



The logo for Cyclotherapeutics features the word "cyclo" in large, teal, lowercase letters. Each letter contains a different image of people: the 'c' shows a woman in a white dress with arms raised; the 'y' shows a young boy jumping; the 'c' shows a woman in a white top and red pants in a yoga pose; the 'l' shows two children with colorful handprints; the 'o' shows an elderly couple embracing; and the final 'o' shows a woman in a pink shirt jumping. The word "therapeutics" is written in a blue, lowercase, sans-serif font below "cyclo".

# cyclo therapeutics

# Forward-Looking Statements

Some of the information in this presentation relates to future events or future business and financial performance. Such statements constitute forward-looking information within the meaning of the Private Securities Litigation Act of 1995. Such statements can be only predictions and the actual events or results may differ from those discussed due to, among other things, the risks described in the public filings and other publications of Cyclo Therapeutics, Inc. Forward-looking statements are identified by words such as “anticipates”, “projects”, “expects”, “plans”, “intends”, “believes”, “estimates”, “target”, and other similar expressions that indicate trends and future events.

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# Investment Opportunity

Deep expertise with Cyclodextrins with over 10 years of patient exposure

Lead program, Trappsol<sup>®</sup> Cyclo<sup>™</sup> demonstrated to be safe and effective in multiple clinical studies in NPC

Potential to be first targeted therapy for patients with neurodegenerative diseases

Leadership team with proven expertise

Manufacturing at commercial scale inclusive of 60-month stability and 96hr In-use stability

## Currently Targeting 2 Serious Diseases with Unmet Medical Need

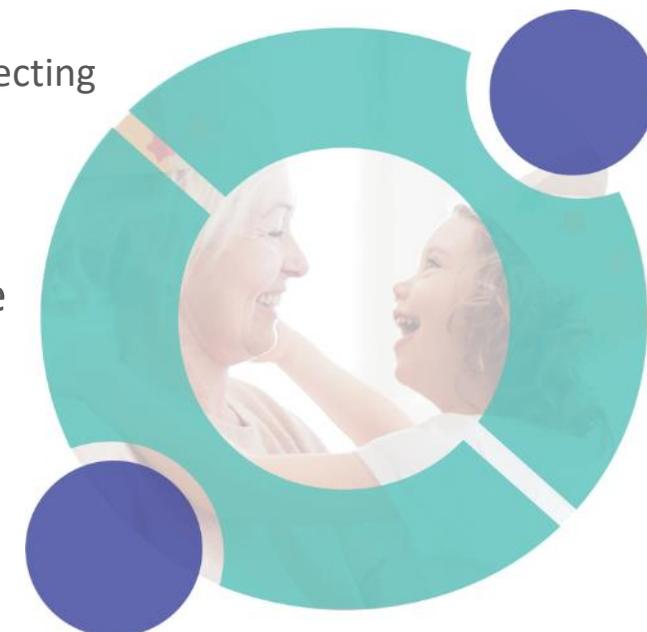
### Niemann Pick Disease Type C

Fatal and progressive genetic disorder  
Orphan indication affecting >9,000 in 80 countries (~400 in U.S. / 320 EU5) <sup>1</sup>

### Alzheimer's Disease

6<sup>th</sup> leading cause of death affecting 5 million people in the U.S.<sup>2</sup>

Platform technology has potential to fuel pipeline expansion opportunities



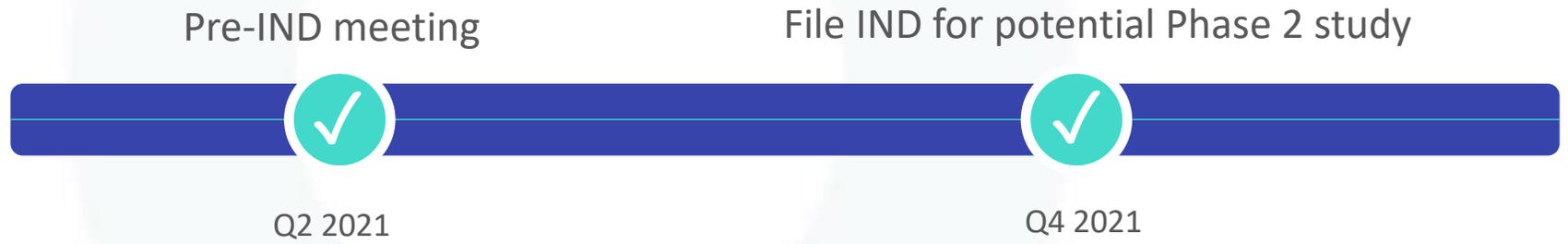
1. April 2021, Tessellon Inc. (former Kantar Health experts with 25+ years of epidemiology and forecasting experience), ([www.Tessellon.com](http://www.Tessellon.com)); Exhaustive literature search with a broad range of MESH terms in United States + 79 other countries.  
2. <https://www.alz.org/alzheimers-dementia/facts-figures>

# Pipeline Milestones Achievements

Niemann-Pick Disease Type C



Alzheimer's Disease



**Niemann-Pick Disease Type C Regulatory Highlights**

Orphan Drug Designation in U.S. | Fast Track Status in U.S. | Potential for Priority Review Voucher (PRV) in U.S

Rare Pediatric Disease Designation | Orphan Designation in EU | EMA Pediatric Investigational Plan Adopted

# Leadership Team with Proven Experience



**N. Scott Fine**  
Chief Executive Officer & Director



**Joshua M. Fine**  
Chief Financial Officer



**Lise Lund Kjems, MD, PhD**  
Chief Medical Officer



**Michael Lisjak**  
Chief Regulatory Officer



**Sharon H. Hrynkow, Ph.D.**  
Chief Scientific Officer



**Russ Belden**  
Acting Chief Commercial Officer



**Jeffrey L. Tate, Ph.D.**  
Chief Operating Officer, Chief Quality Officer & Director



**Lori McKenna Gorski**  
Global Head of Patient Advocacy



# NPC: A Debilitating Disease with Fatal Outcomes

## Incidences

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

## Existing Cases

>9,000 in 80 countries  
(~400 in U.S. / 320 EU5)

## Of Diagnosed Patients

~ 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

\*Scope: United States + 79 other countries; \*Commissioned Tessellon Inc – former Kantar Health experts with 25+ years of epidemiology and forecasting experience, ([www.Tessellon.com](http://www.Tessellon.com)); \*Exhaustive literature search with a broad range of MESH terms.

