# From Bench to Bedside-

## A Review of the Trappsol Cyclo Program for the Treatment of Niemann Pick Disease Type C

Lise Kjems, MD PhD
Chief Medical Officer
Clinical Lead for Trappsol Cyclo Programs
Cyclo Therapeutics

**World Orphan Drug Congress**
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# Forward-Looking Statements

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# Disclosure: Employee of Cyclo Therapeutics, Inc.

## Lise Lund Kjems, MD, PhD

### Chief Medical Officer

Dr. Kjems is a well-established medical executive with over 20 years of preclinical and clinical development experience. As a physician scientist, she has held leadership roles of increasing responsibility for global groups of MDs, clinical pharmacologist/scientists in early and late-stage clinical development, PV/Drug Safety, Clinical Operations and Biostatistics. Over the course of her career, she has amassed a broad range of experience across multiple therapeutic areas in a diversified portfolio of chronic indications, rare and ultra-rare diseases, as well as oncology.

Prior to joining Cyclo Therapeutics, Dr. Kjems served as the Vice President, Head of Clinical Development at Albireo Pharma where she was responsible for leading end-to-end drug development process for rare hepatic cholestatic diseases and other hepatic diseases, culminating with the recent FDA and EMA approvals of Bylvay™ (odevixibat) for Progressive Familial Intrahepatic Cholestasis. Prior to that, she served as the Vice President, Clinical Development at Aldeyra Therapeutics and Executive Medical Director at Intarcia Therapeutics. From 2005 – 2014 she served in a number of roles at Novartis, including Global Program Medical Director/Medical Brand Director, where she was accountable for the global clinical strategy and led clinical teams; two programs in special metabolism, one rare indication and a program in secondary hypogonadism and served as the clinical lead on study in NAFDL and designed a clinical program for NAFLD and NASH. Additionally, she served as Senior Global Program Diagnostic Executive Director, Molecular Diagnostics and Executive Director, Deputy Head of Translational Medicine, Diabetes/Metabolism during her tenure at Novartis. Career appointments also include Executive Director, Project Team Leader – 113715, PTP-1B Antisense Inhibitor and the ApoB 100 inhibitor Programs at Ionis Pharmaceuticals (formerly Isis Pharmaceuticals); Group Director, Clinical Drug Evaluation at Johnson & Johnson; and Senior Clinical Pharmacologist, Clinical Research at Eli Lilly.

# Background

**2007**

**Dr. Benny Liu published seminal paper using hydroxypropyl beta cyclodextrins (HPβCDs) subcutaneously in NPC mouse**

- Showed clearance of cholesterol from cells
- Normalized cholesterol metabolism, shutting down synthesis and increasing cholesterol metabolism
- Prolonged life to almost normal. Even a single dose had profound effect when administered to pups
- Delayed onset of neurologic symptoms

**2009**

**First IND to Dr. Hastings approved by FDA to administer Trappsol Cyclo (HPβCD) to NPC patients, Intravenous route**

**Dr. Hastings posted the compassionate use protocol to the Internet, other physicians in the US and internationally used it or adapted it for their own patients**

**2018**

**CTD Holdings, Inc. launched its US Phase 1 trial based on the work of Benny Liu and the data from compassionate use patients**

**2019**

**12 case reports by Dr. Hastings, multiple physicians and Cyclo Therapeutics published in Orphanet J. Rare Disease. Many different paradigms used, diverse outcomes**

# NPC: A Debilitating Disease with Fatal Outcomes

- Rare, fatal and progressive genetic disorder affecting notably the brain, liver, spleen and lungs.
- Defect in the NPC1 (95% of patients) or NPC2 (5%) protein affects cholesterol transport
- Accumulation of lipids (cholesterol, sphingomyelin, sphingosine and glycosphingolipids) within the endosome
- Impaired intracellular lipid trafficking in major tissues and organs
- Extreme clinical heterogeneity with variable hepatic, pulmonary, neurological, and psychiatric manifestations at presentation, including auditory loss
- Major impact on QoL

