Trappsol® Cyclo™ and NPC: Efficacy Shown Across Individual 5D Domains and Utilization of Future Assessment Tools to Demonstrate Clinically Relevant Outcomes

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Abstract

Background: Clinical scales are critical to characterize and quantify disease progression in degenerative CNS-diseases like Niemann Pick Disease Type C (NPC). The 5D-NPC-CSS (5D), an abridged version of a 17-domain scale (17D), has found broad use within and beyond clinical trials. It comprises fine motor skills, swallowing, ambulation, cognition, and speech, as deemed most important through the patient voice, physicians, and caregivers.

Methods: In a completed phase 1/2 study of intravenously administered Trappsol® Cyclo™ improvement from baseline in the 17D-score of at least one point in two or more domains at 48 weeks was assessed.

Results: Eight of the 9 patients completing the study (89%) met this endpoint. Of these 6 (75%) improved in at least 1 of the 5 domains of the 5D; 6 of 9 showed stabilization or improvement at 48 weeks. Stabilization or improvement in 5D subdomains: ambulation (8/9, 89%), swallowing (9/9, 100%), speech (7/9, 78%), and cognition (7/9, 78%), and fine motor (3/9, 33%). In the Clinical Global Impression of Improvement scale 7 patients showed improvement (1 very much, 1 much, 5 minimally), and 2 showed stability. Scale for the Assessment and Rating of Ataxia showed an overall improvement in 7 of 8 domains, most pronounced Stance, Gait, and Fast-Alternating-Hand-Movements. Sitting was almost unaffected at baseline and showed no change.
In an ongoing phase 3 study, patients were included with a restricted range of estimated annual disease progression rates targeting improved predictive power. Primary outcomes are performance on the 5D and the corresponding 4D scale (modified, without cognition). Secondary outcomes to complement these include the SCAFI scale, the Vineland-2 Adaptive-Behavior-Scales, video aspiration assessments, and speech analytics.

Conclusion: Altogether these assessment tools will add breadth and depth to the 5D-NPC-CSS and further characterize treatment benefit on key characteristics of NPC disease, like broad CNS status, cerebellar function, and behavior.

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clinicaltrials.gov NCT04860960

NPC: A Fatal, Debilitating Disease

- **No cure for NPC disease**
- Rare, fatal and progressive genetic disorder affecting notably the brain, liver, spleen and lungs.
- Mutations in the NPC1 (95% of patients) or NPC2 (5%) protein affects cholesterol transport
- Accumulation of lipids (cholesterol, sphingomyelin, sphingosine and glycosphingolipids) within the endolysosomal system
- Defects of cellular machinery to handle cholesterol uptake leads to brain dysfunction and accumulation/damage in major tissues
- Extreme clinical heterogeneity with variable hepatic, pulmonary, neurological, and psychiatric manifestations at presentation, including auditory loss
- **Major impact on QoL**

Incidence

Pan-ethnic disease with an estimated incidence of 1/100,000 live births[1]

US: ~35 per year

Age at Time of Diagnosis*

Mean: 14.5 yrs[2]
Median: 10.0 yrs[2]

Survival

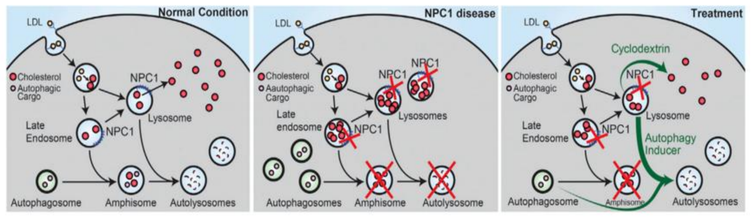
Worse in children with rapidly progressive early infantile neurological onset[2]

Longer survival in adult patients with slowly progressive adult onset[2]

*Based on one large retrospective observational study

1. Gaberhiwot et al., Orphanet Journal of Rare Diseases 2018
2. Patterson et al., Journal of Inherited Metabolic Disease 2020

Mechanism of Action of HPβCD



Maetzel et al., 2014

- HPβCD is taken into cells via bulk phase endocytosis and into the late endosome/ lysosome (LE/L)
- Selectively allows trapped unesterified cholesterol to be released from the LE/L into the cytosol from where it enters cellular cholesterol processing
- Levels up to 1.0 mM mobilize stored cholesterol in LE/L
- Neurotoxicity/acute cell death at concentrations of > 10mM
- During infusion HPßCD reaches plasma concentration of about 1 mM
- Transfer over the BBB happens by micropinocytosis with a transfer rate of 0.1 – 0.2 µl / g tissue / minute
- Assumed peak concentration of HPßCD in brain tissue is 0.04 – 0.08 mM; confirmed by values obtained in lumbar CSF (0.02 – 0.03 mM)

