Update on CTD's Clinical Trials using Trappsol® Cyclo™ by Intravenous Administration in NPC Patients

NPUK 2019 Annual Family Conference
Wyboston, United Kingdom
Saturday, September 21, 2019

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CTD Holdings, Inc.

OTCQB: CTDH

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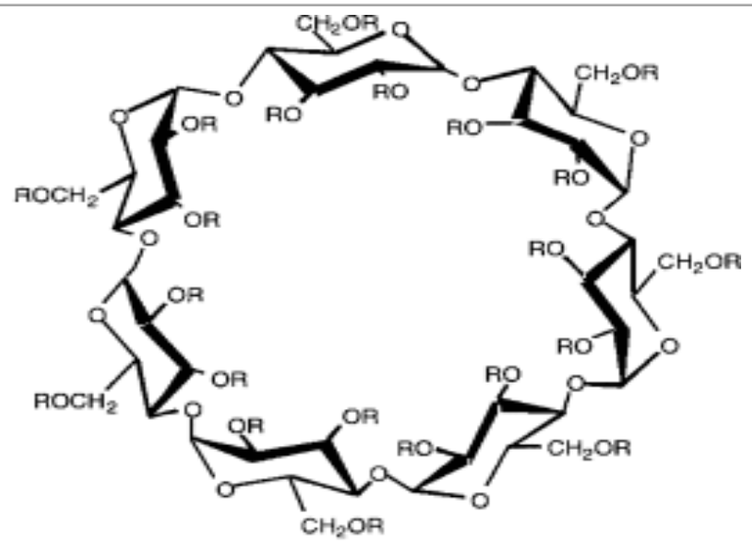
More on CTD's Trappsol® Cyclo™



β-Cyclodextrin, R=H
HPβCD, R=$OCH_2CH(CH_3)OH$ or H

This schematic represents interaction of cylinder shaped cyclodextrins and cholesterol in a 1:1 or 1:2 ratio

Figure is courtesy of David Begley, Kings College

- Trappsol ® Cyclo ™ is CTD's proprietary formulation of hydroxypropyl betacyclodextrin.
- HPβCD = 7 glucose molecules in a ring, modified by adding propyl groups, to enhance solubility. The inner core of HPBCDs can make complexes with cholesterol and other molecules.
- HPβCDs widely used as excipient in products including Sporanox (broad-spectrum anti-fungal), eye drops, and mouthwash.
- Ground-breaking work first in the NPC mouse model showed that HPβCDs given subcutaneously could prolong life, clear cholesterol from liver and brain, and delay onset of NPC symptoms, including neurologic symptoms (B. Liu et al).

Trappsol® Cyclo™ Phase I Study to Evaluate Safety and Impact On Biomarkers of NPC Disease

United States

Randomization 6:6 Between Dose Groups

Trappsol® Cyclo™: Bi-weekly 8 hour intravenous treatment for a period of 14 weeks

RANDOMIZE (N=12)

Dose Group 1	Dose Group 2
1500 mg/kg	**2500 mg/kg**

Primary Endpoint	• Plasma levels of Trappsol® Cyclo™
Secondary Endpoint	• Markers of Cholesterol metabolism/synthesis • CSF Levels of Trappsol® Cyclo™ • hepatic and splenic morphology • global impression of disease
Exploratory Endpoint	• CSF biomarkers of NPC Disease

- **Niemann-Pick Disease Type C**
  - Confirmed diagnosis of NPC – 1
  - NIH NPC Severity Score <30 and with no more then 4 individual domains with a score of > 3
  - Age range: 18 years upwards
- **Total Sites: 2 in United States**
  - Emmes is supporting the study with site management and monitoring
  - UCSF Benioff Children's Hospital Oakland, CA; and, Morristown Medical Center, Morristown, NJ
- **Trial Timeline**
  - First patient enrollment: Q'3 17
  - First patient dosed Q'3 17

Trappsol® Cyclo™
Phase I/II Study to Evaluate Safety and Efficacy

Europe

Randomization 4:4:4 Between Dose Groups

Trappsol® Cyclo™: Bi-weekly 8 hour intravenous treatment for a period of 48 weeks

RANDOMIZE (N=12)

Dose Group 1	Dose Group 2	Dose Group 3
1500 mg/kg	**2000 mg/kg**	**2500 mg/kg**

Primary Endpoint	• Plasma levels of Trappsol® Cyclo™
Secondary Endpoint	• Markers of Cholesterol metabolism/synthesis • CSF Levels of Trappsol® Cyclo™ • Clinical Outcomes (motor Skills, cognition, eye movements, liver morphology et al) • global impression of disease
Exploratory Endpoint	• CSF biomarkers of NPC Disease

- **Niemann-Pick Disease Type C**
  - Confirmed diagnosis of NPC – 1
  - NIH NPC Severity Score <30 and with no more then 4 individual domains with a score of > 3
  - Age range: 2 years upwards
- **Total Sites: 5-6 in 4 Countries**
  - UK, Sweden, Italy, Israel
  - Aptus/Synteract is supporting the trial with site management and monitoring
- **Trial Timeline**
  - First patient enrollment: Q'2 17
  - First patient dosed Q'3 17

