TransportNPC™: A Phase 3 Global Trial of Trappsol® Cyclo™ Administered Intravenously to Patients with Niemann-Pick Disease Type C1 (NPC1)

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Abstract

Background:
NPC is an ultrarare autosomal recessive disease. NPC1 and NPC2 proteins are required to shuttle unesterified cholesterol from the late endosomal/ lysosomal compartment to other cellular membranes. Deficiency of either protein leads to the accumulation of cholesterol and other lipids, which are primarily toxic in the brain and liver. NPC has been categorized by age of presentation, with visceral symptoms seen primarily in infants and neurologic/neurocognitive/psychiatric problems evolving over time. The clinical severity is highly varied. There are no FDA therapies approved for this condition.

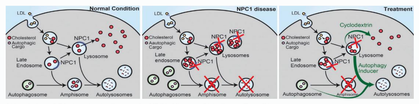
Method:
A 12-week phase 1 study, evaluated safety, tolerability, pharmacodynamics (PD), PK, and efficacy (per change in cholesterol homeostasis) of 2 doses of Trappsol® Cyclo™ (1500 mg/kg or 2500 mg/kg) administered IV every 2 weeks for 14 weeks.
A 48-week phase 1 / 2 trial evaluated the safety, tolerability, PK, and efficacy of 3 doses of Trappsol® Cyclo™ (1500, 2000, or 2500 mg/kg) administered IV every 2 weeks for 48 weeks.
PK and PD assessments in the phase 1 and the phase 1 / 2 studies substantiated the MOA of Trappsol® Cyclo™. The studies confirmed that Trappsol® Cyclo™ penetrates the CSF which correlates clinically with the PD changes in CNS cholesterol metabolism, as well as the neurologic improvements observed in participants.
TransportNPC™, a phase 3 study, is a prospective, randomized, double-blind, placebo-controlled study in 93 patients aged 3 and up with a confirmed diagnosis of NPC1 to evaluate the safety, tolerability, and efficacy of 2000 mg/kg dose of Trappsol® Cyclo™ administered IV every two weeks for 96 weeks. Efficacy will be measured at week 48 and week 96. A sub-study for patients 0-3 years was requested by EMA to evaluate Trappsol® Cyclo™ as a potential preventative treatment.

Results:
The phase 1 trial demonstrated an acceptable safety and tolerability profile. Three drug-related SAEs of transient hearing loss, all subclinical and detected by audiometry, were reported with the 2500 mg/kg dose. Subjects and caregivers reported improvements in speech, swallow, gait, social interactions, and quality of life. A long-term extension study is ongoing. After 1-2 years of treatment, patients 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. The safety and tolerability profile of the phase 1 / 2 study was acceptable. The PK was comparable to the phase 1 trial. 8 (88%) patients met the first efficacy outcome measure of a ≥ 1 point improvement in ≥2 domains of the 17-domain NPC-CSS. All 9 who completed were assessed as clinically stable or improved by their physicians.

Trappsol® Cyclo™ - Mechanism of Action & Clinical Data

Mechanism of Action-Exemplified

Overview of Functional Defects in NPC Disease-affected Cell Types



Abbreviations: LDL, low-density lipoprotein; NPC1, Niemann-Pick disease Type C1.
Source: Maetzel D, et al., Stem Cell Reports (2014).

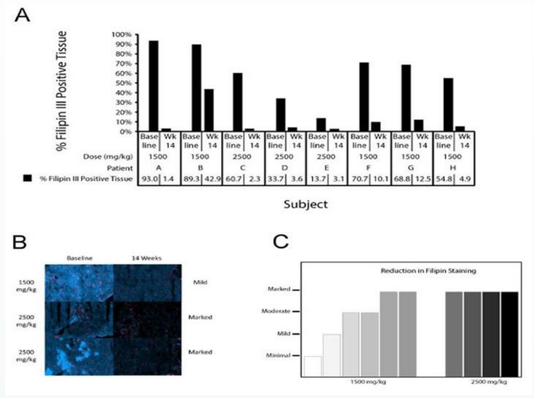
- NPC1 protein located in the membranes of the late endosomal/lysosomal (LE/L) compartment
- Regulates the efflux of unesterified cholesterol to other regions of the cell
- NPC2 protein located in the matrix of the LE/L compartment, transferring unesterified cholesterol to NPC1
- In NPC, deficiency of NPC1 (or NPC2) leads to:
- Accumulation of unesterified cholesterol in the LE/L compartment by inhibiting efflux and causes a block in autophagic flux
- Results in accumulation of autophagosomes and autophagy substrates due to impaired formation of amphisomes
- Trappsol® Cyclo™ (hydroxypropyl-β-cyclodextrin [HPβCD])-mediated cholesterol release is independent of the function of both NPC1 and NPC2 proteins
- Can clear toxic accumulation of cholesterol and other lipids
- Restores efflux from LE/L compartments
- Trappsol® Cyclo™ has the potential to bring significant benefit to patients with NPC