TransportNPC™

5D & 4D NPC Clinical Severity Scales

- The 5-domain Niemann-Pick disease type C Severity Score (5D-NPC-SS) is an abbreviated version of the original 17-domain Niemann-Pick disease type C Severity Score (17D-NPC-SS)
- The 5D-NPC-SS composite score has clinical precedent for being utilized in pivotal programs within the NPC population as a primary outcome measure
- Swallowing, speech, fine motor, ambulation, and cognitive functioning are major concerns for NPC patients. Improvements across thesse clinical outcomes is important to alleviate the heterogeneity of the disease and to derive clinical meaningful benefits
- The 5D-NPC-SS assesses 5 main clinical domains of NPC, identified as meaningful to NPC patients, caregivers and clinical experts
- The 4-domain Niemann-Pick type C Severity Score (4D-NPC-SS) is a slightly modified version of the 5-domain scale, developed to address concerns about evaluating cognition in a shorter clinical trial. Cognition in the 4D-NPC-SS was omitted to simplify the scale and make it more suitable for shorter clinical trials
- Both 4 domain and 5 domain scales are used to used to monitor disease progression and assess therapeutic benefit

5D-NPC-SS

1. Ambulation: Assesses patient's ability to walk and move around
2. Swallow: Assesses patient's ability to swallow and manage oral intake
3. Speech: Assesses speech clarity and communication abilities
4. Fine Motor Skills: Assesses fine motor skills and coordination
5. Cognition: Measures cognitive functions and mental abilities

4D-NPC-SS

The 4-domain scale is not the 5-domain scale minus cognition. There are a few nuances as noted below:

1. Ambulation: Similar to the 5-domain scale; evaluates walking and movement
2. Swallow: Assesses swallowing ability, with an updated scoring methodology for better accuracy
3. Speech: Evaluates speech clarity and communication abilities
4. Fine Motor Skills: Assesses fine motor skills and coordination

Yanjanin N. et al., Am. J. Med. Genet. B. Neuropsychiatr. Genet. 2010
Paterson M. et al., Orphanet J. Rare Dis. 2021

Completed Phase I/II Study

17D-NPC-SS domains show improvement or worsening at the end of study

Patient Number (age, years)	Improvement in Individual Domains at Week 48 compared with baseline	Worsening in Individual Domains at Week 48 compared with baseline	NPCSS Total at baseline	NPCSS Total at Week 48 or end of study
2 (21)	**Swallow − 1** Seizures −2 Gelastic Cataplexy −1 Incontinence −1	**Fine Motor Skills + 1** **Cognition + 1**	24	21
3 (39)	Eye Movement −1 **Fine Motor Skills − 1** Psychiatric −1	None	12	9
5 (4)	Gelastic Cataplexy-1 Auditory brainstem response −1 Memory −1	None	24	21
6 (11)	**Ambulation − 1** **Swallow − 2** Gelastic Cataplexy −2 Hyperreflexia −1 Narcolepsy −1 Incontinence-1 Behavior −1	**Speech + 1** **Fine Motor Skills + 2** Hearing +2	26	22
7 (2)	**Ambulation − 3** **Fine Motor Skills − 1**	**Speech + 1** Hyperreflexia +1	5	3
8 (3)	Eye Movement −1 **Speech-1**	**Fine Motor Skills + 1** Hearing +2	16	17
10 (2)	None	**Cognition + 2** **Fine Motor Skills + 1** Hyperreflexia +1	15	19
11 (2)	Eye Movement −1 **Cognition − 2**	**Fine Motor Skills + 1** Memory +1	9	8
12 (8)	Gelastic Cataplexy −1 Incontinence −1	**Ambulation + 1** **Fine Motor Skills + 1** Memory +2 Hyperreflexia +1	13	16

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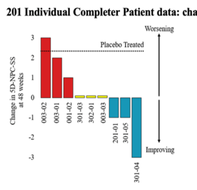
Key Outcomes

- Improvements from baseline in the 17D score of at least one point in two or more domains at 48 weeks was assessed
- Eight of the 9 patients completing the study (89%) met this endpoint
- Data on 3 patients missing: 1 patient withdrew, 1 patient did not consent for 17D score, 1 patient unable to attend week 48 assessment due to COVID-19

Phase 1/2 Study (CTD-TCNPC-201):
Individual data suggestive of potential benefit on 5D-NPC-SS and CGI-I

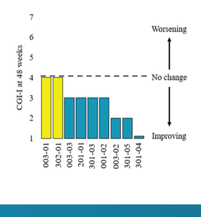
201 Individual Completer Patient data: change in 5D-NPC-CSS score at 48 weeks



- Scores ranked by benefit: least (left) to most (right)
- Individual patient numbers shown
- Majority of patients (6 of 9) exhibit stabilized or improved 5D-NPC-CSS scores at 48 weeks