Global Investigators

Caroline Hastings, MD	• Pediatric hematologist/oncologist, Co-PI, UCSF Benioff Children's Hospital Oakland
Benny Liu, MD	• Gastroenterologist, Alamada Health System and UCSF Benioff Children's Hospital Oakland, Co-PI
Darius Adams, MD	• Clinical geneticist and pediatric metabolic disease expert, PI, Morristown, NJ
Robin Lachmann, MD	• Metabolic disease expert and PI, University College London
Reena Sharma, MD	• Metabolic disease expert, and coordinating lead for Phase I/II trial, PI for Salford Royal Trust site, UK
Ronen Spiegel, MD	• Clinical geneticist and Chair, Pediatrics, PI, Emek Medical Center, Israel
Orna Staretz, MD	• Neonatologist, PI, Soroka Medical Center, Israel
Martin Paucar Arce, MD, PhD	• Neurologist, PI, Karolinska Institute, Sweden
Julian Raiman, MD	• Pediatric metabolic disease expert, PI, Birmingham Childrens, UK
Maurizio Scarpa, MD	• Metabolic disease expert and Coordinator, European Reference Network for Hereditary Metabolic Diseases, PI for site at Udine University Hospital, Italy

Atlantic Health System

UCL

SOROKA Medical Center *feeling secure*

Affiliated to the Rappaport Faculty of Medicine Technion-Haifa, Israel

Salford Royal NHS Foundation Trust

KAROLINSKA INSTITUTET ANNO 1810

UCSF Benioff Children's Hospitals

UNIVERSITÀ DEGLI STUDI DI UDINE

Initial Data from CTD's Formal U.S. and E.U./Israel trials

- Safety data show positive profile.
  - Adverse events are minor and as expected based on knowledge from compassionate use programs.
  - Hearing losses have been noted, but all have been transient. No permanent hearing losses.
- Trappsol® Cyclo™ releases cholesterol from cells of NPC patients, allowing for cells to normalize.
- Trappsol® Cyclo™ crosses the blood-brain-barrier following IV administration.
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- Clinical efficacy data are limited but encouraging. Disease specific features, including fine motor, gait, and cognition improve in some subjects. Most patients for which data are available either stabilized or improved in disease specific features.

Safety Summary - 101

Adverse Event (AE) Toxicity Grading (CTCAE) N = 30				
	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4
No. of AE''s	15	10	5	0
Related *	1 rash	4 Infusion reaction, rash, fever, hypoxia	2 Hypersensitivity pneumonitis, reduced hearing	0

* Events deemed at least possibly related by the investigator

Safety Summary - 201

Adverse Event (AE) Toxicity Grading (CTCAE) N = 112				
	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4
No. of AE''s	84	15	11	2
Related *	24 Loose stools pyrexia, tinnitus, reduced hearing at higher frequencies, rash (vein irritation), cannula site redness, increased cataplexy, raised ALT/ AST , increased LDL chol, increased total chol, decreased HDL Chol	1 Loose stools	0	0

- Events deemed at least possibly related by the investigator,

  ALT (ALAT) = Alanine transferase, AST (SGOT)= Aspartate Transaminase

  5 not assigned a grading yet. Increased LDL chol, reduced HDL chol, reduced valproic acid drug level, 'cold; x 2.

Safety Summary - 201

SAEs

001-02

Patient was hospitalized intermittently for general health deterioration, aspiration pneumonia and non-study medication overdose. This subject was withdrawn by the physician due to missed dosing and the deterioration in their general condition.

SAE 1. Aspiration pneumonia

SAE 2: unconsciousness / decline in physical health

003-01

SAE 1: Erythema and hand swelling after the cannula extravasated.

301-02

SAE 1-7: Intermittent seizures requiring hospitalization. This was considered as not related to the study treatment but attributed to non-compliance with their normal anti-epileptic medication. The subject was withdrawn from the study by family despite positive improvements in their disease.

301-03

SAE 1:The patient experienced a CSF leak with subsequent headache and backache post lumbar puncture. Observed overnight and went home the next day.