## Incidence

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

## Age at Time of Diagnosis

~ 3% are age 3 and below
~ 97% are age 3 and above
~ 60% age 16 and above

## Median Survival

Early Infantile (2m-2): 4.6y

Late Infantile (3-6): 9.4y

Juvenile (7-15): 15.4y

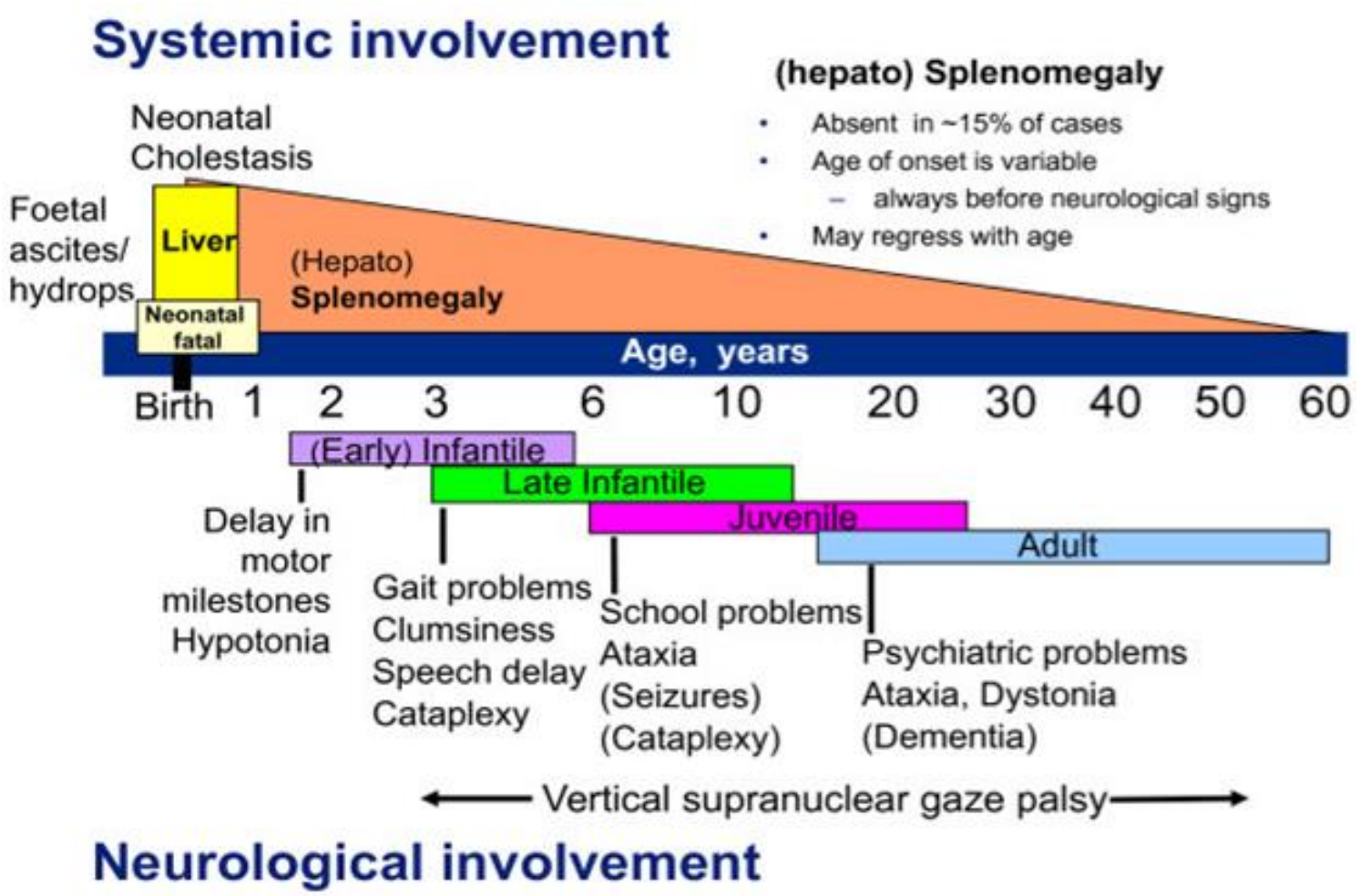
Adolescent/Adult (16+): 12.2y

**0** U.S. Approved NPC Therapies

**1** EU Approved Therapy with no systemic effects

# NPC -Systemic Manifestations Disease Presentation and Progression

- Fetal ascites/hydrops
- Neonatal hepatic cholestasis
- Prolonged jaundice
- Hepatomegaly
- Hepatic steatosis
- Splenomegaly
- Splenic lipid accumulation: abdominal pain and tenderness
- Thrombocytopenia
- Pulmonary infiltrates
- Recurrent pneumonia (aspiration)
- Loss of appetite
- Failure to thrive
- Impaired growth




Vanier 2010

# NPC – Neurological Clinical Signs and Symptoms

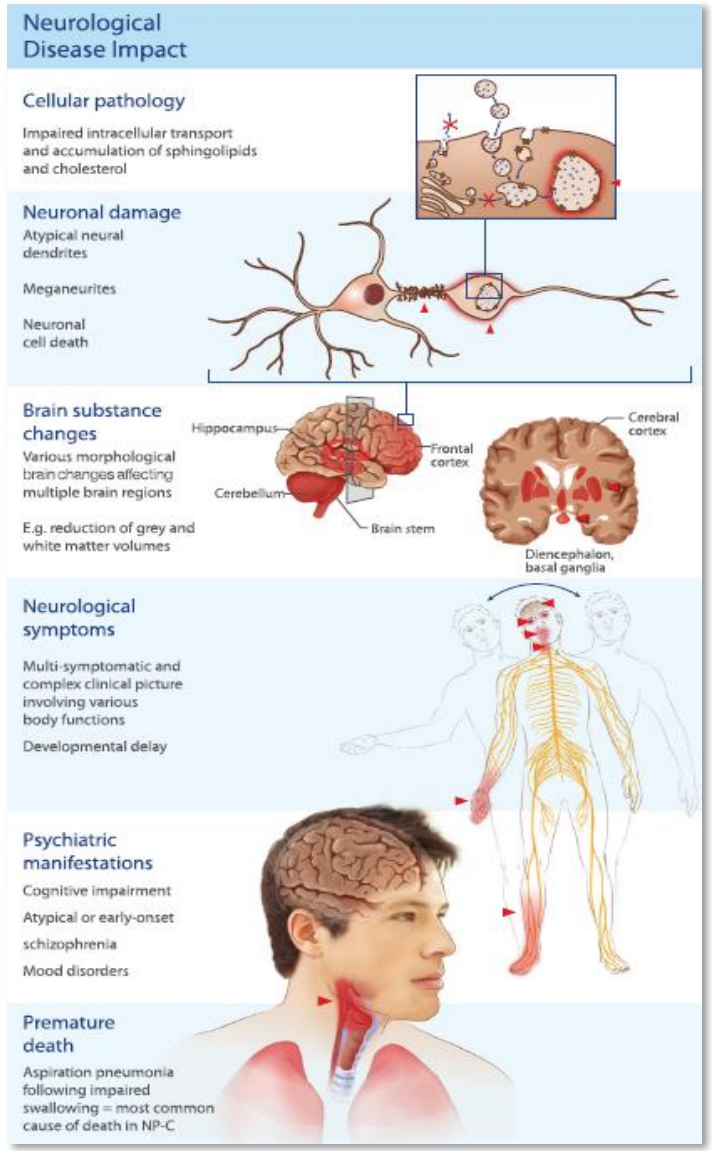
## Central Effects

Basal Ganglia, Brain Stem, Cerebellum

- Apraxia
- Cerebellar Ataxia
- Vertical Supranuclear Gaze Palsy (VSGP)
- Dysarthria/Dysphagia
- Cataplexy
- Deafness