Trappsol® Cyclo™ is a formulation of hydroxypropyl-beta-cyclodextrin (HPβCD) and has an affinity for cholesterol

What distinguishes the clinical program is the Intravenous Route of Administration allowing the drug to reach major peripheral organs

. . . and **centrally**, demonstrated in data from our completed trials (data on file)

Release of Trapped Liver Cholesterol Following 12 Weeks of IV Treatment with Trappsol® Cyclo™

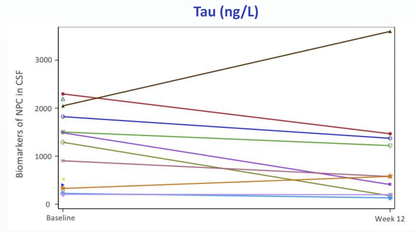


A. The percentage of filipin III (filipin)-stained positive tissue area in liver tissue samples from 8 NPC1 subjects at Baseline and 2 weeks after the seventh HPβCD infusion
B. Representative images of filipin staining of liver tissue at Baseline and 14 weeks post-treatment with low (1500 mg/kg) and high (2500 mg/kg) doses of HPβCD
C. Level of reduction (minimal, mild, moderate, and marked) in filipin staining for each subject (each bar represents a subject) according to the dose of HPβCD received

Hastings et al. 2022

Reduces Rate of Apoptosis of Cells in the CNS and Brain Cholesterol

Tau (ng/L)



Tau: A protein related to onset and disease progression in neurodegenerative diseases, including NPC

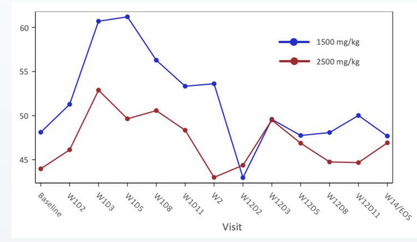
Tau levels measured in the CSF from 10 NPC patients pre- and post IV dosing Trappsol® Cyclo™

60% of patients had a reduction in Tau levels, 20% remained stable, and 20% increased

Suggestive of a neuroprotective benefit in CNS

Source: CTD-TCNPC- Study 101

24S-hydroxycholesterol (µg/L)



24S-hydroxycholesterol, a cholesterol metabolite from the CNS transported across the BBB, increases in serum following IV administration of Trappsol® Cyclo™.

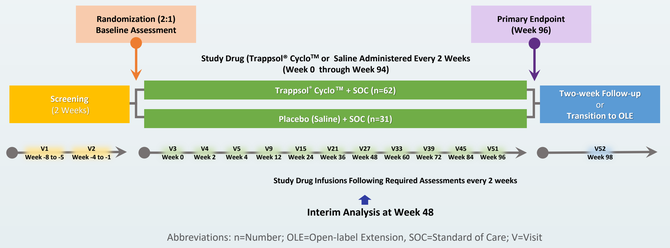
Shown here are data after 1st dosing and 7th dosing. 24S-hydroxycholesterol increases in serum following IV infusion of Trappsol® Cyclo™, signaling removal of excess cholesterol from the brain.

TransportNPC™ - Ongoing Phase 3 Pivotal Efficacy Registration Trial

Double-blind, Randomized, Placebo-controlled, Parallel-group study and is currently the most advanced clinical research program underway to identify a treatment for NPC

Number of Subjects	93
Current Sites	23 across 9 countries
Duration	96-week trial, with Interim Analysis at 48 weeks
Dose	2000 mg/kg via IV infusion
Primary Endpoint	NPC Composite Severity Score
Secondary Endpoints	SCAFI, Swallow, Vineland-2
Exploratory Endpoints	Inclusive of Speech, Liver and Lung function

Global Randomized, Controlled Phase 3 Pivotal Registration Trial



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

Key Design Features of Core study-Transport NPC

TransportNPC, largest (N=93) and longest (up to 2 years) controlled Phase 3 to be conducted in subjects with NPC1

Design and duration optimal to demonstrate clinical benefit and the potential for disease modification, given the central and systemic effects of the study drug

Interim analysis planned, once all subjects have completed the Week 48 clinic visit assessments
- Performed and reviewed by an independent DMC
- Determination if primary endpoint 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.

