Topline Results from Phase 1/2 Study to Evaluate Safety and Efficacy of Intravenous Trappsol® Cyclo™ in Patients with Niemann-Pick Type C1 Disease

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Disclosures

- Consulting Fees/Advisory Board(s):
  - Biomarin, Sanofi/Genzyme, Takeda/SHIRE, Actelion
- Travel support
  - Biomarin, Sanofi/Genzyme, Takeda/SHIRE, Actelion

Overview of Phase 1/2 Study

Background:
Trappsol ® Cyclo™, the proprietary formulation of Hydroxypropyl Betacyclodextrin (HPBCD) of Cyclo Therapeutics Inc., has been found to remove cholesterol from cells, normalize cholesterol homeostasis, and cross the blood-brain-barrier when administered intravenously in NPC patients (Phase I study completed in 2020).

The Phase I/II trial:

- Randomized double blinded, parallel group study with no control group
- Evaluation of safety, tolerability, PK, efficacy of HPBCD in 12 subjects aged 2 years and older.
- Three doses studied: 1500 mg/kg BW, 2000 mg/kg BW and 2500 mg/kg BW
- Intravenous infusion over 8-9 hours every two weeks, for a 48-week period
- 5 sites in the UK, Sweden and Israel
  - Demographics: Age range 2 years to 39 years; 7 male, 5 female; 11 White, 1 Black or African Caribbean
  - Last Patient, Last Visit February 2021

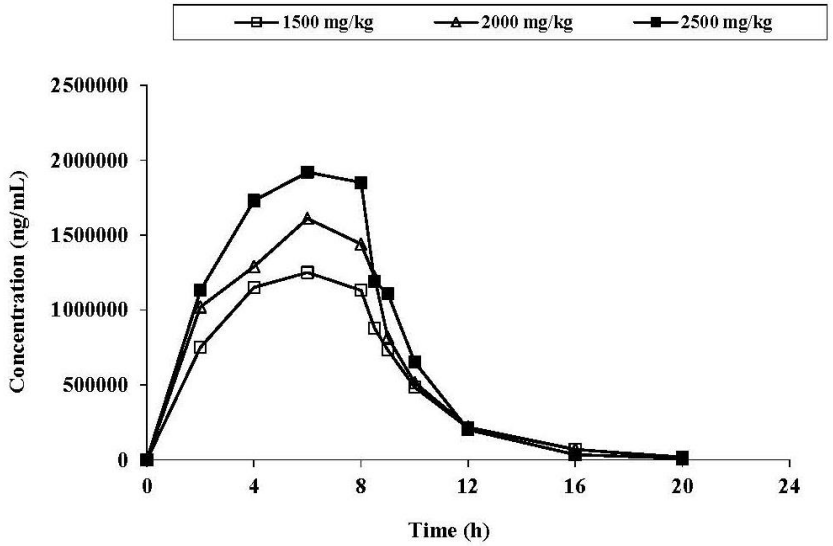
9 patients completed the study. 1 patient was withdrawn due to intercurrent illness, 1 patient was withdrawn due to non-compliance with study procedures, and 1 patient was withdrawn due to inability to cross a national border to reach the study site (COVID-related).

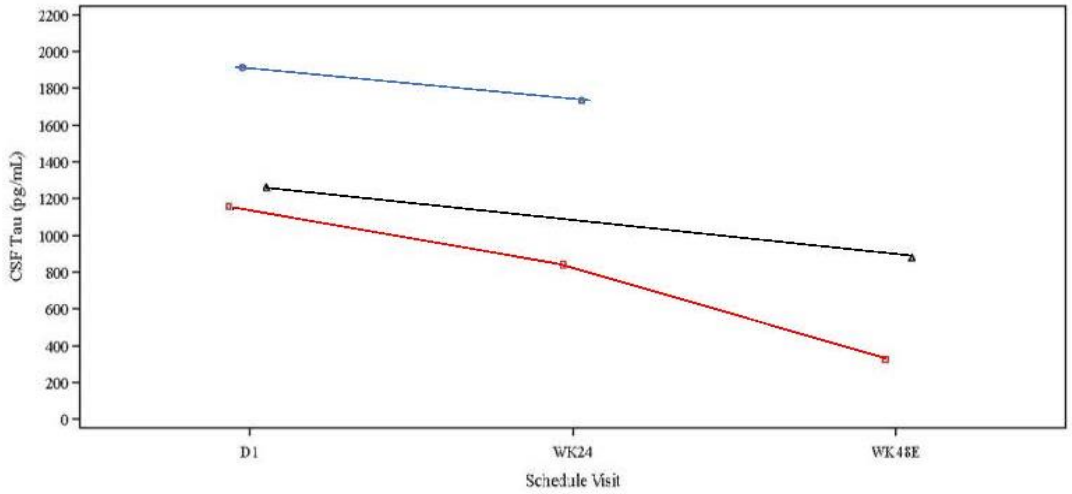
Favorable Safety and Tolerability Profile

