a stable dose for at least 3 months prior to the Screening Visit or have discontinued miglustat for at least 3 months prior to the Screening Visit).
4. Body weight greater than 4.5 kg and less than or equal to 125 kg
5. Manifesting at least 1 neurological symptom of the disease

**Key Exclusion Criteria**

1. Recipient of a liver transplant or planned liver transplantation
2. Patients with active liver disease from any cause other than NPC1 or prolonged icterus or malformation of organs other than NPC1
3. Clinical evidence of acute liver disease including symptoms of jaundice or right upper quadrant pain or international normalized ratio >1.8
4. Stage 3 chronic kidney disease or worse as indicated by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2.
5. In patients aged ≤18 years, eGFR is calculated according to the Schwartz equation, and in patients aged >18 years eGFR is calculated using the Modification of Diet in Renal Disease equation
6. Use of curcumin or fish oil within 12 weeks prior to enrollment
7. Known or suspected allergy or intolerance to the study treatment
8. Treatment with HPβCD prior to entering the study
9. Treatment with any investigational drug during the 3 months prior to entering the study, including leucine in a clinical trial; however, leucine as a nutraceutical is allowed
10. Patients with uncontrolled, severe epileptic seizure periods
Primary Endpoint

For EU EMA
Mean change in the 5-domain NPC-CSS (Ambulation, Fine Motor, Speech, Swallow, and Cognition) between Trappsol® Cyclo™ and placebo groups from Baseline (Week 0) to Week 48, and if necessary, Week 96

For US FDA
Mean change in the 4-domain modified NPC-CSS (Ambulation, Fine Motor, Speech, and Swallow) between Trappsol® Cyclo™ and placebo groups from Baseline (Week 0) to Week 48, and if necessary, Week 96

All subjects will be assessed for both primary endpoints. For EMA, the 5-domain NPC-CSS is the primary endpoint, while the 4-domain modified NPC-CCS is exploratory. For FDA, the 4-domain modified NPC-CCS is the primary endpoint, while the 5-domain NPC-CSS is exploratory.

All investigators have undergone training on the NPC-CSS assessment to reduce intra-rater and inter-rater variability.

Secondary Endpoints

- Ataxia, as measured by the SCAFI (Spinocerebellar Ataxia Functional Index) composite score, which includes timed tests for the 8-meter walk, 9-hole pegboard, and PATA speech.
- Activities of daily living, as measured by the Vineland 2
- Aspiration, as measured by the Penetration aspiration Scale using endoscopy or video-fluoroscopy

Exploratory Outcome Measures, Including

- Speech analytics, pre-infusion and 24-hours post infusion
- Caregiver surveys
- Forced Expiratory Volume in 1 second (FEV1)
- Liver enzymes (AST and ALT)

Summary

Transport NPC is a Phase 3, global study that will evaluate the efficacy and safety of Trappsol® Cyclo™ in subjects with NPC1 is open for enrollment.

If you are a patient interested in participating in the study, please email Lori Gorski at lori.gorski@cyclodex.com

If you are clinician interested in participating in the study, please email Dr. Lise Kjems at lise.kjems@cyclodex.com