# Niemann-Pick Disease Type C (NPC)

- Rare, fatal and progressive genetic disorder
- Characterized by a defect in the NPC1 protein
- Cholesterol and lipids accumulate in cells of major organs and tissues
- Leading to cell and tissue dysfunction

## Average Life Expectancy:

Before age 5 if symptoms appear in infancy

Age 20 in juvenile onset

Increasing diagnosis in later onset disease

No U.S. Approved NPC Therapies

Only 1 EU Approved Therapy  
with no systemic effects

Symptomology Inclusive of Systemic  
and Neurological Manifestations

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

# The Distinguished Dual Action of Trappsol® Cyclo™ Supports the Scientific Rationale for NPC

Trappsol® Cyclo™ : formulation of hydroxypropyl-beta-cyclodextrin (HPBCD) with an affinity for cholesterol

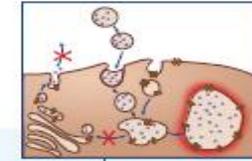
Allows the drug to reach major peripheral organs; clearing cholesterol from cells **peripherally**

... and **centrally**, affects CNS biomarkers and underpins neurologic outcomes supported by data from our clinical studies in NPC

## Neurological Disease Impact

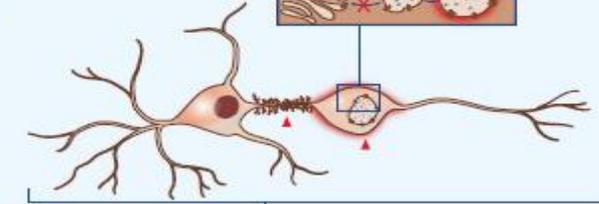
### Cellular pathology

Impaired intracellular transport and accumulation of sphingolipids and cholesterol



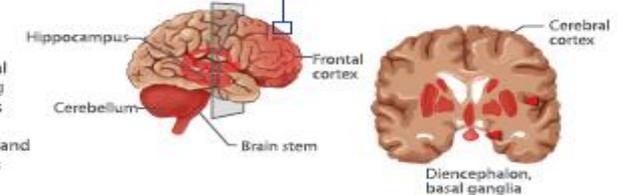
### Neuronal damage

Atypical neural dendrites  
Meganeurites  
Neuronal cell death



### Brain substance changes

Various morphological brain changes affecting multiple brain regions  
E.g. reduction of grey and white matter volumes



### Neurological symptoms

Multi-symptomatic and complex clinical picture involving various body functions  
Developmental delay



### Psychiatric manifestations

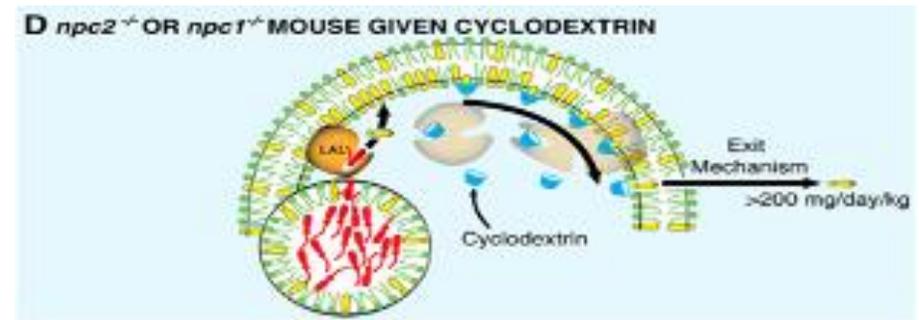
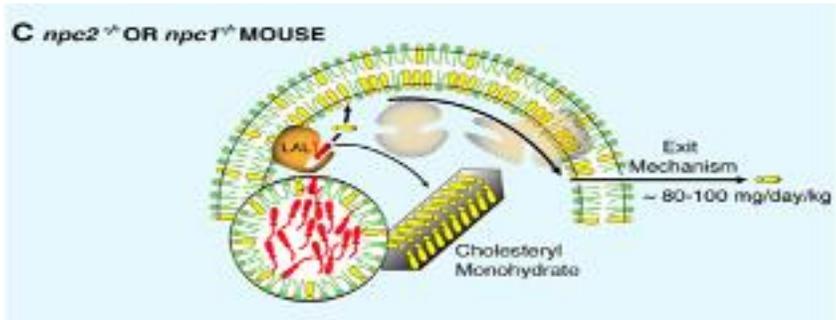
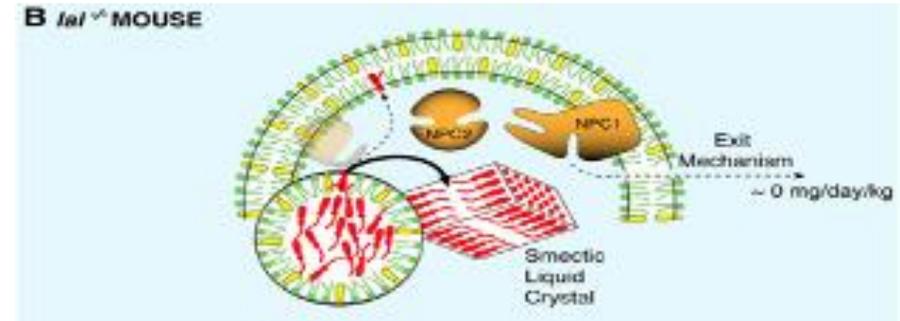
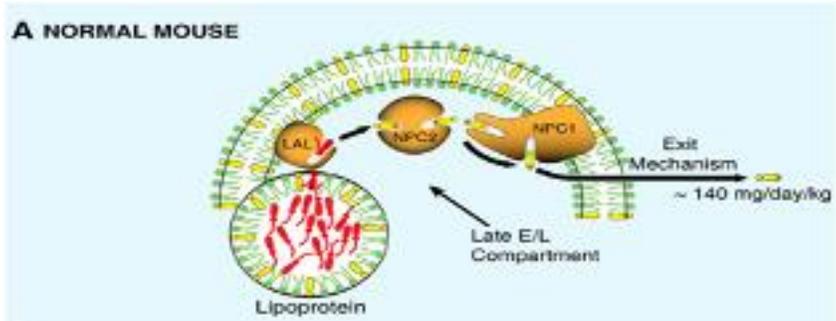
Cognitive impairment  
Atypical or early-onset schizophrenia  
Mood disorders