Adverse Events (AE) by Treatment Group (N = 204)		Dose: 1500 mg/kg N = 5	Dose: 2000 mg/kg N = 4	Dose: 2500 mg/kg N = 3
	Total Number AE's N = 204 (Considered to be possibly, Probably or Related)	64 (8)	66 (16)	74 (8)
	Total Number TEAE's N = 185	51	62	72
	Total Number SAE's N = 15	9	2	4
	Total Number Treatment-Emergent SAE's N = 14	8 (in 2 patients) Aspiration pneumonia, x 7 hospitalization for seizures	2 (in 1 patient) CSF leak, Deterioration in hearing	4 (in 2 patients) Erythema, hand swelling Influenza B, Acute tonsillitis

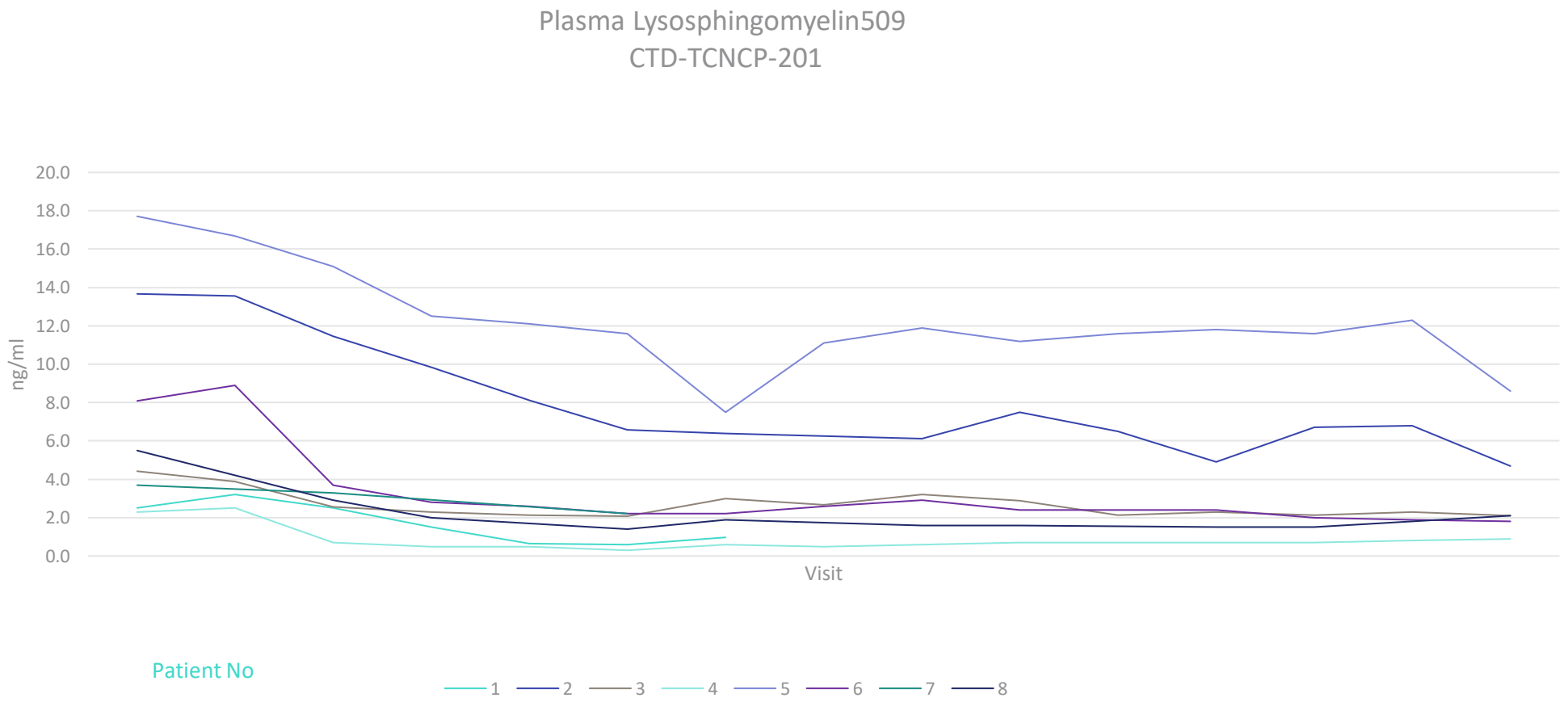
Safety, PK and PD

- Safety profile favorable: 3 SAEs related to study drug (2 related to infusion, 1 related to hearing loss (Grade 2), which resolved)
- Single-dose kinetics: Tmax 6 hrs; Half-life in plasma, 2 hrs; drug detected in CSF at 4 hrs after start of infusion and persists even 4 hrs after end of IV infusion (lower left).
- PD markers support effect of HPβCD on cholesterol homeostasis: within 2-3 days post-infusion, cholesterol precursor, lathosterol, in serum is reduced and cholesterol metabolite, 4-beta-hydroxycholesterol is increased (not shown). Tau in CSF is reduced in 3 patients who opted for additional lumbar punctures, suggestive of a neuroprotective benefit (lower right).