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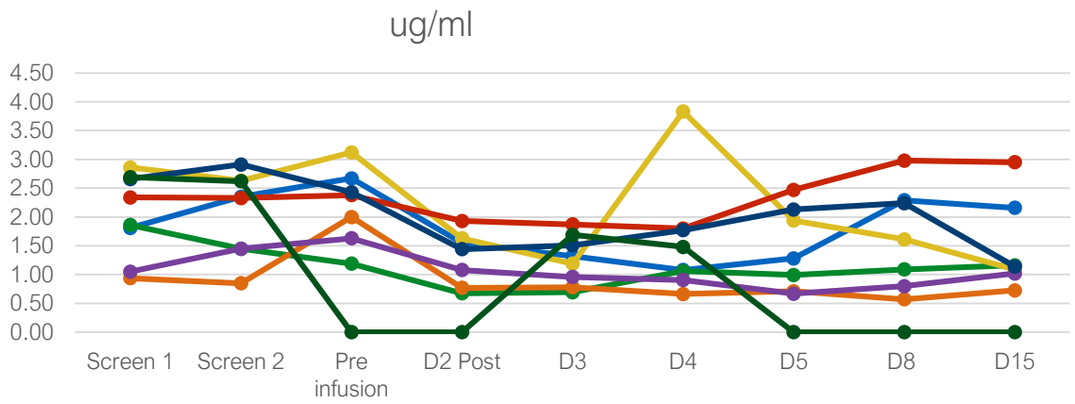
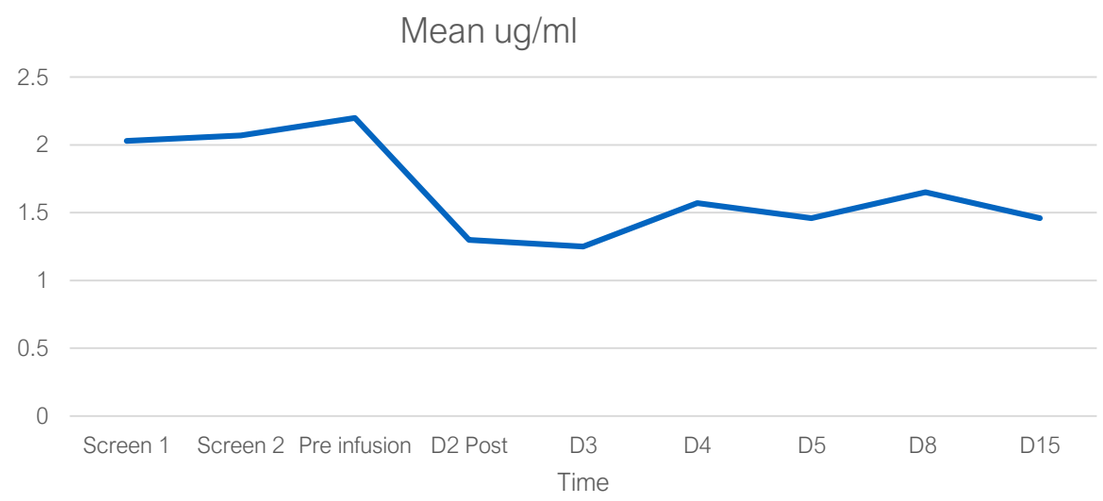
Cholesterol Precursors

Individual Serum levels of Lathosterol at each visit
from 4 subjects in the 101 study and 4 subjects in 201 study

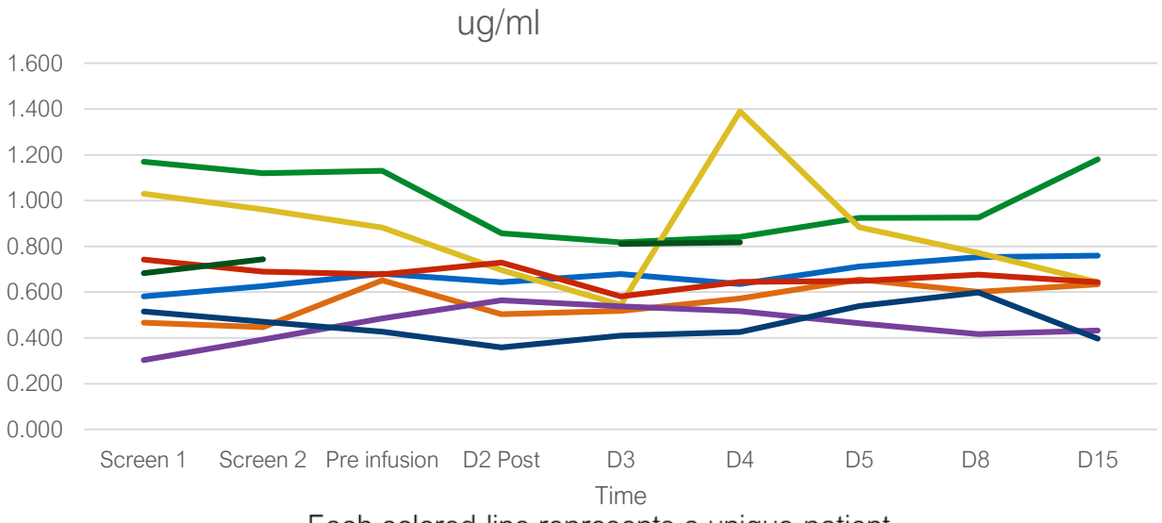


Each colored line represents a unique patient.

Mean Serum levels of Lathosterol



Individual Serum Levels of Desmosterol at each visit
from 4 patients in the 101 study and 4 subjects in 201 study