### Premature death

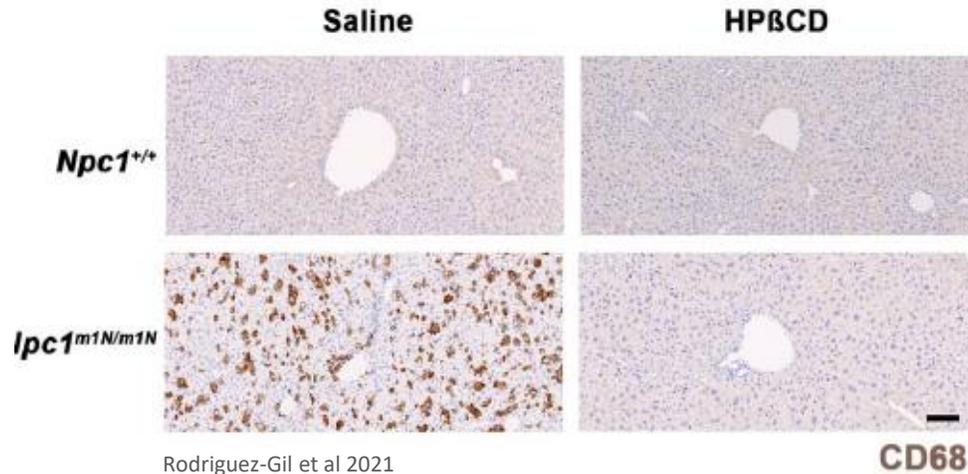
Aspiration pneumonia following impaired swallowing = most common cause of death in NP-C

# Trappsol<sup>®</sup> Cyclo<sup>™</sup>: Mechanism of Action



Ramirez et al., 2011

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



To Man - Direct Evidence of Release of Sterols from the Liver  
Data from Trappsol<sup>®</sup> Cyclo<sup>™</sup> Treated NPC patients

## 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

Source : Study 101

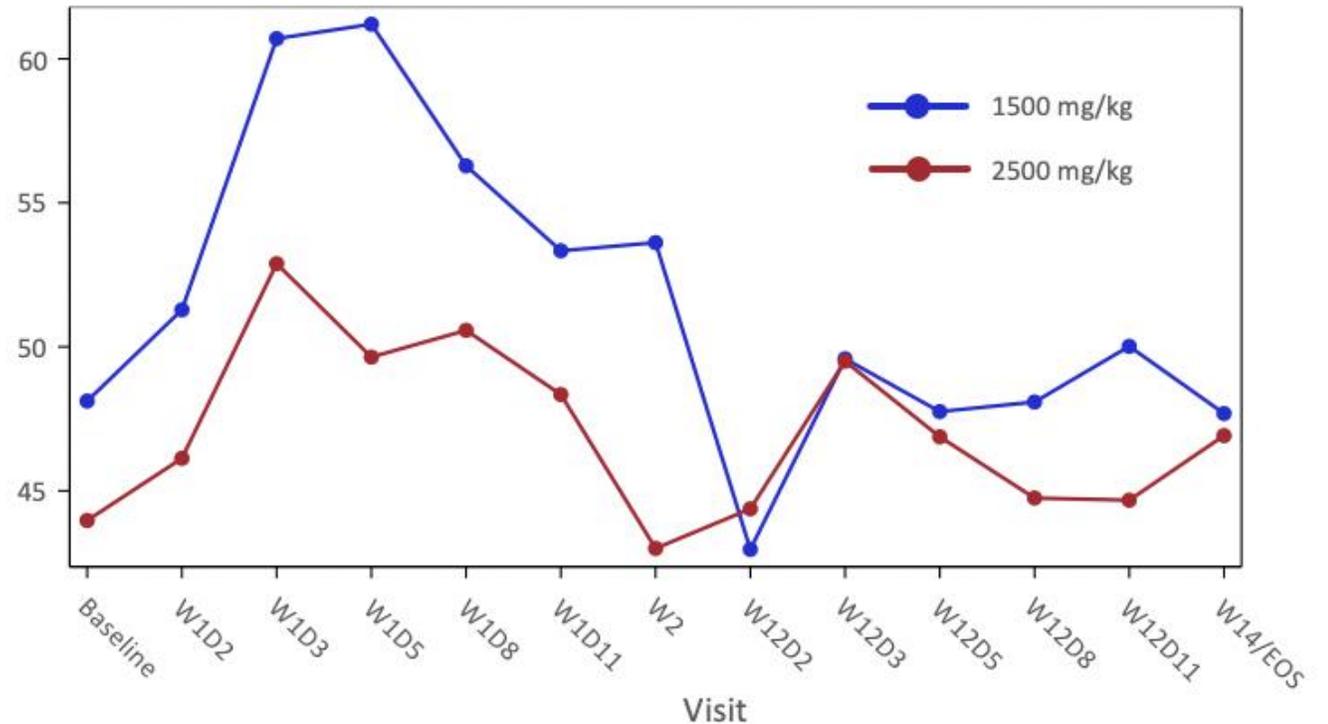
# Increased Serum 24S-Hydroxycholesterol Levels Signals Removal of Excess Cholesterol From the Brain

