Initial safety and efficacy findings for a Phase I/II trial of hydroxypropyl beta cyclodextrins administered intravenously in patients with Niemann-Pick type C disease.

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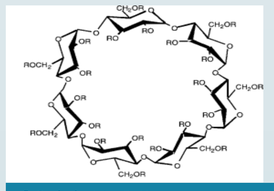
Abstract

Niemann-Pick disease type C is a rare and fatal genetic disorder characterized by cholesterol accumulation in every cell of the body. Hydroxypropyl Beta Cyclodextrins (HPBCDs) have been found in pre-clinical studies to release cholesterol from cells, normalize cholesterol homeostasis, delay symptom onset, and increase lifespan. We present data from the first four patients participating in a Phase I/II study using Trappsol® Cyclo™, the proprietary formulation of HPBCD of CTD Holdings. The trial is randomized, double-blinded, with no control group (NCT02912793). Patients were randomized to receive one of three doses of Trappsol® Cyclo™ (1500 mg/kg, 2000mg/kg, or 2500 mg/kg) administered intravenously over 8 to 9 hours twice monthly for 48 weeks. Results presented remain blinded with respect to dose. The review of individual and cumulative safety data to date has shown the study drug to be well tolerated with no serious safety signals observed. In particular, no clinically significant or permanent hearing problems were observed from dosing of Trappsol® Cyclo™ given intravenously as measured by standard audiometric testing. A plasma biomarker for severity of NPC disease, lysosphingomyelin-509, shows a clear downward trend with successive dosing: in 3 of 4 patients, there was a 30% to 50% reduction. Blinded results from standardized tests for ataxia, cognitive capacity, and NPC Severity Scores and Global Impression of Disease as well as subjective assessments from investigators show variation among patients in terms of outcome measures. Three of four patients showed improvement in one or more outcome measures, including ataxia, saccadic eye movements, speech and overall well-being. Initial impressions are encouraging. Clinical efficacy will be fully evaluated on unblinding.

Introduction

This presentation provides initial data from four subjects (4 female; age range 15 to 39 years, all Caucasian) in CTD's Phase I/II clinical trial using Trappsol® Cyclo™, its proprietary formulation of hydroxypropyl beta cyclodextrin, given intravenously (IV). IV administration is relatively low-risk compared to CNS-directed administration, and compassionate use data generated since 2009 on IV administration of this drug show safety/tolerability as well as varying degrees of benefit in individual compassionate use patients to liver, lung, spleen and the neurologic system. The current trial is randomized, double-blinded, multi-center, parallel group study with no control group. Doses are 1500 mg/kg, 2000 mg/kg, or 2500 mg/kg of a 25% (w/v) Trappsol® Cyclo™ solution over an 8- or 9-hour IV infusion, every two weeks for a period of 48 weeks of treatment (24 doses).



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

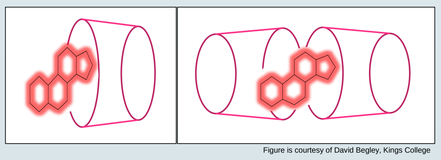


Figure is courtesy of David Begley, Kings College

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

Plasma pK levels for Trappsol® Cyclo™ peak 6-8 hours after start of infusion, with half-life of 1-2 hours (see presentation from January 2019 Brains for Brain at www.ctd-holdings.com)

Methodology

Safety outcomes were assessed by a Safety Review Committee comprised Professor Alan Boyd (UK), Dr. Caroline Hastings (US) and Medical Monitor for the study (Bryan Murray). Serum biomarkers for cholesterol synthesis and metabolism and CSF levels of Trappsol® Cyclo™ and CSF biomarkers tau, TNF-alpha and GFAP were measured by LC/MS or ELISA at Medpace Bioanalytical Labs (Cincinnati, OH). Lysosphingomyelin-509 was measured at Centogene (Rostock, Germany). Audiology was standard PTA (0.5 Hz to 8K Hz) or ABR if PTA was not feasible. Where noted, data from a companion Phase I study (NCT02912793) are included. All data are blinded with respect to dose.