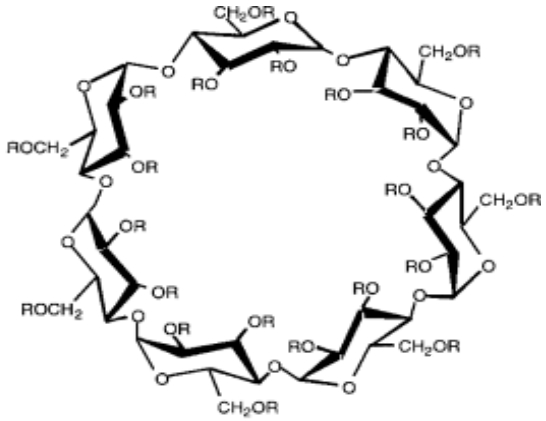
## Cortical

- Psychiatric Disorders
- Dementia
- Epilepsy




Pineda et al. 2018

# Trappsol® Cyclo™



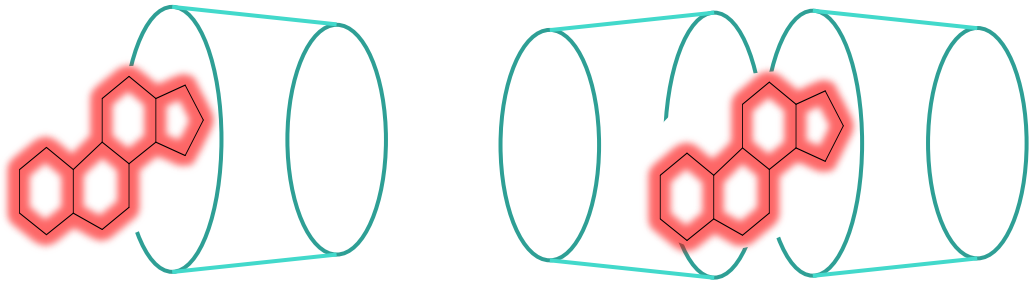
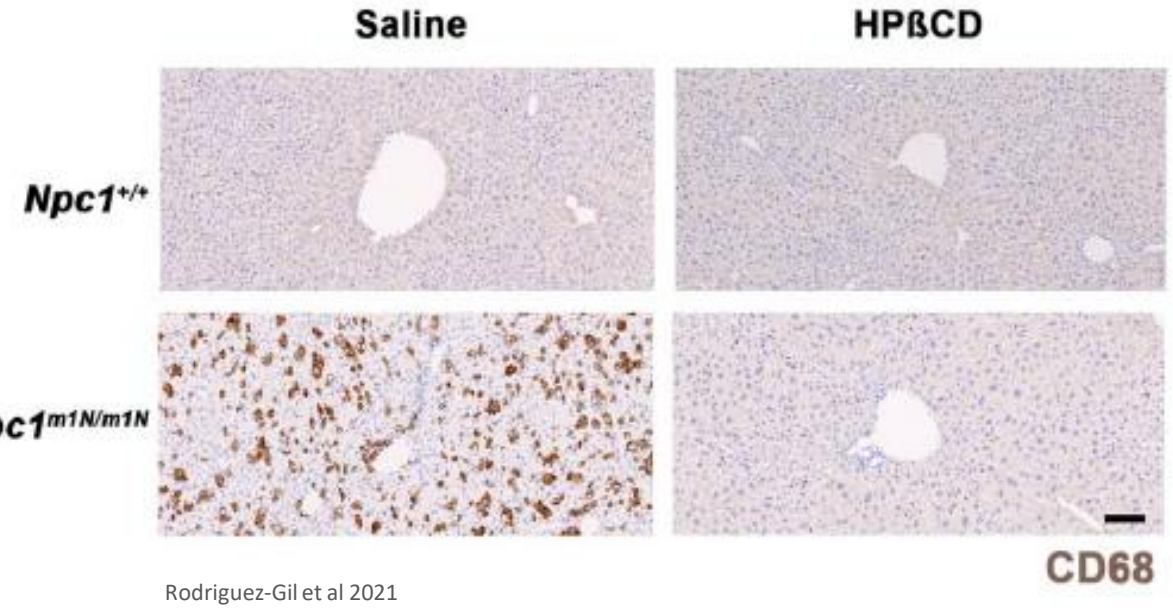



Figure is courtesy of David Begley, Kings College

- Proprietary formulation of hydroxypropyl-beta-cyclodextrin (HPBCD)
- 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)