**24S-hydroxycholesterol**, a cholesterol metabolite from CNS transported across the BBB

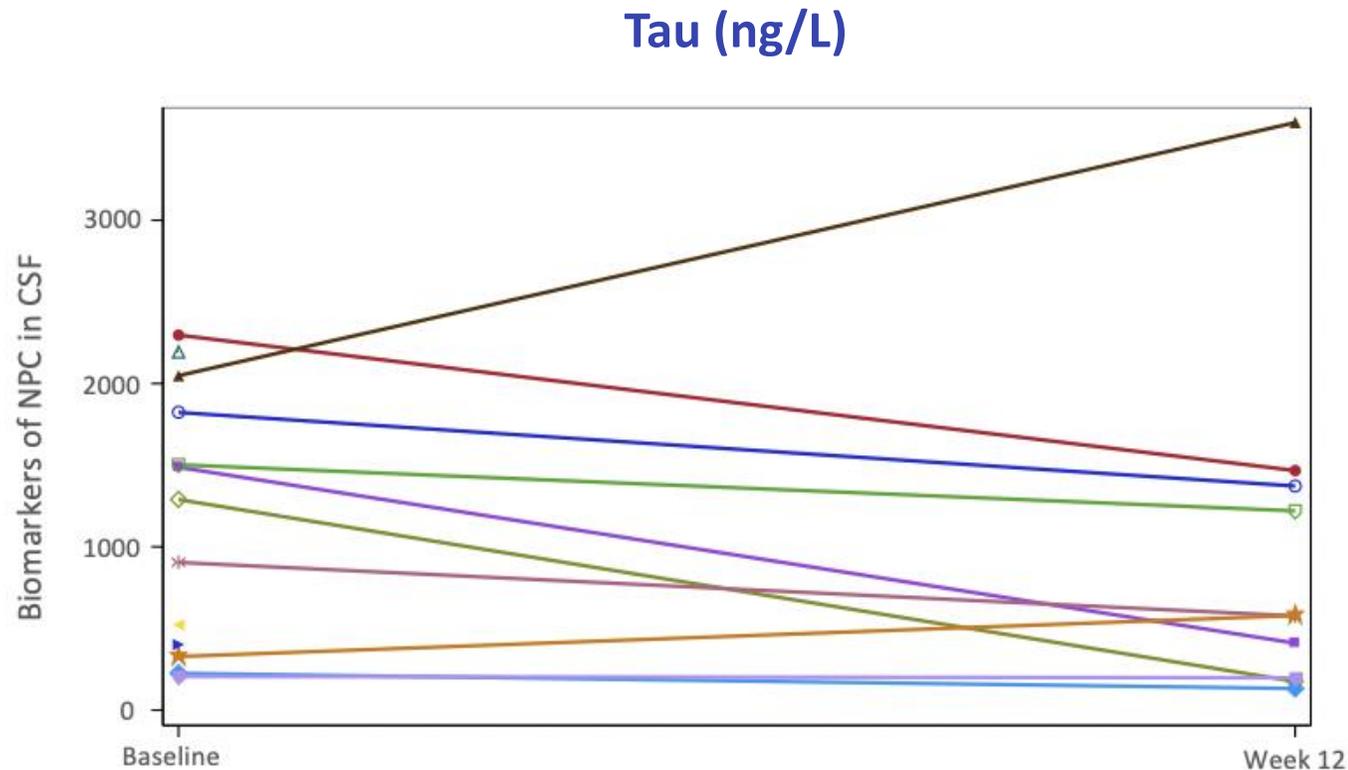
Play a major role in maintaining cholesterol metabolism in the brain

Evidence that Trappsol<sup>®</sup> Cyclo<sup>™</sup> active in the brain

24S-Hydroxycholesterol (mg/L)



# 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

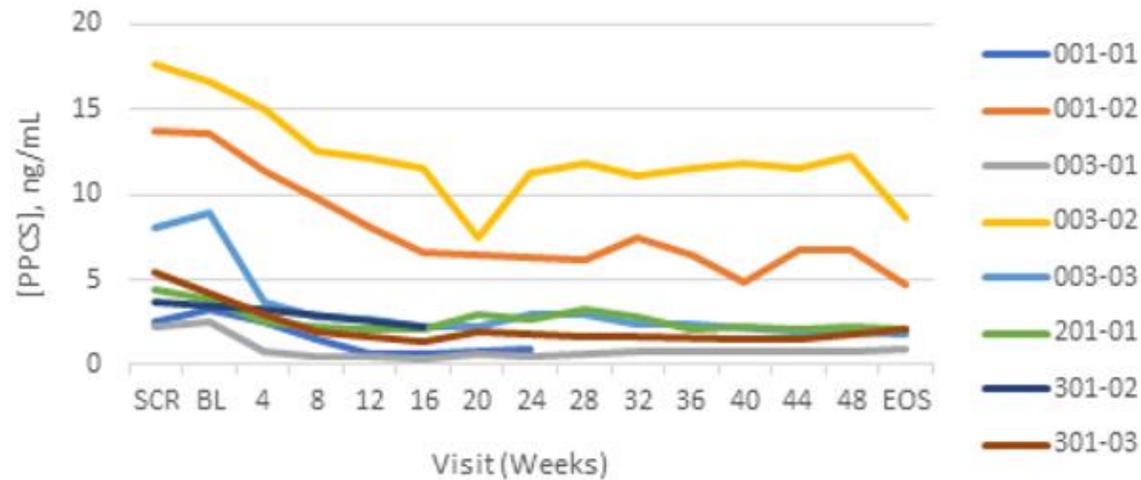
Suggestive of a neuroprotective benefit in CNS