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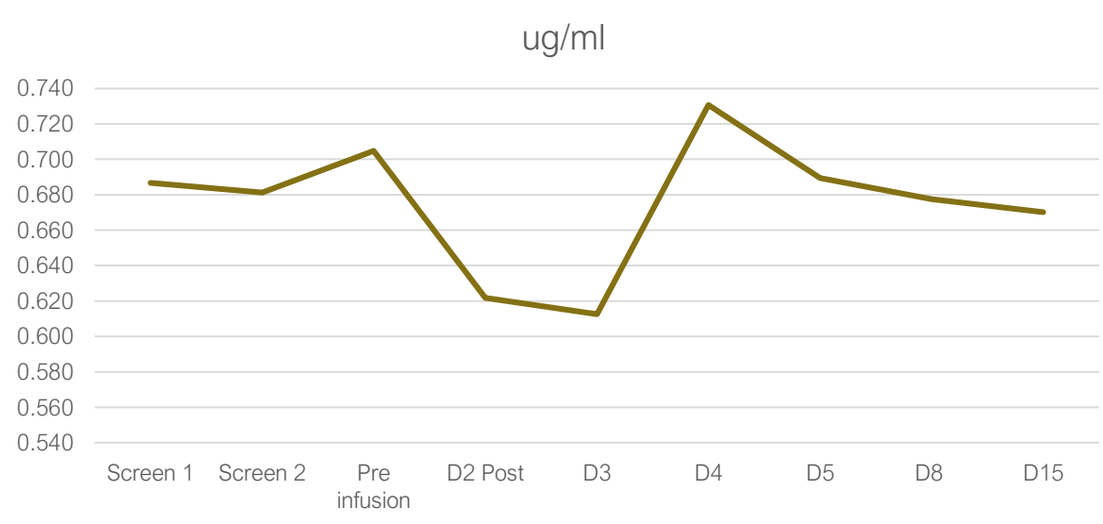
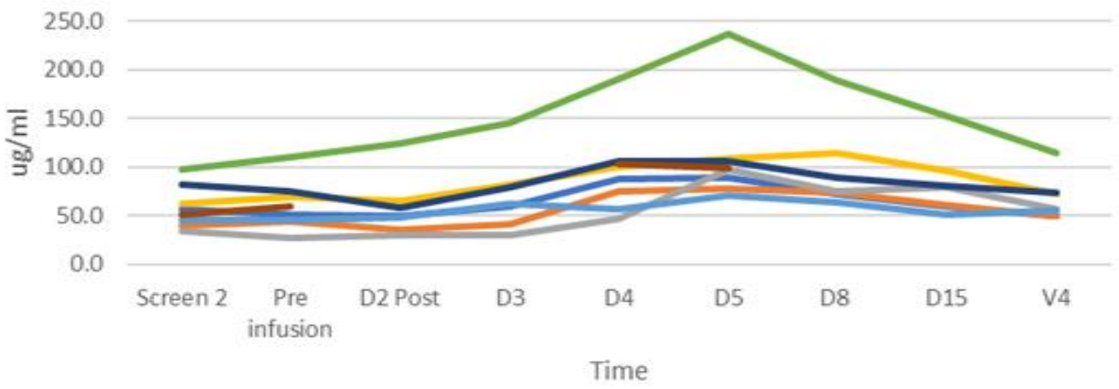
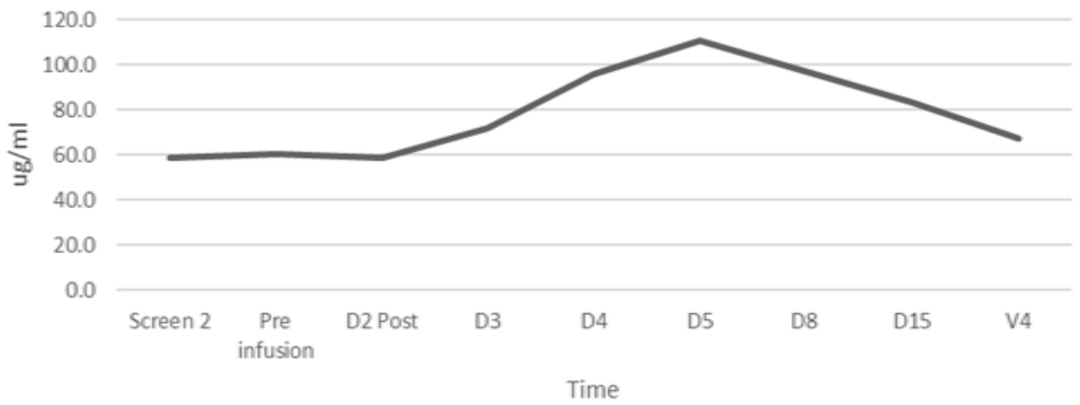
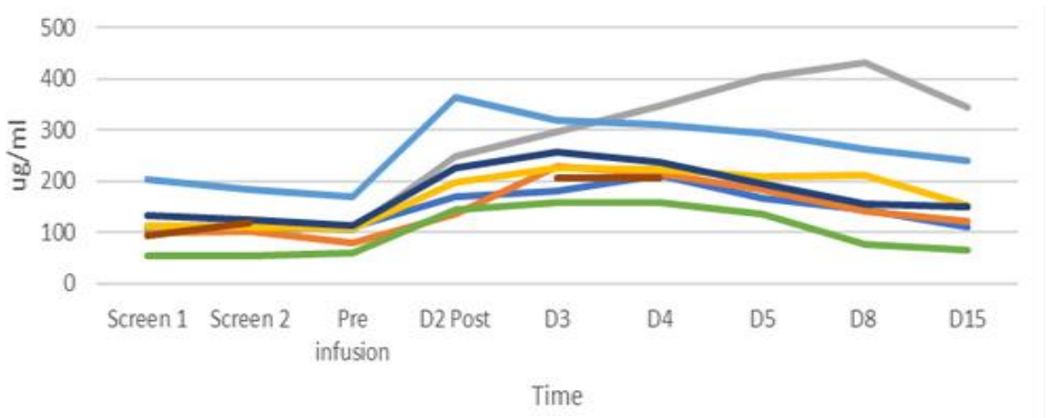
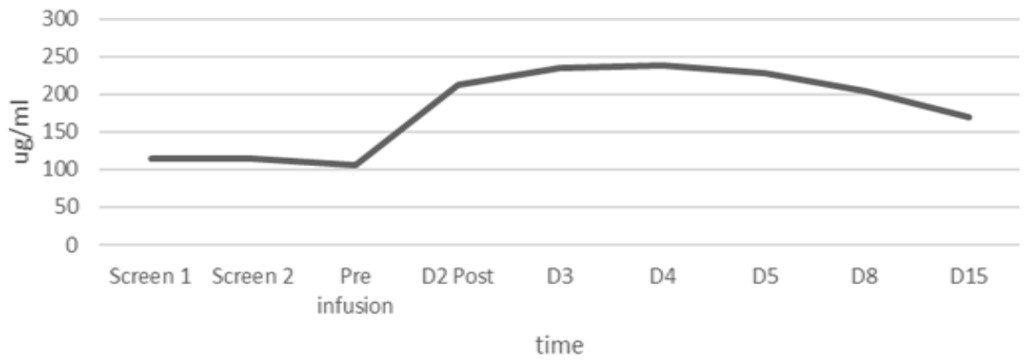
Mean Serum Levels of Desmosterol