# Peripheral Treatment Effects - Clearance of Toxic Hepatic Cholesterol Deposits Translation from NPC1 Mouse Model



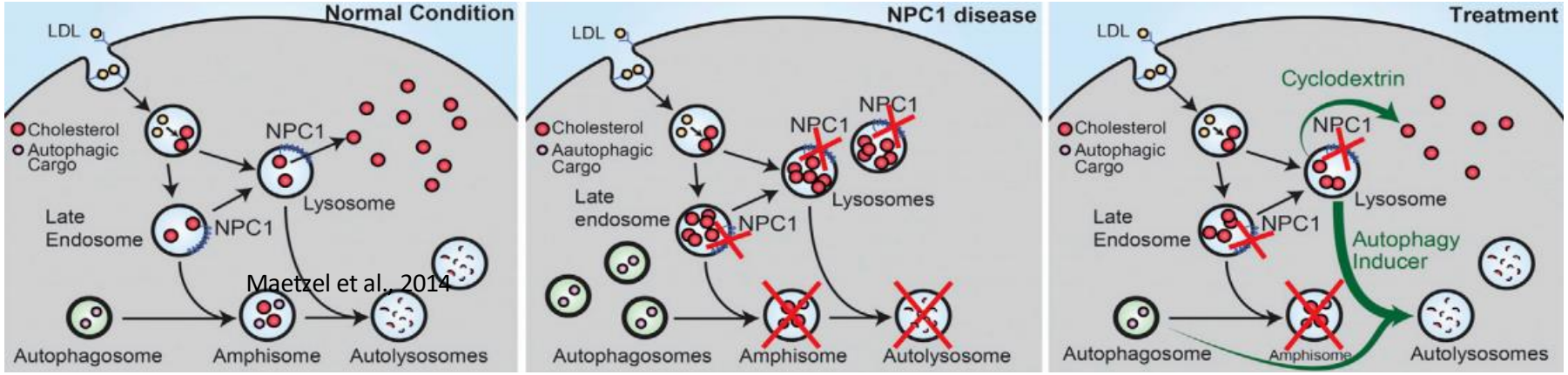

Rodriguez-Gil et al 2021

## To Man - Direct Evidence of Release of Sterols from the Liver

Data from Trappsol® Cyclo™ Treated NPC patients

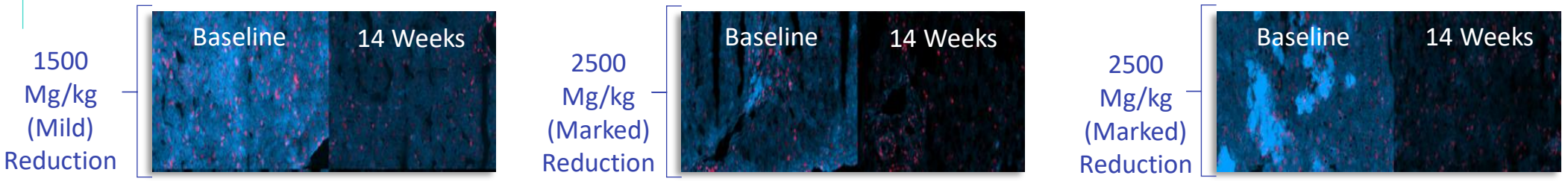
# Trappsol® Cyclo™

## Enables the Effective Transport of Cholesterol Out of Cells




Maetzel et al., 2014

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




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



Maetzel et al., 2014
Source : Study 101

# Expanded Access with Intravenous Hydroxypropyl-β-Cyclodextrin to Treat Children and Young Adults with Niemann-Pick Disease Type C1: A Case Report Analysis

Hastings C, Vieira C, Liu B, Bascon C, Goa C, Wang RY, Casey A, Hrynkow S, Orphanet J Rare Dis 2019

- IV HPβCD has been administered to >20 patients worldwide
  - Acceptable tolerability profile amongst patients treated to date
  - Safety profile enabling physicians to continue treatment >8 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 (communication, focus)
- Clinical experience warrants further investigation of intravenous HPβCD in the management of NPC
  - Treatment of clinical manifestations, systemic and neurologic
  - Halting or slowing the rate of disease progression
  - No added benefit of IT HPβCD (except hearing improvement in our 2 patients!)

# Trappsol® Cyclo™ Summary of Completed Clinical Studies in NPC

## Study 101

Phase 1 study in NPC patients age ≥18 years showed Trappsol® Cyclo™ was well-tolerated with an acceptable safety and tolerability profile, for further testing in phase 3 trial

- 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

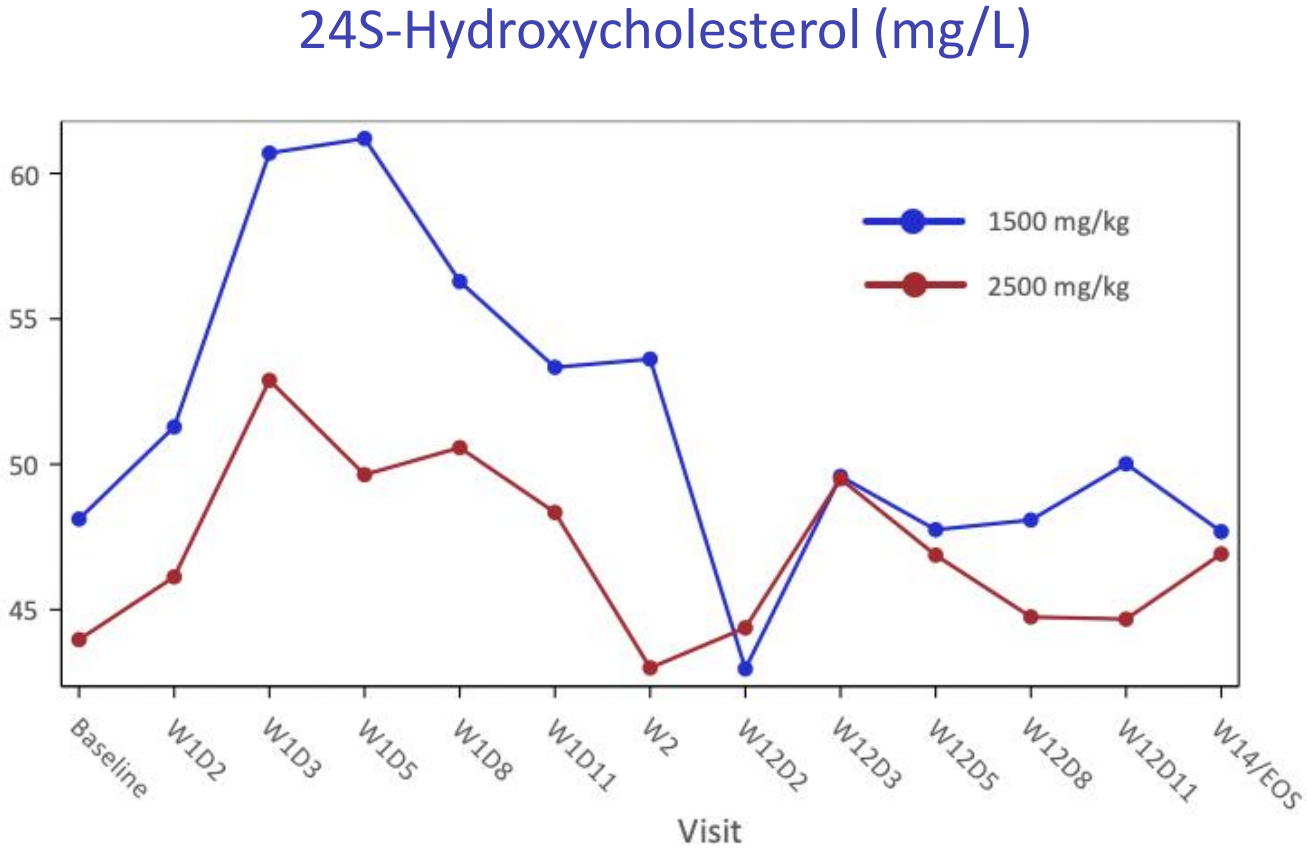
- 100% of patients assessed by treating physicians to be either stable or improved
- 88% (8 of 9 patients who completed the study), experienced clinically meaningful improvements in one or more efficacy endpoints, assessed by the 17 Domain NPC Severity Scale
- Based on totality of data from the Phase 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