# 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



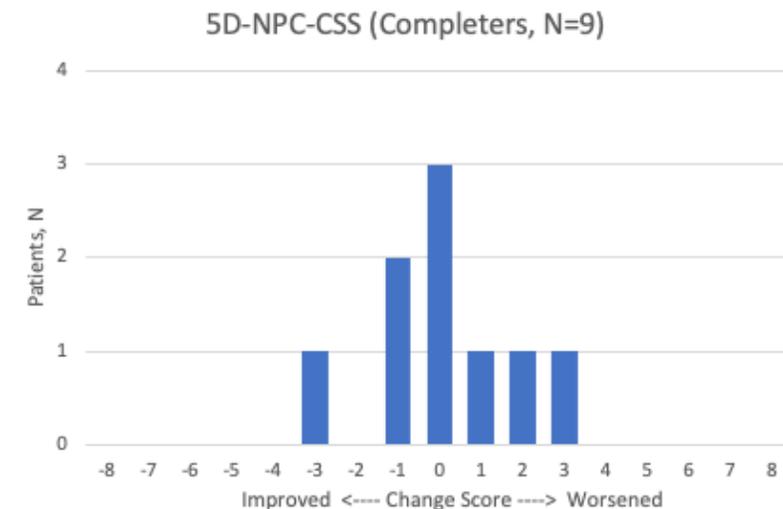
Source: Study CTD-TCNPC-201

## Clinical Signs and Symptoms

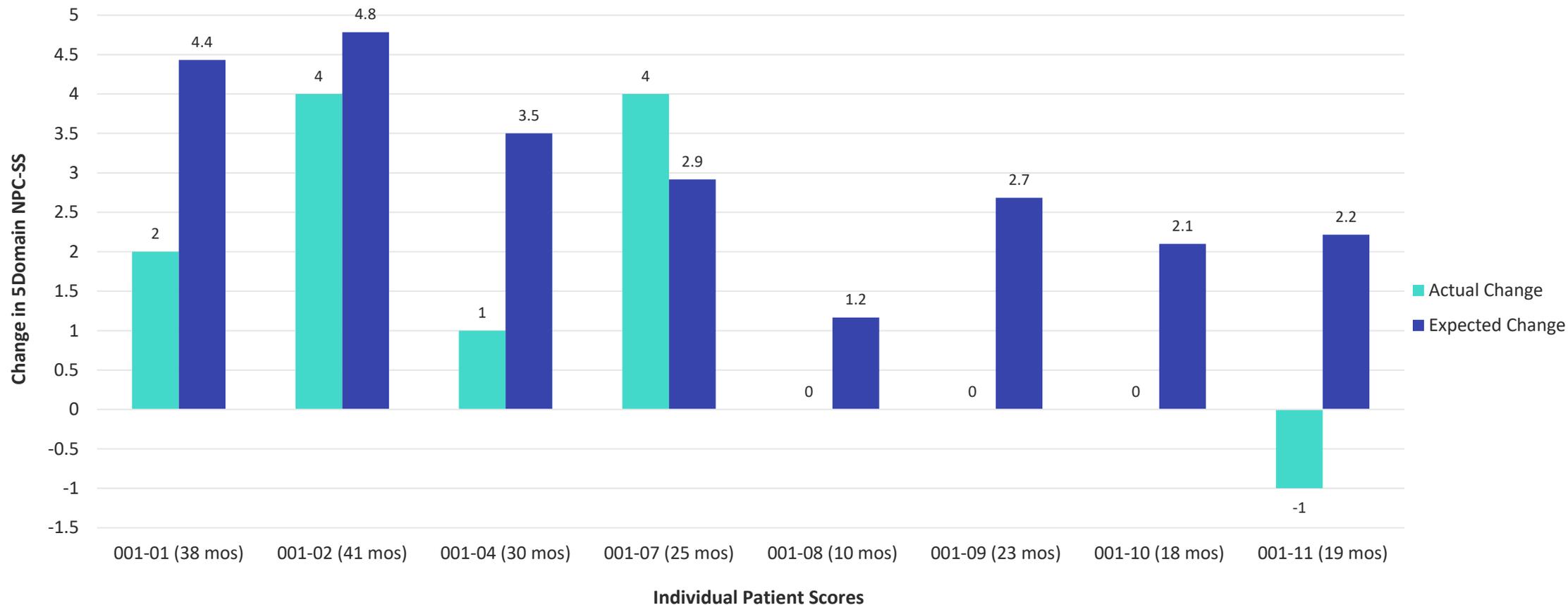
67% (6/9) of subjects either improved (33%, 3/9) or stabilized (33%, 3/9)

33% worsened (3/9)

Stabilization (change score of 0) or slowing of disease progression (change score < 1.4 points/year) is clinically meaningful



# Long-Term Treatment with Trappsol® Cyclo™: Disease Progression Slower than Expected



Clinical Outcomes assessed by the 5-Domain NPC Severity Scale, a disease specific scale

# Clinical Treatment Benefits Observed in Completed Phase 1/2 Study in Pediatric and Adult Patients with NPC

A 48 Week Phase 1/2 Study:

Double-blind, Randomized, Uncontrolled Trial Evaluating the Safety, Tolerability, PK and Efficacy of 3 Doses of Trappsol<sup>®</sup> Cyclo<sup>™</sup> IV Administered Every 2 Weeks

Number of Subjects	12 (2-34 years)
Completed	9 Subjects, 3 discontinuing early for reasons not related to study drug
Duration	96-week trial, with Interim Analysis at 48 weeks
Dose	1500, 2000, or 2500 mg/kg

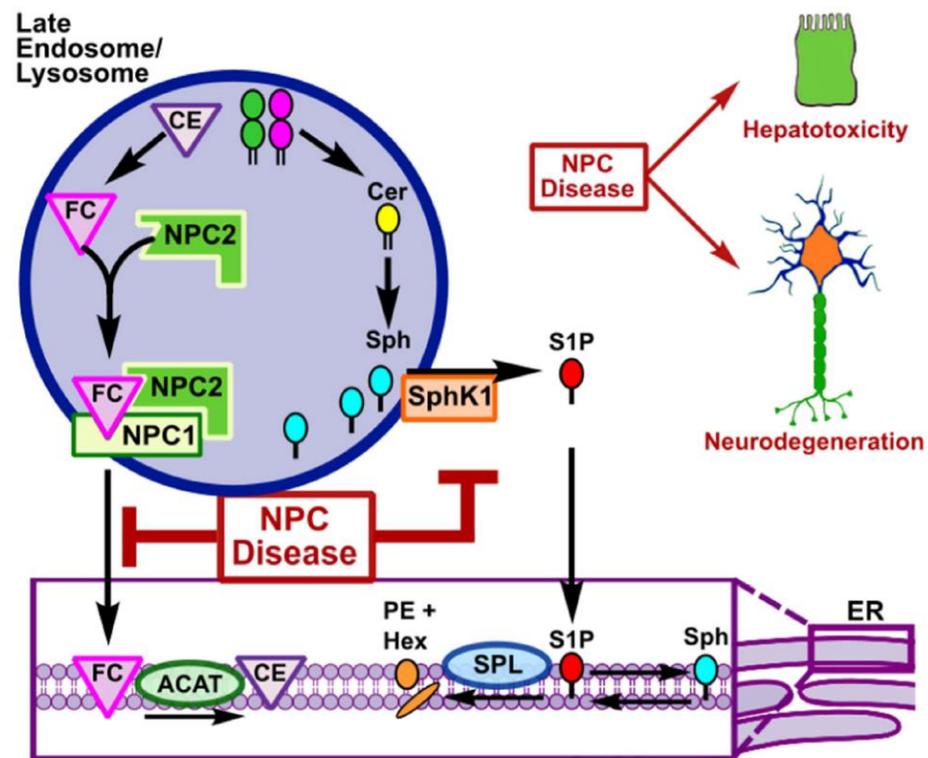
## Predictable PK-PD Profile | Clinically Meaningful Treatment Benefits