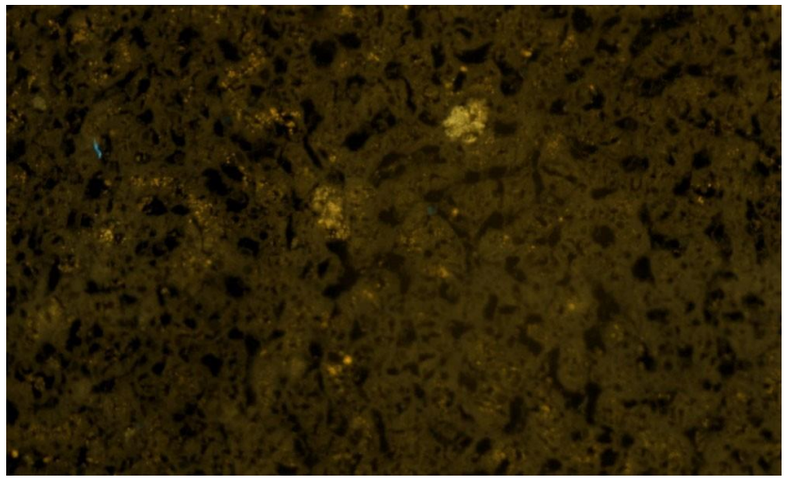


Cholesterol Metabolites

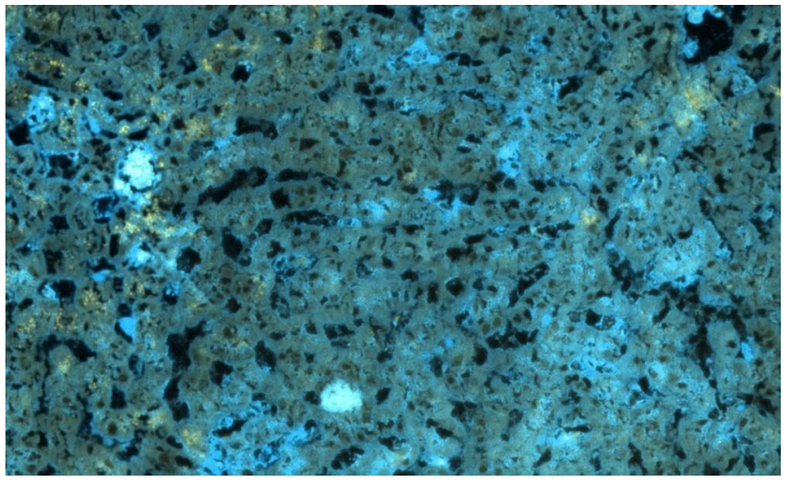
Individual Patient Values for Serum 4B-hydroxy cholesterol	Mean values for Serum 4B-hydroxy cholesterol
 Each colored line represents a unique patient.	
Individual Patient Values for Serum 27-hydroxycholesterol	Mean values for serum 27-hydroxy cholesterol
 Each colored line represents a unique patient.	