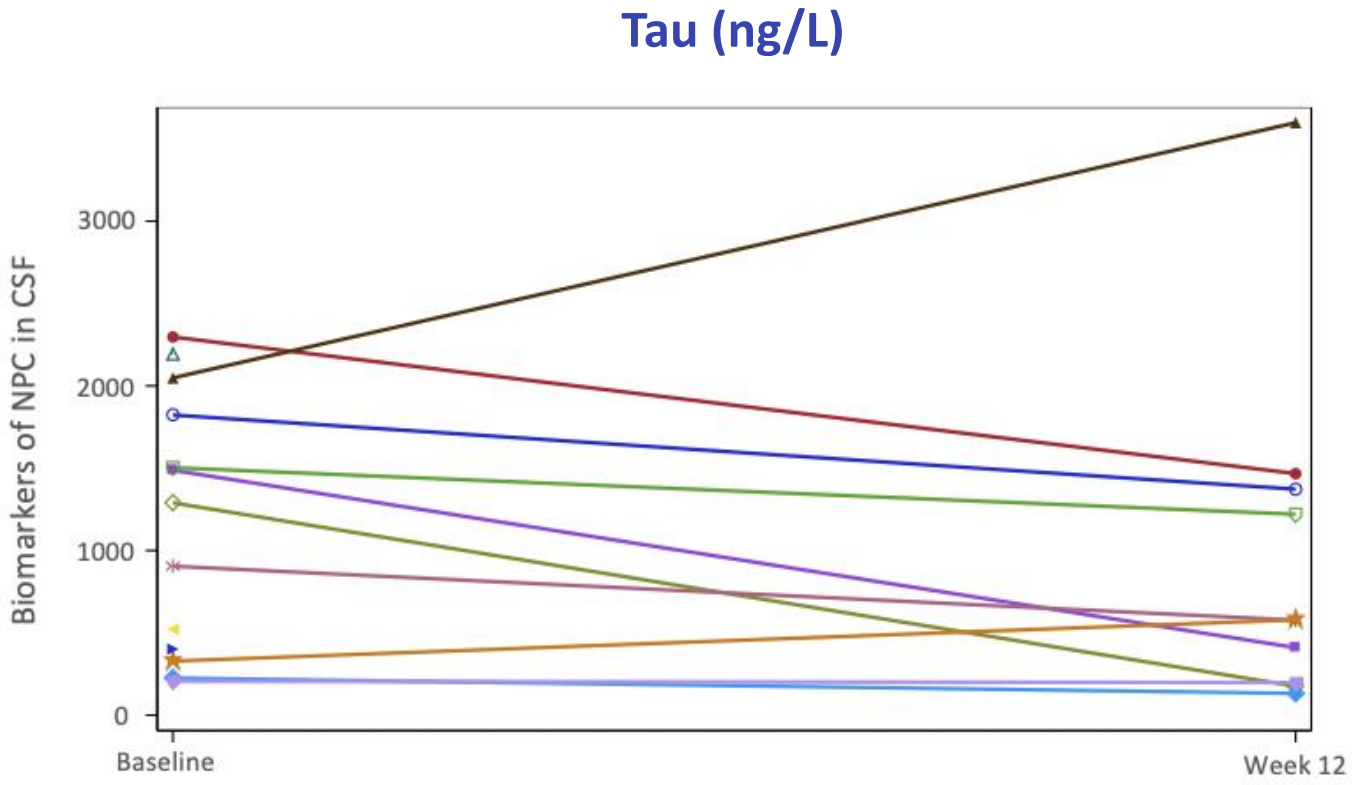
Treatment-Emergent Adverse Events majority mild to moderate in severity, manageable and monitorable and most considered unrelated to Trappsol® Cyclo™

# Increased Serum 24S-Hydroxycholesterol Levels Signals Removal of Excess Cholesterol From the Brain

- 24S-hydroxycholesterol, a cholesterol metabolite from CNS transported across the BBB
- Play a major role in maintaining cholesterol metabolism in the brain
- Evidence that Trappsol® Cyclo™ active in the brain



# IV Trappsol® Cyclo™ Reduces Rate of Apoptosis of Cells in the CNS



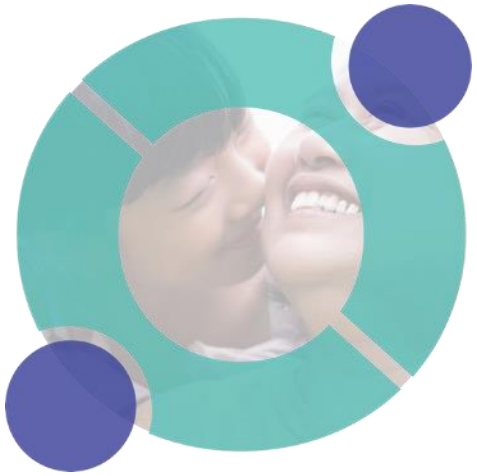

## *Tau: A protein related to onset and disease progression in NPC*

- 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

# Study 201- 9 Patients to Complete Study Met Primary Outcome Measures for Efficacy

- **Efficacy Outcome Measure 1:**
  At least a one-point reduction (or improvement) in two or more of the 17-Domain NPC Clinical Severity Scale measure.
  - 8 of 9 patients met this endpoint (89% of those who completed)
- **17-domain NPC Severity Scoring Tool developed by NIH to measure clinical signs and symptoms in:**
- **9 major domains** – ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, swallowing
- Major domains are scored 0 - 5, with 0 as no disability
- **8 minor domains** – auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, respiratory problems
  - Minor domains add points for severity of condition up to 2 additional points per domain
  - Patients not receiving any intervention beyond Standard of Care would be expected to worsen in total score by
    **1.4 (1) points over one year**



(1) Yanjanin, N et al. , AM J Med Genet B Neuropyshiatr Genet 2010, 153B: 132-140.