Safety

First 4 Subjects - Adverse Event (AE) profile shown below

- AE's Largely of a Grade 1-2 (mild to moderate) severity
- 9 Laboratory AE's
- 2 hearing related AE's, both mild

- * - Related incorporates events at least Possibly or Probably related
- ^ - Not Related incorporates events considered Unlikely and Not Related
- ALT (ALAT) = Alanine transferase, AST (SGOT)= Aspartate Transaminase

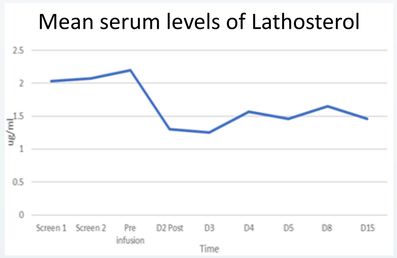
Adverse Event (AE) Toxicity Grading (CTCAE) - N = 64 AEs

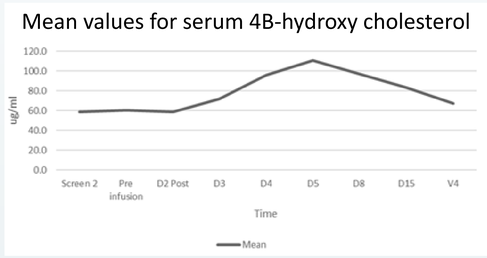
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-Threatening)
No. of Events	42	12	8	2
* Related AE's	15 - ↑bowel movement, fever, ↑ALT, ↑AST, tinnitus, worsened hearing at higher frequencies	1 - ↑bowel movement	0	0
^Not Related AE's	27 - including, ↓platelets, raised CRP, coughing, vomiting, weight loss, nausea, fall, intermittent absence seizures	11, including, rash, seizure, cough, vomiting, headache, anaemia	X 1 anaemia X 7 in the same subject for intermittent seizures / hospitalized	Aspiration pneumonia, declining health / unconscious

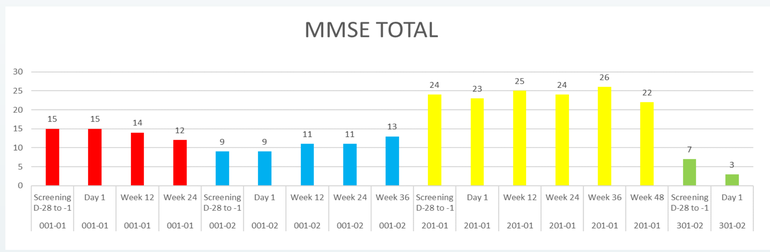
301-02: SAE: Intermittent seizures requiring hospitalisation. This was discussed and considered as not related to study treatment but down to non-compliance with their normal anti-epileptic medication. The subject was withdrawn from the study by family despite positive improvements in their disease.
001-01: SAE: Hospitalised intermittently for general healthy deterioration, aspiration pneumonia and non-study medication overdose. This subject was also withdrawn, by the physician, due to missed dosing and the deterioration in their general condition.

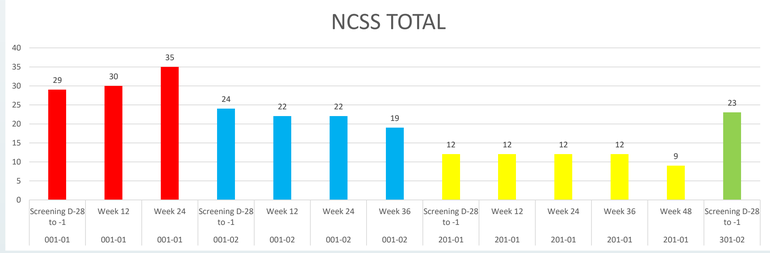
201-01: Hearing: An initial tinnitus was reported and documented at the patient's Week 2 Study Visit. The event was self-limiting, lasting only 48 hours and resolved. At the Week 24 Study Visit, routine audiometry was performed and a reduction of hearing at higher frequencies was noted. However, with no natural history data in this patient population with regards to hearing, and the examination being performed at frequencies outside of the protocol defined range, interpreting this was difficult and continues to be monitored.