Initial Histology

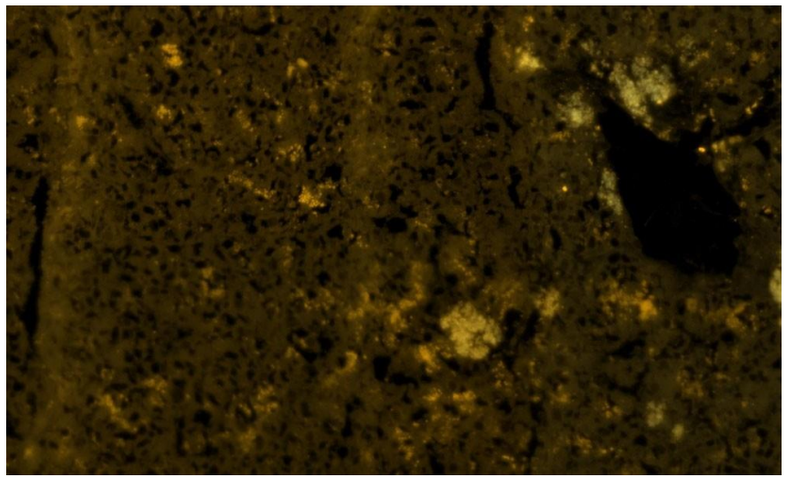
United States



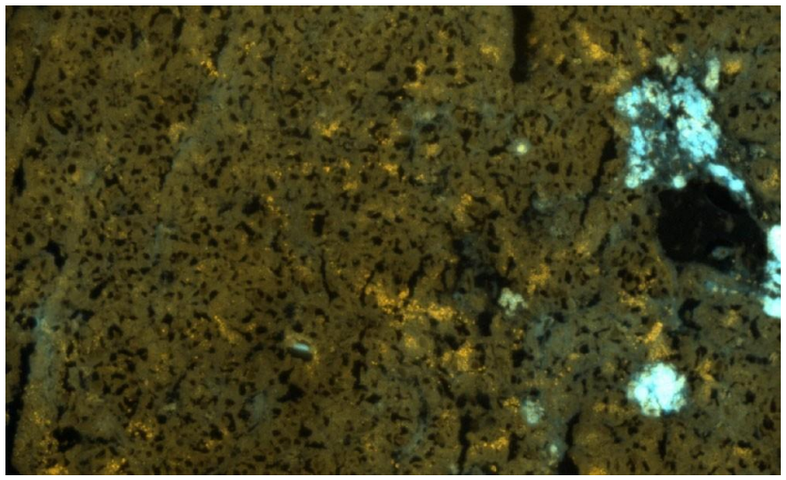
Baseline negative buffer control



Baseline



Week 14 negative buffer control



Week 14

Liver tissue from NPC patient in the US trial. Left panels, no filipin, control.
Upper right, baseline. Lower right, after 7 doses of Trappsol® Cyclo™ over 14 weeks.

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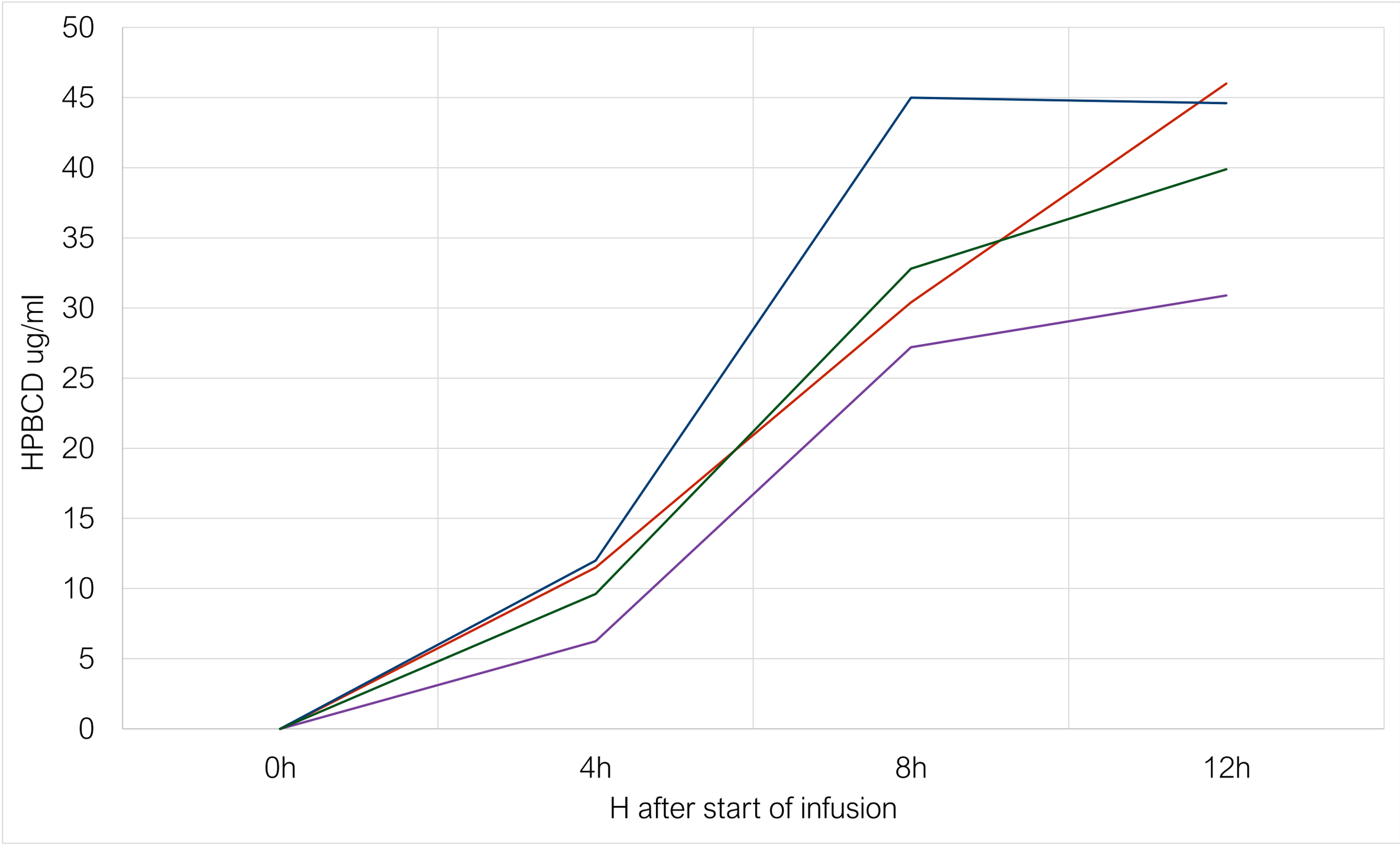
Trappsol® Cyclo™ in cerebrospinal fluid