Pharmacodynamics: Individual Plasma Concentrations of Lysosphingomyelin 509 (ng/mL)



Liver and Spleen Size Affected

- Ultrasounds of liver and spleen were obtained at Baseline and Weeks 12, 24, 36 and 48 and provided to a central reader.
- Liver and spleen size were measured using standard radiographic metrics.
- Liver mean size was reduced by 0.5 cm at w48 compared with baseline.
- Spleen mean size was reduced by 0.95 cm at w48 compared with baseline.
- Individual patient changes are shown in the Table below.

Pt No	Age (Y)	Change in liver size (cm)W48-baseline	Change in spleen size at w48- baseline
2	21	+0.2	-0.4
3	8	NC	-1.0
4	3	-1.6	-0.9
5	5	+1.7	-4.2
6	39	NC	ND
7	3	-1.5	-1.0
9	11	ND	-0.2
10	2	ND	+1.8
11	3	ND	+0.5
12	6	ND	-2.0

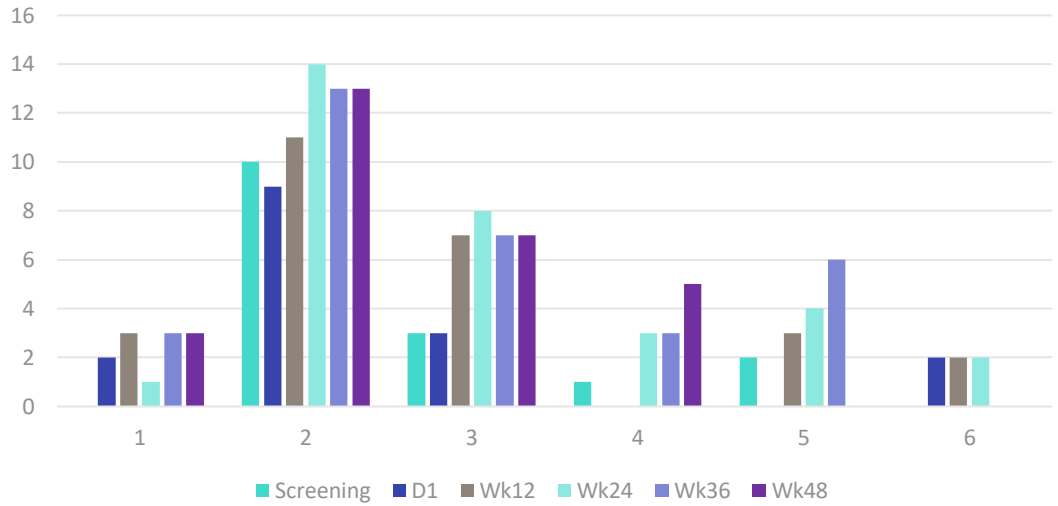
Liver size- Six patients had data at baseline and 48 w. Of these, 2 increased in size,2 reduced in size, and 2 did not change.
Spleen size-Nine patients had data at baseline and 48w. Of these, 2 increased in size and and 7 reduced.