8 (88%) of 9 completers met the primary efficacy outcome measure of a  $\geq 1$  point improvement in  $\geq 2$  domains of the 17-domain NPC-CSS

All 9 completers assessed as stable or improved in disease presentation by treating investigator

Acceptable and Consistent Safety and Tolerability Profile

# Trappsol® Cyclo™ Targets Primary Pathophysiology of NPC



Compelling direct and indirect 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, 4 $\beta$ -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

# Long Term Treatment with Trappsol<sup>®</sup> Cyclo<sup>™</sup> 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<sup>®</sup> Cyclo<sup>™</sup>

No evidence of any untoward effects of Trappsol<sup>®</sup> Cyclo<sup>™</sup> on core organ systems (cardiovascular, respiratory, renal, hepatic, gastrointestinal systems or CNS)

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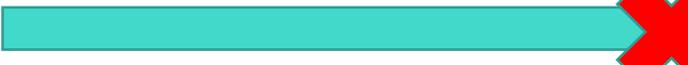
Hearing loss and infusion reactions (most localized) are adverse events of interest

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

# Significant Competitive Advantages

Company	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Potential Indication (Systemic and Neurological)	Safety Profile	Summary
 cyclo therapeutics	Trappsol® Cyclo™ (Intravenous every 2 weeks, Home infusions)							Met all primary endpoints of the Ph1 and Ph1/2 showing favorable safety and efficacy. Ph3 currently enrolling and additional site activation ongoing.
 ACTELION	Zavesca* (Oral 3 times daily)							FDA: Data did not support benefit risk. Off-label in US. EMA: Approved January 2009.
ORPHA  ZYME	Arimoclomol (Oral 3 times daily)							FDA: CRL received June 18, 2021, noting additional data required to support benefit risk. EMA: CHMP Opinion and potential MAA anticipated Q1 2022 as Adjunct Therapy.
 IntraBio	IB1001 (Oral 3 times daily)							Met with FDA, EMA and UK, Phase 3 study required, 6-month placebo-controlled crossover trial with approximately 50 patients (4 years of age and above). Study enrollment anticipated H1 2022.
 Mandos Health	Adrabetadex (VTS-270) (Intrathecal every 2 weeks)							MNK concluded program 20-Jan-2021 noting the benefit risk is negative. Mandos received Court Approval to buy from MNK 29-Jun-2021. FDA has not found drug to be safe and effective for use to treat NPC1 or for any other use.
 ESCAPE BIO	ESB1609 (Oral, brain-penetrant)					TBD	TBD	Selective sphingosine-1-phosphate 5 (S1P5) receptor agonist.

# Trappsol<sup>®</sup> Cyclo<sup>™</sup> Summary in Clinical Studies in Patients with NPC

## Study 101

Phase 1 study in NPC patients age 18 years and older showed Trappsol<sup>®</sup> Cyclo<sup>™</sup> to well-tolerated with an acceptable safety and tolerability profile

After IV infusion, the drug 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

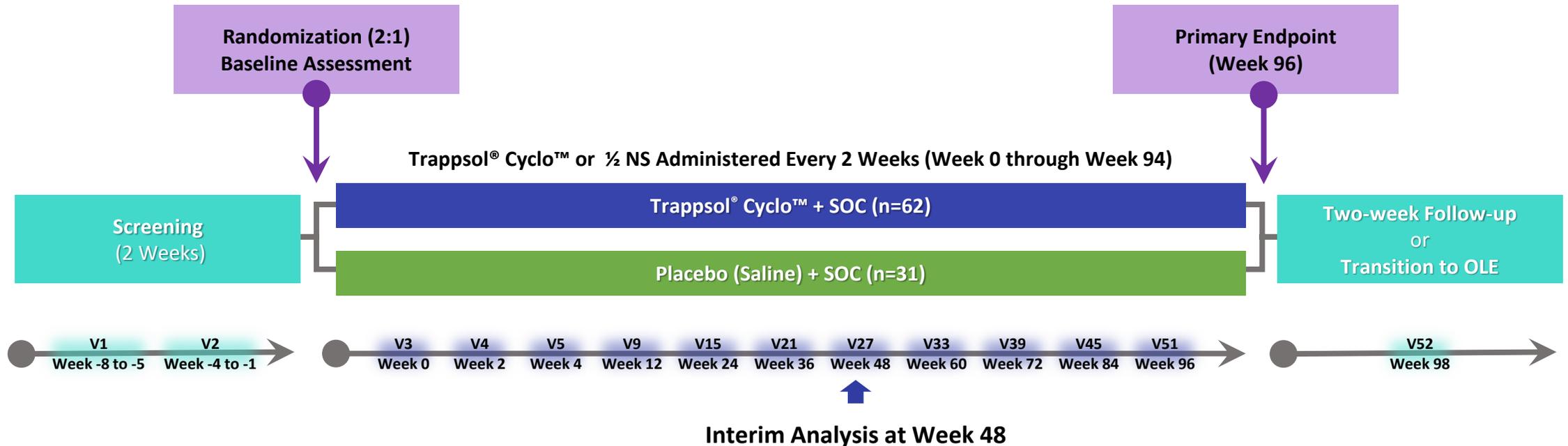
Based on totality of data from the Phase 1 and Phase 2 studies, the 2000 mg/kg dose was selected for the Phase 3 study

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 United States, United Kingdom, Italy, Germany, Spain, France, Poland, Israel, 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

# TransportNPC<sup>TM</sup> Trial Design

## Global Randomized, Controlled Phase 3 Pivotal Registration Trial



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

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

# Key Design Features of Core Study **TransportNPC**<sup>TM</sup>

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

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

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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.
- 

EMA PDCO feedback stated Trappsol<sup>®</sup> Cyclo<sup>TM</sup> has potential as a preventative

## **Rescue Criterion:**

Subjects who experience a substantial clinical decline ( $\geq 2$  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.