United States



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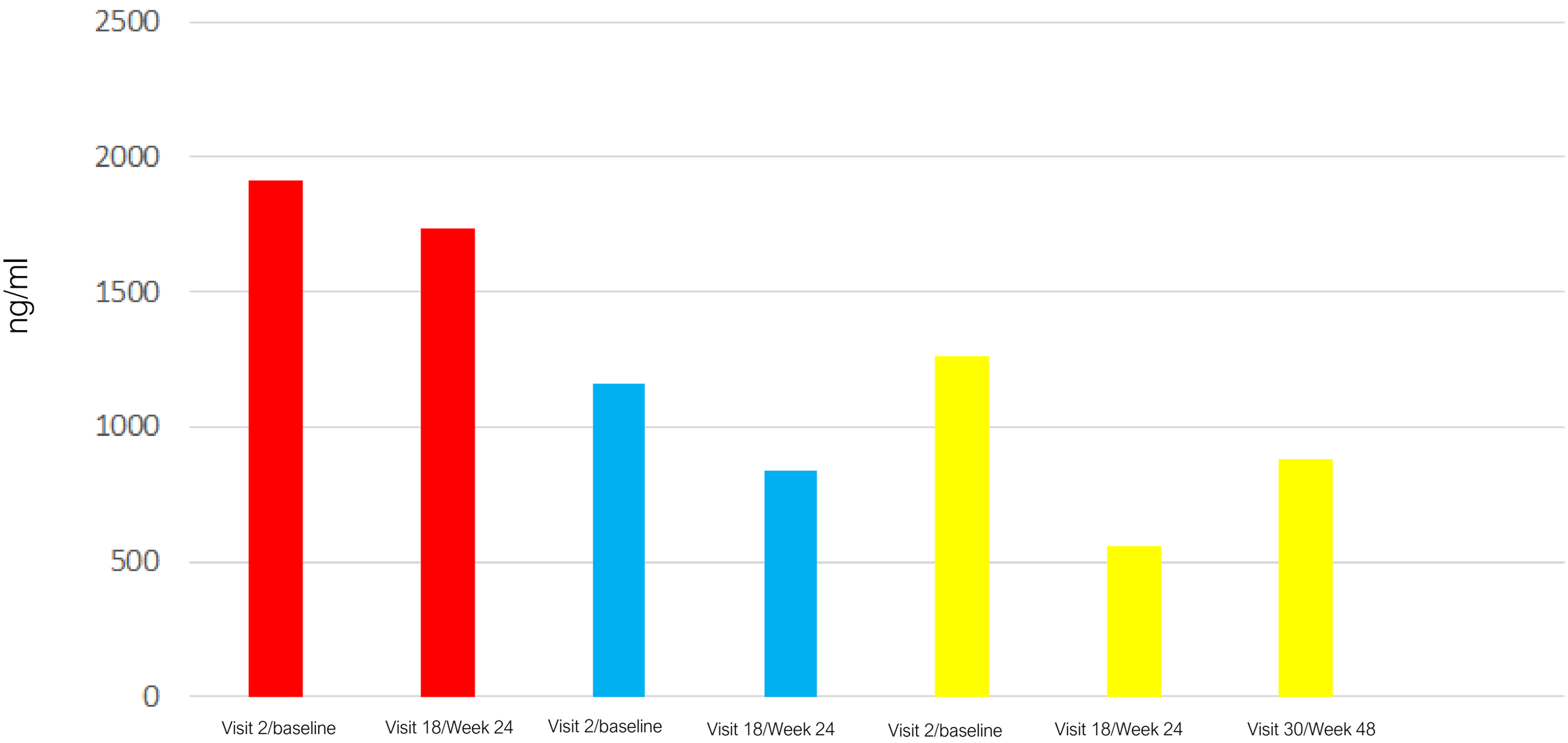
Levels of Tau in CSF

Europe



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Clinical Impressions – US Study

United States

This **Phase I** study is designed to measure pharmacokinetics (drug levels in the blood and CSF) and understand how cholesterol homeostasis is affected by IV cyclodextrin.