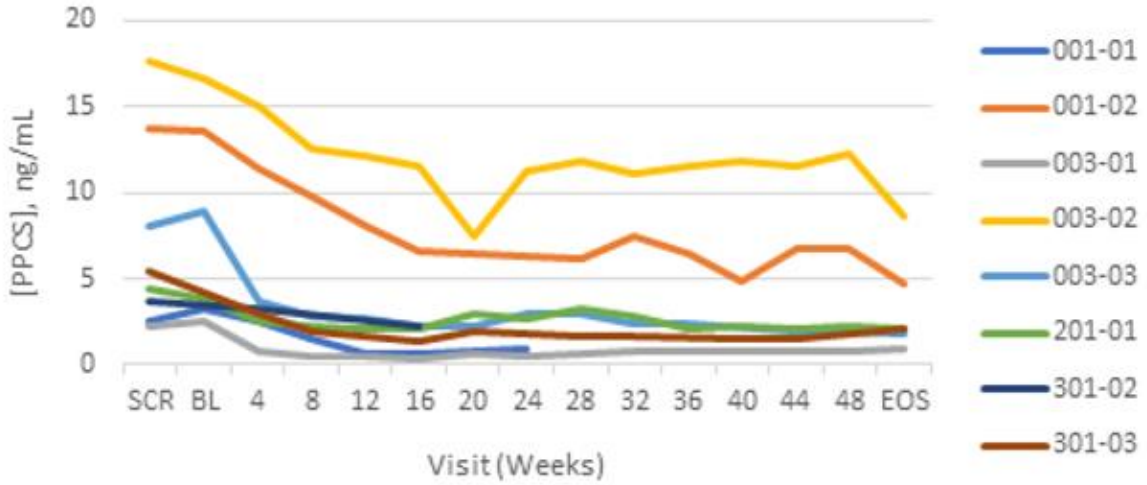
# Efficacy Outcome Measure 1: Domains in which 8 Patients Improved

**Bolded** domains are those which patients and families believe contribute greatest to quality of life

| Pt No. | Improvement in Individual Domains |
|---|---|
| 2 | Eye Movement-1, **Fine Motor Skills-1**, Psychiatric-1 |
| 3 | **Swallow-1**, Seizures-2, Gelastic Cataplexy-1, Incontinence-1 |
| 4 | **Ambulation-1, Swallow-2**, Gelastic Cataplexy-2, Hyperreflexia-1, Narcolepsy-1, Incontinence-1, Behavior-1 |
| 5 | **Ambulation-3, Fine Motor Skills-1** |
| 6 | Eye Movement-1, **Cognition-2** |
| 7 | Eye Movement-1, **Speech-1** |
| 9 | Gelastic Cataplexy -1, Incontinence-1 |
| 11 | Gelastic Cataplexy-1, ABR-1 |

# Treatment with Trappsol® Cyclo™ Results in Rapid and Durable Reduction in LysoSM-509 (PPCS) Paralleled by Improvement in Clinical Signs and Symptoms

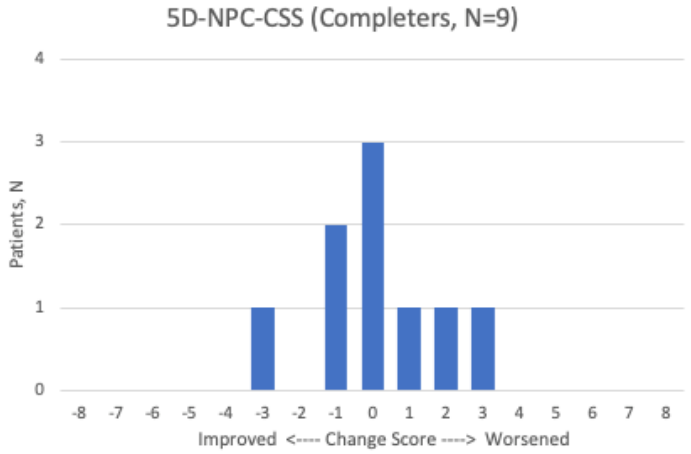
- Diagnostic and Prognostic Biomarker, linked to disease severity
- LysoSM-509 accumulates in plasma in NPC patients
- Trappsol® Cyclo™ reduces the overall burden of lipid accumulation in NPC patients