# Patient Progress: A Case Study

## 61-year-old patient with NPC: Improvements with intravenous (IV) Trappsol<sup>®</sup> Cyclo<sup>™</sup> over 15 months

Diagnosed at age 59 years: slurred speech, ataxia, vertical gaze palsy, mild dysmetria/dystonia, mild hearing loss, mild short term memory loss with intact cognition, cough with eating

Completed Phase 1 trial and received 7 infusions IV Trappsol<sup>®</sup> Cyclo<sup>™</sup>; no toxicities

Currently enrolled on extension protocol and receives IV Trappsol<sup>®</sup> Cyclo<sup>™</sup>, 1500 mg/kg every 2 weeks at home

Patient and spouse see notable improvements in speech and swallow, seen within hours of the infusion and maintained for 5-10 days

- Increased speech fluency and word finding, more comfortable to communicate, more interactive and happy, positive impact on quality of life
- Takes solids and un-thickened liquids without cough; rare cough on saliva every few weeks
- Clinical severity score improved by 1 point due to change in cough; scale for speech does not include changes in speech fluency/word finding
- Cognition remains stable



# Alzheimer's Disease

## The Most Common Form of Dementia

An irreversible, progressive neurologic disorder that slowly degrades memory, thinking and social skills that affects a person's ability to function independently.

### Similarities with NPC

Cognitive decline

Elevated levels of tau

Amyloid plaques

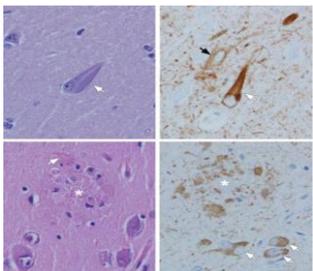


- Affects more than 5 million people in the U.S.<sup>1</sup>
- 6th leading cause of death in the U.S.<sup>1</sup>
- 500,000 new cases every year<sup>2</sup>
- 13.8 million cases projected by 2050<sup>1</sup>