Disease Background & Clinical Program

NPC: A Debilitating Disease with Fatal Outcomes

- Rare, fatal and progressive genetic disorder affecting notably the brain, liver, spleen and lungs.
- Characterized by a defect in the NPC1 (95% of patients) or NPC2 (5%) protein
- Causes a cholesterol transport defect which results in the accumulation of lipids (cholesterol, sphingomyelin, sphingosine and glycosphingolipids) within the endosome
- Impaired intracellular lipid trafficking in major tissues and organs, responsible for the clinical features of the disease
- Extreme clinical heterogeneity with variable hepatic, pulmonary, neurological, and psychiatric manifestations at presentation, including auditory loss

Incidence
1/100,000 (~35 per year in U.S.)

Age at Time of Diagnosis
~ 3% are aged 3 and below
~ 97% are aged 3 and above
~ 60% aged 16 and above

Median Survival
Early Infantile (2m-2): 4.6y
Late Infantile (3-6): 9.4y
Juvenile (7-15): 15.4y
Adolescent/Adult (16+): 12.2y

0 U.S. Approved NPC Therapies

1 EU Approved Therapy with no systemic effects

Trappsol® Cyclo™ Summary of Completed Clinical Studies in NPC

Study 101

Phase 1 study in NPC patients aged 18 years and older showed Trappsol® Cyclo™ was well-tolerated with an acceptable safety and tolerability profile

- After IV infusion, the drug is detectable in the cerebrospinal fluid within hours after the start of infusion
- Cholesterol synthesis and metabolism affected, and cholesterol cleared from cells, mimicking effects from nonclinical studies (in vitro and in vivo) in NPC models

Study 201

Consistent pharmacodynamic effects and safety profile observed in a 48-week Phase 1/2 study in NPC patients aged 2 years and older

- 100% of patients assessed by treating physicians to be either stable or improved
- 88% (8 of 9 patients who completed the study), experienced clinically meaningful improvements in one or more efficacy endpoints, assessed by the 17 Domain NPC Severity Scale
- Based on totality of data from the Phase 1 and Phase 2 studies, the 2000 mg/kg dose was selected for the Phase 3 study

- The observed safety and tolerability profile consistent across studies and treatment duration, irrespectively of age spectrum and disease severity
- Treatment-Emergent Adverse Events: majority mild to moderate in severity, manageable and monitorable and most considered unrelated to Trappsol® Cyclo™

Endpoints and Outcome Measures

Primary Endpoint

All subjects will be assessed for both primary efficacy endpoints.

For EU, EMA
- Mean change in 5D 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 modified 4D-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 investigators have undergone training on the NPC-CSS assessment to reduce intra-rater and inter-rater variability

Secondary Endpoint

- Ataxia, as measured by the SCAFI (Spinocerebellar Ataxia Functional Index) composite score
  - Includes timed tests for 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 videofluoroscopy

Exploratory Outcome Measures

- Speech analytics, pre-infusion and 24-hours post infusion
- Caregiver surveys
- FEV
- Liver enzymes AST and ALT

Phase 3 Study Eligibility 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 Screening Visit).
4. Body weight greater than 4.5 kg and less than or equal to 125 kg
5. Presenting 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 equation50, 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. Patients with uncontrolled, severe epileptic seizure periods

Conclusion

- The results from this Phase 1 and Phase 1 / 2 study support the mechanism of action of systemically (intravenous) twice weekly administration of Trappsol® Cyclo™ in mobilizing intracellular cholesterol stores in subjects with NPC1 as demonstrated previously by preclinical studies.
- In the Phase 1 study Trappsol® Cyclo™ showed positive pharmacodynamic effects in plasma with normalization of cholesterol homeostasis) and clearance of hepatic cholesterol and lipid deposits and Cerebrospinal fluid (CSF) (increase in 24S-hydroxycholesterol and reduction in total Tau).
- 8 of 9 patients who completed the Phase 1 / 2 study experienced clinically meaningful improvements in one or more efficacy endpoints (assessed by the 17 Domain NPC Severity Scale)
- 100% of patients who completed were assessed by treating physicians in the Phase 1 /2 were rated as either stable or improved over 48 weeks.
- The administration of Trappsol® Cyclo™ has shown an acceptable safety and tolerability profile.
- TransportNPC™ Phase 3 study is the largest and most advanced global Phase 3 pivotal efficacy study in NPC; it evaluates the long-term efficacy and safety and tolerability of Trappsol® Cyclo™ in subjects with NPC1 and is open for enrollment.
- Contact: Lori M Gorski +1(508) 410-0104; Lori.Gorski@cyclodex.com
- www.clinicaltrials.gov NCT04860960

TransportNPC™