14 week trial is not powered to measure long term effect on progression of disease.

Clinical observations were documented and include:

- 4 of 6 patients reporting change note increased alertness, focus, enhanced communication and speech fluency
- 3 of 6 patients note increased strength and motivation leading to improvement in self directed movement or ambulation
- 2 patients remain clinically stable
- 1 patient was withdrawn from the trial due to hypersensitivity

Global Impression of Disease scores, standardized tool, to be analyzed.

NPC Clinical Severity Score

- Widely used tool in clinical research community starting in 2010

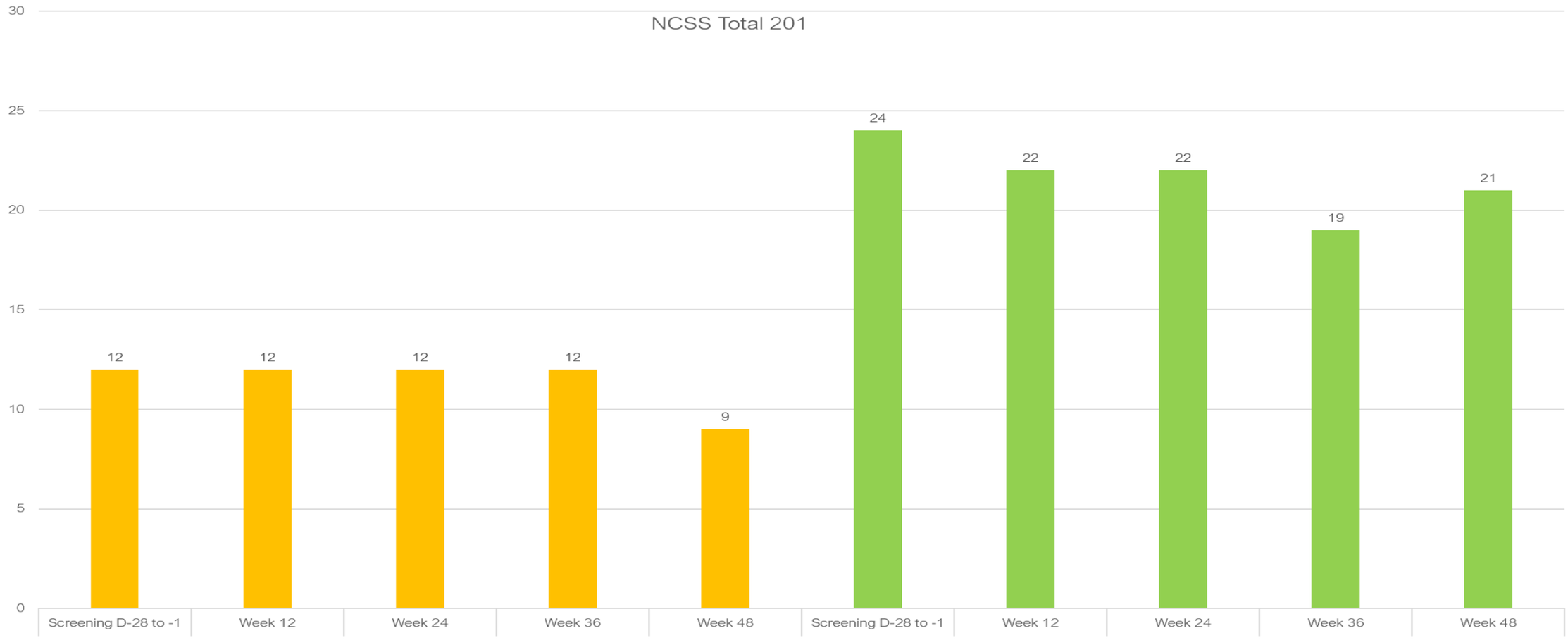
- Based on 9 major domains, or features of NPC disease: eye movement, ambulation, speech, swallow, fine motor skills, cognition, hearing, memory, and seizures.

- And 8 modifying domains: Gelastic cataplexy, narcolepsy, behavior, psychiatric, hyperreflexia, incontinence, auditory brainstem response, and respiratory.

- Each major domain is scored 0 – 5, modifying domains 0 – 2 with 0 being normal or no history of the disease manifestation. Most severe patients are scored 61 with this tool.

NPC Clinical Severity Scores

Europe



- **For patient 1** (yellow): The improvement in total score of 3 points (compared with baseline) is due to reductions in severity in the eye movement (1 to 0), fine motor skills (2 to 1) and psychiatric modifier (1 to 0). **For patient 2** (green): The improvement in total score (compared with baseline) is due to reductions in severity in eye movement (1 to 0), cognition (5 to 3), gelastic cataplexy (2 to 1) and incontinence (1 to 0). However, ambulation worsened (1 to 2) as did speech (3 to 4). Total score change reflects an improvement of 3 points. **N=2**

A Special Thank You

to all of the patients, families and physicians who support CTD's ongoing clinical trials

and who provided their data from compassionate use programs early on, making our trials possible.

Thank You!