Fine Motor Assessments: Bead Threading and SARA

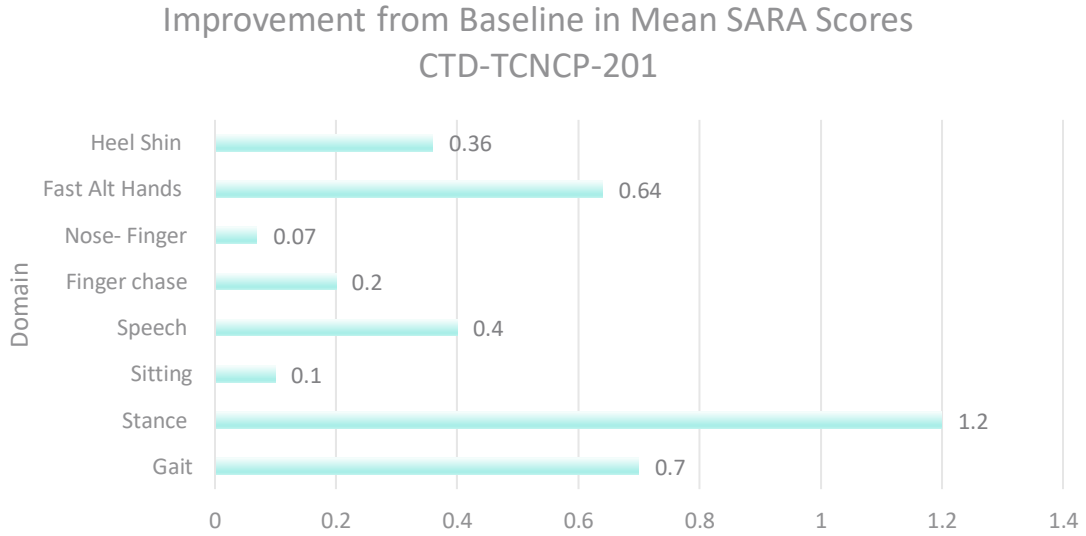
Bead Threading: 6 patients completed the test on up to six timepoints

Outcomes:

- 5 patients improved
- 1 patient was stable



Missing data points are shown by spaces/no bars (subjects 1, 4, 5, 6)



Scale for Assessment and Rating of Ataxia
All dose groups shown. Patients either had no change or were improved in SARA domains as shown at 48 weeks compared to Baseline. No patient worsened.

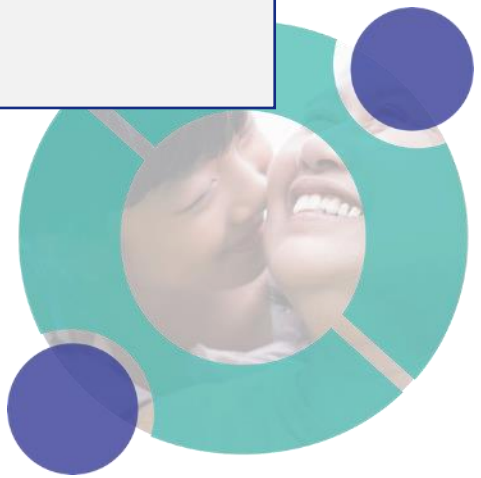
9 Patients to Complete Study Met Primary Outcome Measures for Efficacy

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 **1.5(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,Behaviour-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

Efficacy Outcome Measure 2

- *Efficacy Outcome Measure 2:* Change from baseline in Global Impression of Disease severity at 48 weeks
- Using the Clinician's Global Impression of Improvement scale, 7 of 9 patients who completed the trial improved
- One improved very much; one were much improved; five were minimally improved.
- The other 2 patients remained Unchanged (meaning that the patients remained stable per the Clinician, neither patient worsened).
- Stability in this progressive disease can be considered success.

Patients at Week-48 Compared to Baseline	Clinical Global Impression – Global Improvement (CGI –I) Scale	score
	Very much worse	7
	Much worse	6
	Minimally worse	5
2	No change	4
5	Minimally improved	3
1	Much improved	2
1	Very much improved	1
3	Not assessed	0

Summary

- Data shown demonstrate a favorable safety profile and expected PK parameters.
- Trappsol® Cyclo™ reduced Tau in the cerebrospinal fluid of NPC patients who opted for additional LPs, suggesting a neuroprotective benefit, and it led to a consistent decrease in a plasma biomarker, lysosphingomyelin-509, further support that the drug clears lipids from cells. (Similar biochemical data on cholesterol synthesis and metabolism were observed in this study as in the Phase I study, not shown here.)
- Ultrasound data for liver and spleen show trend in reduction of hepatosplenomegaly.

- Data from all dose groups showed Improvement in Ataxia as measured by the Scale for Assessment and Rating of Ataxia, and with supportive, albeit limited, data on Bead Threading.

- 8 of 9 patients who completed the study showed improvement in their 17-Domain NPC Severity Score.
- All 9 patients were assessed as either Improved or Stable by their treating physician after the 48 week study.

Acknowledgements

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