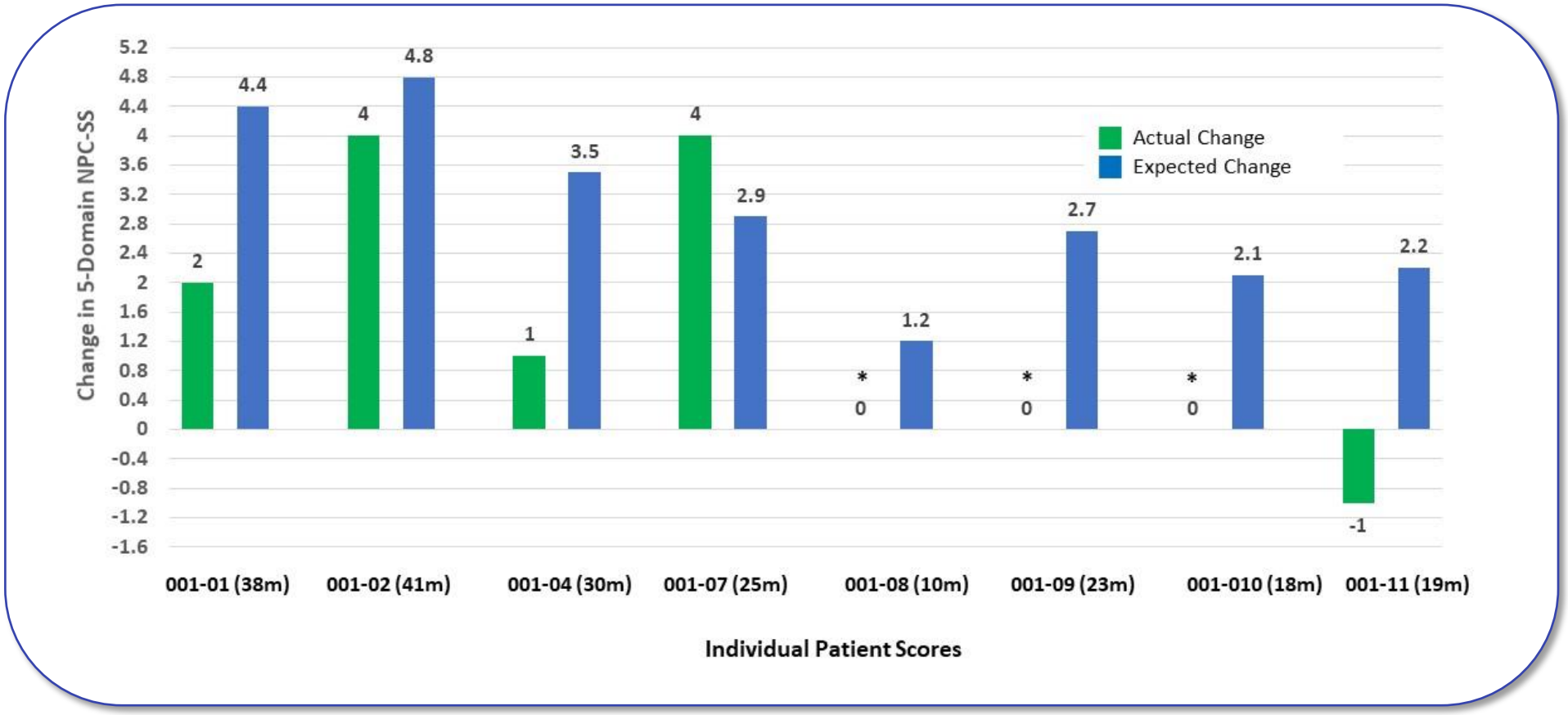

Source: Study CTD-TCNPC-201

## Clinical Signs and Symptoms

- 67% (6/9) of subjects were either improved (33%, 3/9) or stable (33%, 3/9)
- 33% worsened (3/9)
- Stabilization (change score of 0) or slowing of disease progression (change score < 1.4 points/year) is clinically meaningful



# Ongoing Extension Study (102) with Trappsol® Cyclo™ In NPC – Disease Progression Slower than Expected




Eight patients who completed the CTD-TCNPC-101 Phase 1 trial had the opportunity to participate in an extension trial, CTD-TCNPC-102; all enrolled. Green bars are actual change in 5D-NPC-CSS from baseline (at start of Phase 1 trial) through last data point available in extension protocol. Blue bars are expected changes without intervention using 1.4 point change per year after Cortina-Borja et al., 2018.

* = no change observed. Patient 001-09 added miglustat after 1 year with no change to 5-D score or overall disease progression. Mean change in this group overall is 0.4 points per year.

# Long Term Treatment with Trappsol® Cyclo™ IV – Overall Well Tolerated

- The observed safety and tolerability profile consistent across studies and treatment duration, irrespectively of age spectrum and disease severity

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- Treatment-Emergent Adverse Events majority mild to moderate in severity, manageable and monitorable and most considered unrelated to Trappsol Cyclo
- No evidence of any untoward effects of Trappsol Cyclo on core organ systems (cardiovascular, respiratory, renal, hepatic, gastrointestinal systems or CNS)

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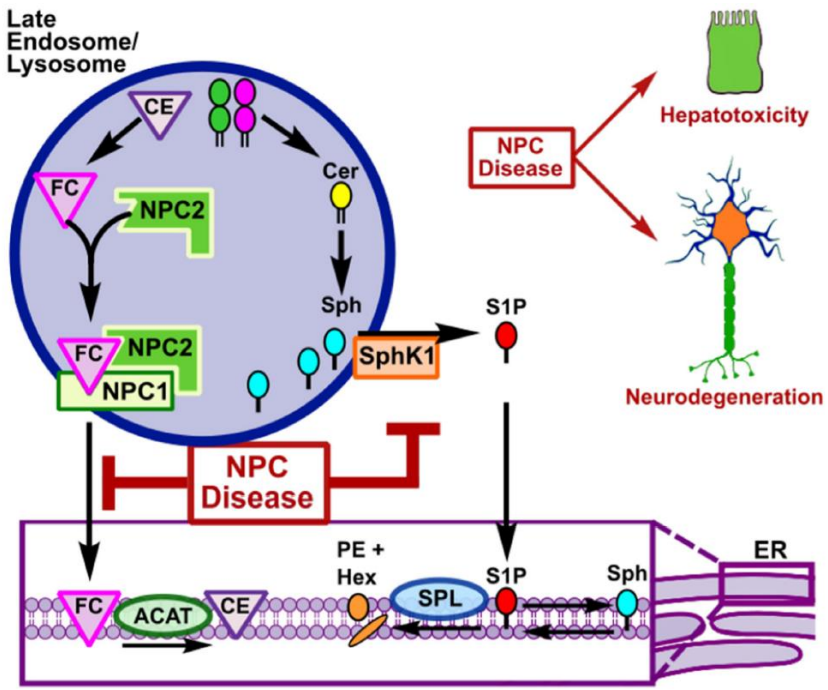
- Hearing loss and infusion reactions (most localized) are adverse events of interest
- Events of hearing loss resolved in most patients, with hearing returning to baseline levels or improved and stabilized while patients continued on study drug
- A degree of hearing impairment remained at the last available auditory assessment in a limited number of patients
- The effect on hearing will continue to be monitored closely in the ongoing studies