Reference cohorts from the literature 2.15 points per annum (Mengel, 2021)

201 Individual Completer Patient data: CGI-I score at 48 weeks



- All patients (9 of 9) exhibit stabilized or improved CGI scores at 48 weeks
- Scores ranked by benefit: least (left) to most (right)
- Individual patient numbers shown

Data Included

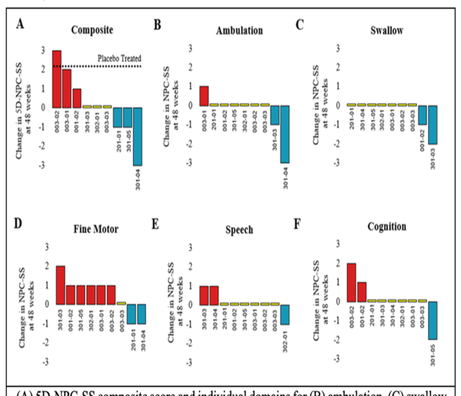
- 9 completers (2 patients in the 1500 mg/kg group; 4 patients in the 2000 mg/kg group; 3 patients in the 2500 mg/kg group).
  - Three patients were excluded from this analysis due to 1 only having baseline data and 2 patients discontinued prior to Week 48 for non-safety reasons.

Key Outcomes

- In a disease characterized by linear disease progression, treatment with Trappsol Cyclo resulted in the stabilization or improvement in 6 of 9 (67%) completer patients on the 5D-NPC-SS
- 8 of 9 (89%) completer patients showed Improvements over disease progression (2.15 points per annum) in the 5D-NPC-SS
- 9 of 9 (100%) completer patients exhibited stabilized or improved in CGI-I ratings, a clear indicator of efficacy in NPC-1 patients

Completed Phase I/II Study

Data suggestive of the utility of the 5D-NPC-SS alongside secondary endpoints



(A) 5D-NPC-SS composite score and individual domains for (B) ambulation, (C) swallow, (D) fine motor, (E) speech, and (F) cognition. Patients (n = 9) ranked by benefit: left (least) to right (most). Change in 5D-NPC-SS calculated by subtracting baseline 5D-NPC-CSS composite score value from the score at 48-week timepoint. Individual patients labeled. Dashed line represent comparison to placebo-treated disease progression (based on Mengel et al, 2021).

Key Outcomes

- On a patient-specific level, no consistent treatment patterns were observed across 5D-NPC-SS domains at 48 weeks.
- Although some domains were universally stabilized (i.e., swallowing), each patient stabilized or improved on a unique combination of assessments that contributed to their composite score.
- Observations may be attributed to the diverse ages of enrolled patients (2-39 years of age) and reflects the heterogeneity of disease stage and progression, yielding differential sensitivity to drug effect based upon patient phenotype.
- Data suggest the utility of the 5D-NPC-SS composite score alongside planned secondary outcome measures (i.e., Spinocerebellar Ataxia Functional Index [SCAFI], Vineland-2, PAS) to holistically observe disease progression across diverse patient population, consistent with those randomized and that have reached the 48-week endpoint in the ongoing Phase 3 pivotal study

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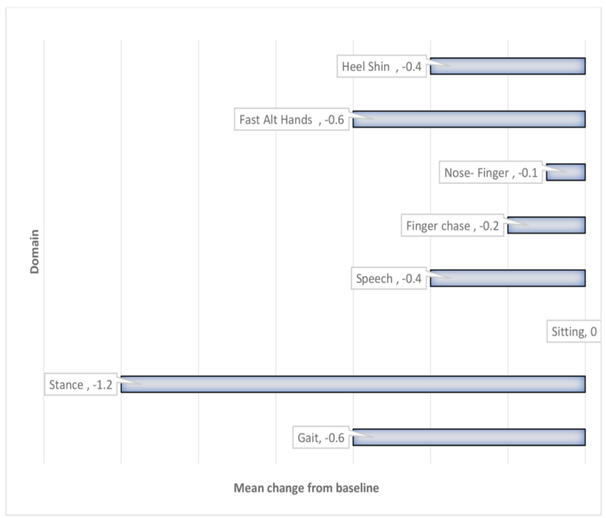
Additional clinical assessment of ataxia: SARA



Change from baseline in mean SARA scores at week 48

Key Outcomes

- SARA showed an overall improvement in the mean score in 7 of 8 domains
- Most pronounced improvements seen in Stance, Gait, and Fast-Alternating-Hand-Movements
- Sitting was almost unaffected at baseline [all patients had a score of 0 (normal) or 1 (slight difficulties)], leaving little room for improvement
- Importantly, there was no overall worsening in any domain
- No correlation to dose given the small number of patients per study cohort