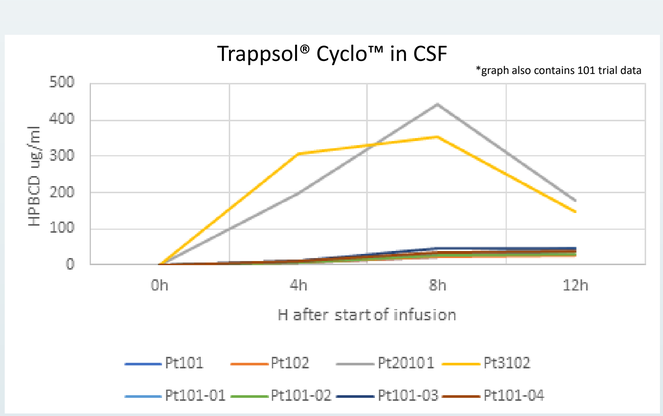
Results

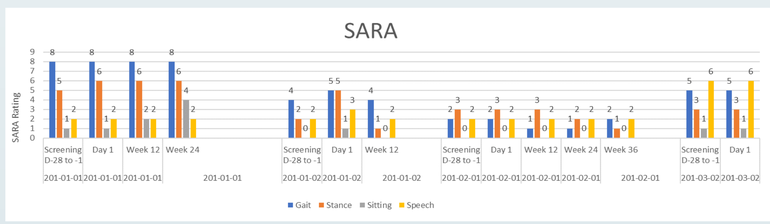


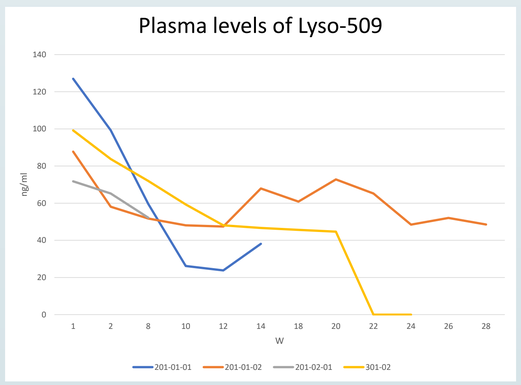






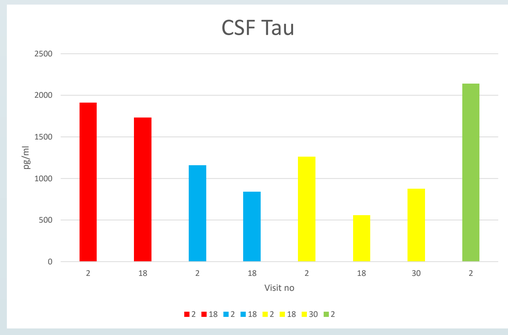






CGI

Subject ID	Visit	CGIS	CGII
001-01	Screening D-28 to -1	3 = Mildly ill	
001-01	Week 12		4 = No change
001-01	Week 24		6 = Much Worse
001-02	Screening D-28 to -1	3 = Mildly ill	
001-02	Week 12		4 = No change
201-01	Screening D-28 to -1	4 = Moderately ill	
201-01	Week 12		3 = Minimally improved
201-01	Week 24		3 = Minimally improved
201-01	Week 36		3 = Minimally improved
301-02	Screening D-28 to -1	1 = Normal, not at all ill	



Summary

Positive safety profile.

Serum biomarkers for cholesterol metabolism indicate that the drug clears cholesterol from cells.

Trappsol® Cyclo™ provided intravenously is detectable in the cerebrospinal fluid (CSF) at levels ranging from 30 ug/ml to 450 ug/ml: the drug enters the CSF

Two biomarkers of NPC disease, lyso-sphingomyelin 509 and tau, show decreasing trends with successive administration of the study drug. Decreases in tau suggest that Trappsol® Cyclo™ may address the neuropathologic aspect of NPC.

Standardized tools show clinical improvements in specific features of the disease in individual subjects (ataxia, cognition, fine motor): more analysis underway

Overall, initial data on safety, pK, serum biochemistry for cholesterol homeostasis, biomarkers for NPC disease, and clinical efficacy are encouraging.

Acknowledgements

We are grateful to all of the patients and families who are participating in this trial, and all of those who contributed compassionate use data to support our trial application regulatory authorities. We also acknowledge partners across Boyd Consultants, especially Professor Alan Boyd, Aptus Clinical, Synteract, Medpace, Centogene, Accenture, and ProductLife. We thank Professor David Begley, Kings College, for critical review of pK data.