# Trappsol® Cyclo™ Targets Primary Pathophysiology of NPC




- Compelling direct and indirect data that Trappsol Cyclo releases accumulated cholesterol from cells in peripheral organs and the CNS and restores cholesterol homeostasis in NPC patients
- The marked reduction in filipin staining in liver cells after treatment with Trappsol Cyclo indicates the clearing of stored cholesterol
- Decrease in the serum level of the cholesterol precursor, lathosterol and an increase in the cholesterol metabolite, 4β-hydroxycholesterol
  - Expected feedback mechanisms when the block in cholesterol trafficking relieved, and more cholesterol becomes available for cell metabolism
- Increased serum levels of the brain-specific cholesterol metabolite, 24S-hydroxycholesterol supports Trappsol Cyclo active in the brain and restores the normal export of cholesterol transport across the blood-brain-barrier

# Niemann-Pick Disease Type C

## Ongoing Pivotal Transport NPC™ Phase 3 Study

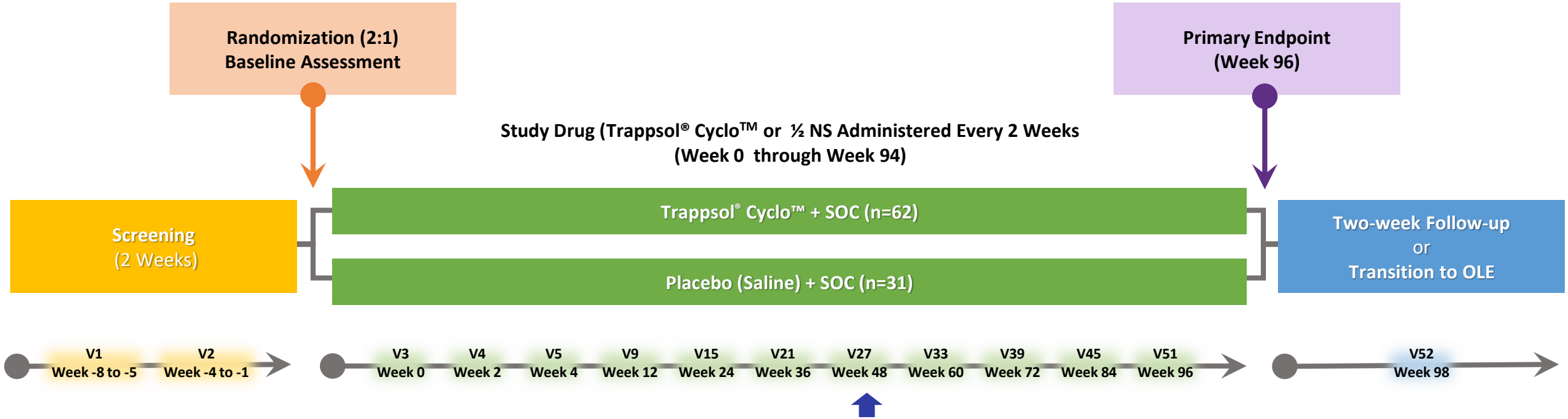
# Transport NPC™ Ongoing Pivotal Phase 3 Study in Niemann-Pick Disease Type C

*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 | Incl. United States, United Kingdom, Italy, Germany, Spain, France, Poland, Israel, Brazil and Australia |
| 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 | |

# Trial Design- Transport NPC

## *Global Randomized, Controlled Phase 3 Pivotal Registration Trial*

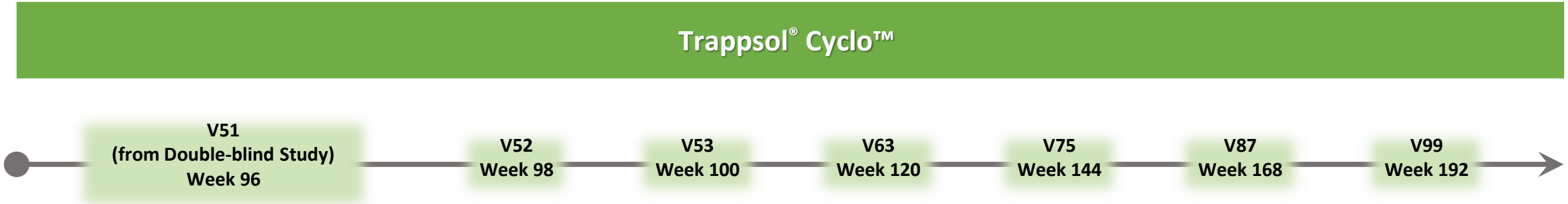



**Study Drug Infusions Following Required Assessments every 2 weeks**

Abbreviations: 1/2 NS= Half-normal Saline (0.45 %) ; n=Number; OLE=Open-label Extension, SOC=Standard of Care; V=Visit

# Open-Label Extension Study -Trial Design

## Trappsol® Cyclo™ Administered Every 2 Weeks (Week 96 through Week 190)




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

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

# Sub-Study in Patients < 3 years of Age-Trial Design, EU and RoW

- Sub-study requested by EMA to evaluate Trappsol® Cyclo™ as a potential preventative treatment and is being conducted ex-US only
- Safety and efficacy results from the sub-study to be analyzed separately form the main study cohort

## Objective

To evaluate the safety, tolerability, and preliminary efficacy of Trappsol® CycloTM.

## Population

Up to 12 subjects <3 years of age with confirmed NPC1, who may be symptomatic or asymptomatic, are eligible to receive open-label Trappsol® CycloTM for up to 4 years

# A Special Thank You

*To all of the patients, families and physicians who support Cyclo Therapeutics, Inc. ongoing clinical trials and who provided their data from compassionate use programs early on, making our trials possible.*