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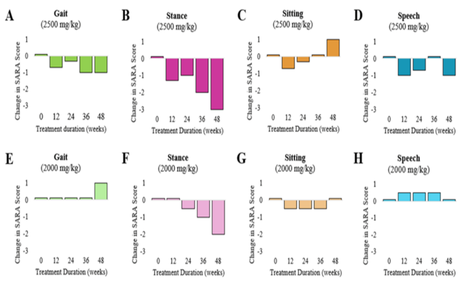
Dosage data suggestive of potential benefit on SARA, an exploratory measure



Scale for Assessment and Rating of Ataxia (SARA) scores for select domains: (A, E) gait, (B, F) stance, (C, G) sitting, and (D, H) speech. Patients receiving (upper panel) 2500 mg/kg dose (n = 3) or (lower panel) 2000 mg/kg dose (n = 4) for 48 weeks. Change in scores for individual SARA domains was calculated by subtracting respective value at baseline from the value at 12-, 24-, 36-, or 48-week timepoint. A negative change in score for individual SARA domain suggests improvement, whereas a positive change suggests worsening of the disease progression.

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Data Included

- Scores for individual SARA domains on a group level for multiple doses: 2500 mg/kg, 2000 mg/kg, and 1500 mg/kg. Descriptive presentation of patient-level data focused on the following SARA domains: gait, stance, sitting, and speech. Patients receiving a 1,500 mg/kg dose were not included in subsequent analyses due to incomplete or missing data at 48 weeks.

Key Outcomes

- Multiple domains are reflected in these average scores: gait, stance, sitting, speech, finger chase (L/R), nose-finger (L/R), fast alt hands (L/R), and heel shin (L/R).
- Patients who received (2500 mg/kg or 2000 mg/kg), exhibit stabilized or improved scores for the SARA domains considered (gait, stance, sitting, and speech) compared to baseline.
- Higher dose (2500 mg/kg) suggestively improved gait, stance, and speech at 48 weeks (Figure A-D).
- Lower dose (2000 mg/kg) suggestively improved stance and stabilized sitting and speech at 48 weeks (Figure E-H).
- Potential benefits, at least descriptively, are dose-ordered and higher exposures may produce a more consistently favorable effect, acknowledging small sample size and heterogeneity of patient presentation.

Use of Future Assessment Tools to Demonstrate Clinically Relevant Outcomes

Phase 3: Clinical Outcome Assessments at Baseline and other Critical Timepoints

SCAFI	CGI-S Overall Disease	CGI-S Functional Ability
5D-NPC-SS	Vineland 2 Socialization	CaGI-S Functional Ability*
4D-NPC-SS	Vineland 2 Motor Skills	Caregiver Questionnaire*
Vineland 2 Communication	Vineland 2 Maladaptive Behavior Index	EQ-5D-Y Patient**
Vineland 2 Daily Living Skills	Vineland 2 About the Interview	EQ-5D-Y Proxy*
CaGI-C24*	Vineland 2 Score Summary	

Clinician-based, caregiver-focused* and patient-focused** disease outcome assessments

Primary Endpoints

All subjects will be assessed for both primary endpoints.

For EU, EMA

- Mean change in 5D NPC CSS (Ambulation, Fine Motor, Speech, Swallow, and Cognition) between hydroxypropyl-beta-cyclodextrin 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 hydroxypropyl-beta-cyclodextrin 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 Endpoints

- 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

Conclusions and Ongoing Efforts

- Slowing down disease progression through cholesterol mobilization is an important consideration for patients with established disease, who can expect to experience neurodegeneration without treatment
- Clear indication that therapeutic concentrations are present in the CNS based on drug concentrations in lumbar CSF
- The 17D-NPC-CSS and its simplified derivatives (5D-NPC-SS and 4D-NPC-SS) have been used in late-stage clinical studies
- The 5D-NPC-SS and 4D-NPC-SS as applied by trained raters seek to provide consistent and accurate monitoring of disease progression and assessment of therapeutic benefit
- Data on the 5D-NPC-SS, CGI and the individual swallow and speech domains demonstrate the potential for NPC patients to gain clinical benefit that could improve quality of life
- In a disease characterized by steady disease progression, treatment with HPβCD in the phase 1 / 2 resulted in stabilization or improvement in 6 of 9 (67%) completer patients on the 5D-NPC-SS
- Results from the phase 1 /2 study are being confirmed in the ongoing Phase 3 study, a 2-year multicenter, double-blind, randomized, placebo-controlled pivotal trial to evaluate the safety, tolerability, and efficacy of 2000 mg/kg of HPβCD via IV and standard of care (SOC) compared to placebo and SOC in patients with NPC
- Data suggest the utility of the 5D-NPC-SS alongside planned secondary outcome measures to globally observe disease progression across diverse patient population.
- Novel exploratory outcomes will add robustness to better understand disease progression and include the utilization of newly developed speech analytics technology