# Commonality Across Target Neurodegenerative Diseases

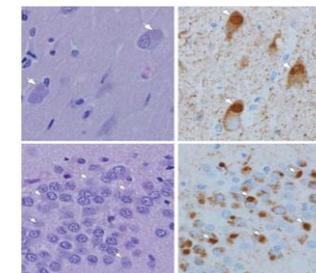
## Alzheimer's Disease

### Secondary Tauopathy



## Niemann-Pick Disease Type C

### Primary Tauopathy



### Biologic Similarities

Cholesterol Accumulation in Regions of Brain

Elevated Levels of Tau in CSF

Amyloid Plaques in the Brain

### Disease Manifestation

Cognitive decline / dementia

Premature death

Clumsiness

Progressive motor symptoms

Ataxia, dystonia, dysarthria, dysphasia

Psychiatric signs: psychosis, depression

Weight loss

### Disease Manifestation

Progressive cognitive decline/early dementia

Premature death

Clumsiness, gait disturbance

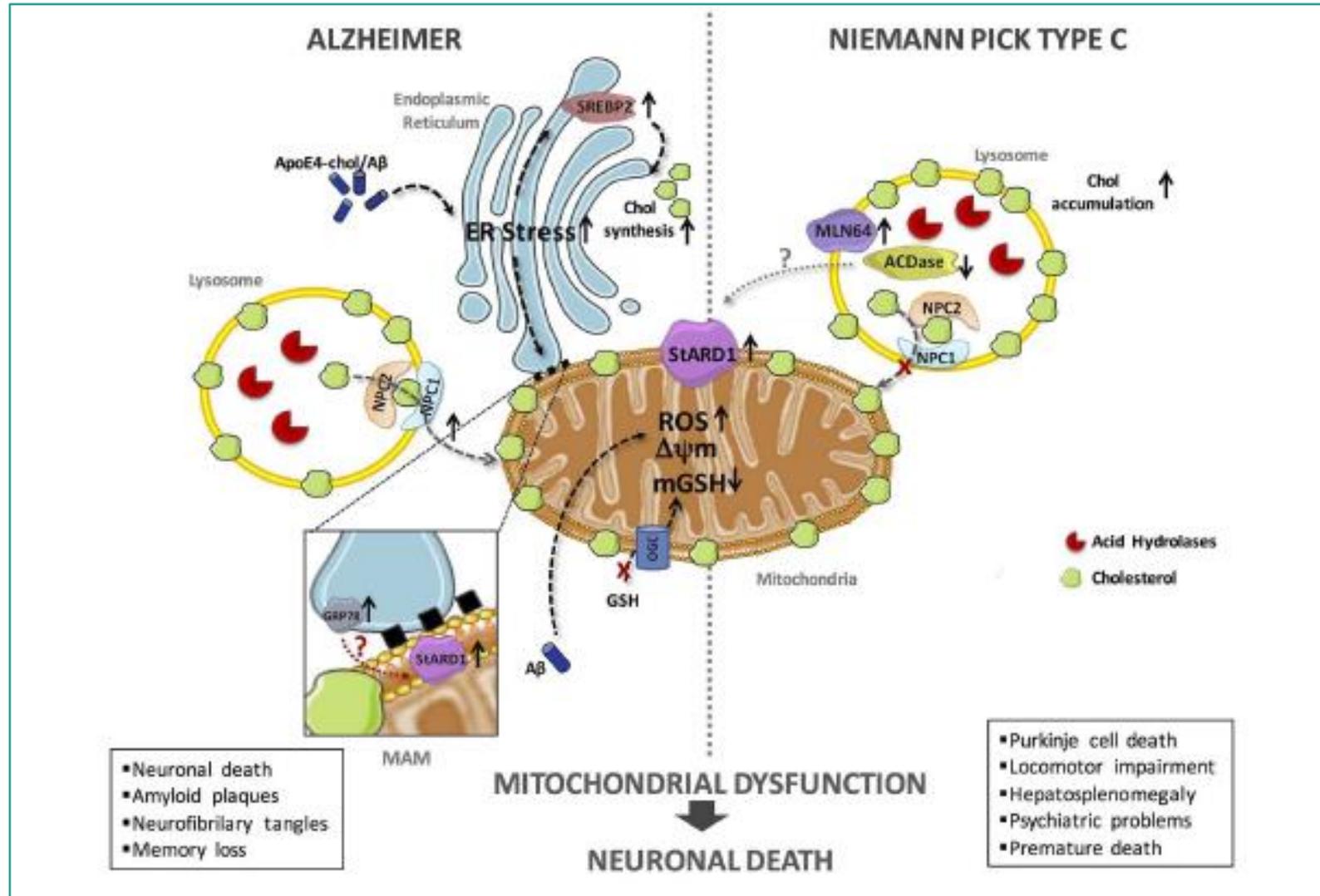
Delayed motor milestones

Progressive: ataxia, dystonia

Seizures

Weight loss

# Trappsol® Cyclo™: Targeting Disease Pathway of Two Debilitating Neurodegenerative Diseases



# Trappsol® Cyclo™ for the Potential Treatment of Alzheimer's Disease Targeting Reduction of Amyloid Beta and Tau

Filed IND November 2021

Preeminent Neuroscientist and World-Renowned Researcher,  
Cynthia A. Lemere, PhD Senior Advisor for Advancement of Alzheimer's Disease Asset

## Positive Results in Alzheimer Patient Under Compassionate Use Program

FDA authorized use of Trappsol® Cyclo™  
in geriatric patient

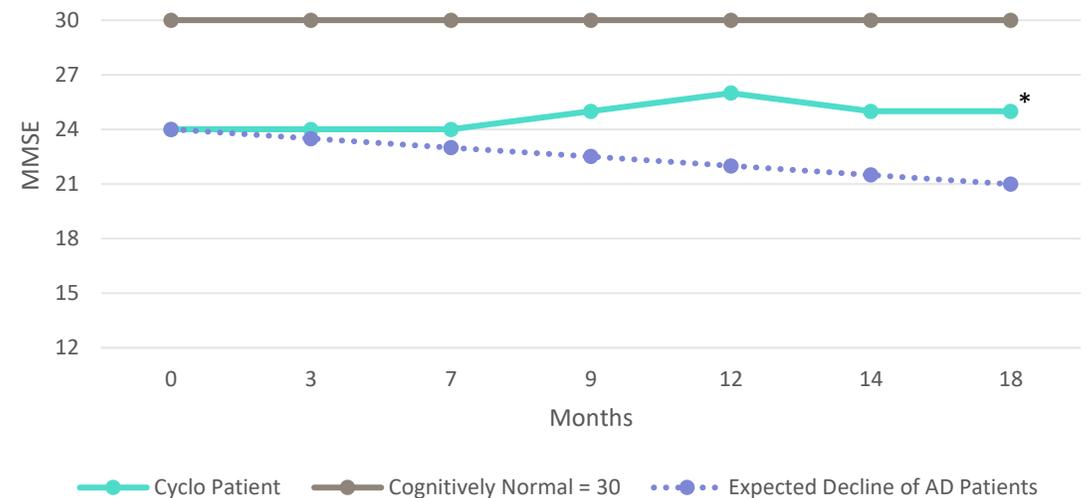
18 months of monthly IV infusion

Disease did not progress

Family reported less volatility and greater word-  
finding ability

18 months of data has led to development  
of Phase 2 protocol

### Alzheimer's Mini-Mental State Evaluation Performance<sup>1</sup>



*"The patient has shown cognitive and neurologic stability in serial examinations during this study that indicates possible benefit as there would be an expected measurable cognitive and functional decline over an 18-month period in persons with Alzheimer's disease dementia,"* Treating Physician

\*Treating physician reported the 18-month score as a range between 24-26

1: Rate of MMSE decline in AD patients: Eldholm, RS et al, J. Alz. Disease, 61: 1221, 2018. Suh, GH et al., Intl. J. Geriatric Psychiatry, 19(9): 817, 2004.

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Sharon H. Hrynkow, Ph.D.

Co-Chair

Neuroscientist with more than 25 years' experience in global health arena, public and private sectors. Senior executive at NIH. First president of non-profit Global Virus Network. Former Member of President's Council of Advisors on Science and Technology. 5 years at Cyclo Therapeutics leading clinical and scientific programs.



Benny Liu, M.D.

Key Opinion Leader in Niemann-Pick Disease Type C

Gastroenterologist at Alameda Healthy System, CA and Highland Hospital. Globally recognized expert in lipid metabolism. First to discover that cyclodextrins release cholesterol from cells using an animal model. Assistant Clinical Professor, UCSF.



Caroline Hastings, M.D.

Key Opinion Leader in Niemann-Pick Disease Type C

Pediatric hematologist oncologist, Director of NeuroOncology, and Professor of Pediatrics, UCSF Benioff Children's Hospital Oakland. First physician in US to use cyclodextrins for treatment in NPC, compassionate use. Advisor to US and Australian NPC Advocacy organizations and to physicians globally on NPC.



Gerald F. Cox, M.D., Ph.D.

Internationally Renowned for Clinical Drug Development

Seasoned biotechnology executive with 20-year successful track record of drug development for rare genetic diseases and extensive worldwide regulatory experience



# Investment Summary

Leveraging over 3 decades of experience with cyclodextrins to advance clinically de-risked programs towards approval in diseases with unmet medical need

Lead asset demonstrated to be safe and effective with over 10 years of patient exposure

## TransportNPC™

Site activation ongoing and currently enrolling patients in Pivotal Phase 3 study in Niemann-Pick Disease Type C

Significant market opportunity with no approved therapy to treat both systemic and neurological manifestations of NPC

Planning and executing pre-approval commercialization imperatives

Pipeline expansion into Alzheimer's Disease (AD), patent pending

Filed IND November 2021



Multiple value-driving milestones expected

Platform technology with opportunity to expand into multiple indications

Leadership team with proven track-record in execution and value creation

NASDAQ: CYTH  
cyclotherapeutics.com



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*Thank you!*