Initial findings from a Phase I clinical trial using Hydroxypropyl Beta Cyclodextrin intravenously in Niemann-Pick type C patients

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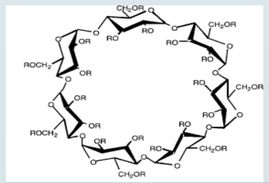
Abstract

Niemann-Pick disease type C is a rare genetic disorder characterized by cholesterol accumulation in every cell of the body. Hydroxypropyl beta cyclodextrins (HPβCDs) 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 in a Phase I study using Trappsol® Cyclo™, the proprietary formulation of HPβCD of CTD Holdings. The trial is randomized, double-blinded, with no control group (NCT02939547). Patients received either 1500 mg/kg or 2500 mg/kg of the drug intravenously over 8 to 9 hours every two weeks for 7 doses total. Results presented remain blinded to dose. Individual and cumulative safety data to date show the drug to be well tolerated. In particular, no clinically significant or permanent hearing problems were observed from IV dosing of Trappsol® Cyclo™ as measured by standard audiometric testing. Lathosterol, a validated serum biomarker reflecting whole body cholesterol synthesis, was reduced after IV administration of the drug, accompanied by a concomitant rise in cholesterol metabolites (24S-, 25-, 27-, and 4B- hydroxycholesterol), suggesting that trapped cholesterol is released and cleared from cells, and cells are responding by suppressing cholesterol synthesis. CSF sampling at timed intervals following the start of IV administration showed increasing levels of drug in the CSF up to 12 hours, indicating that the drug crosses the blood-brain-barrier. Measurements of CSF tau taken at baseline and after the 7th dosing were reduced on average of 30% while two other biomarkers of neuro-inflammation, TNF-alpha and GFAP, were below limits of detection at baseline and after the 7th dose. Results on liver ultrasound and elastography taken at baseline and after the 7th dose will be presented. Overall, initial findings and clinician impressions are encouraging.

Introduction

This presentation provides initial data from four subjects (3 male, 1 female; age range 21 to 37 years, all Caucasian) in CTD's Phase I 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 a randomized, double-blinded, multi-center, parallel group study with no control group. Doses are 1500 mg/kg or 2500 mg/kg of a 25% (w/v) Trappsol® Cyclo™ solution over an 8 – 9 hour IV infusion every two weeks for a period of 14 weeks of treatment (total 7 doses).



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

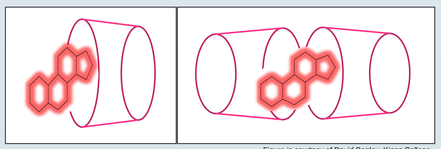


Figure is courtesy of David Begley, Kings College

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 hrs after start of infusion, with half-life of 1-2 hrs (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. Reena Sharma (UK) 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/II study (NCT02912793) are included. All data are blinded with respect to dose.

Safety

Adverse Event (AE) Toxicity Grading (CTCAE)

	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)
No. of Events	5	6	3
Related AE's	nil	Infusion reaction*, Hypoxia*, Fever*	Hypersensitivity Pneumonitis*, Hearing loss*
Not Related AE's	Hematuria, Hearing loss x 3, IV Infiltrated	Headache, Nausea, Vomiting	Hearing Loss

* - Subject 001-03: Withdrawn due to an SAE – discussed further below

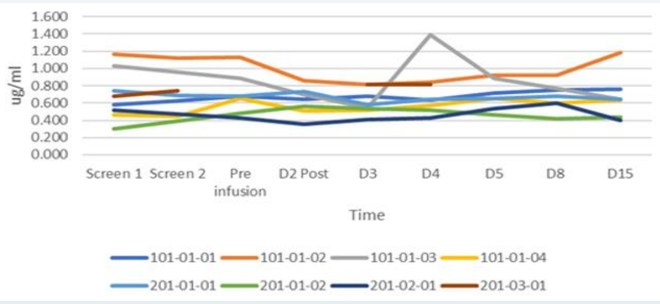
001-01: Hearing: Clinically perceptible reduced hearing of one month duration

001-03: Hearing: Subject experienced an SAE of hypersensitivity pneumonitis resulting in their withdrawal from the study after the first infusion. The subject and family noted a hearing loss and so audiology was performed after their withdrawal. A sensorineural loss was diagnosed and was likely related to an immune-mediated global inflammatory process. Of note also was a complex medical and concomitant medication history making causality association difficult. The reduction in hearing resolved concurrently with an improvement in the hypersensitivity associated interstitial lung disease findings.

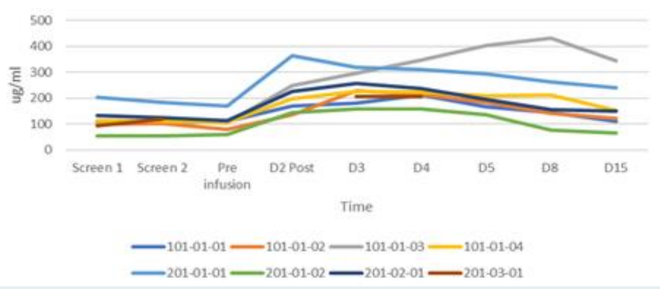
001-04: Hearing: Variable hearing loss from a Grade 1 to Grade 3 severity over the course 3 months. Not perceived by the subject and is fully resolved.

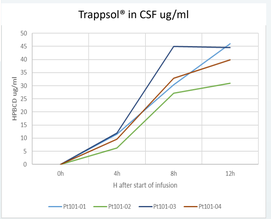
Results

Individual serum levels of Desmosterol at each visit from 4 subjects in the 101 study and 4 subjects in the 201 study

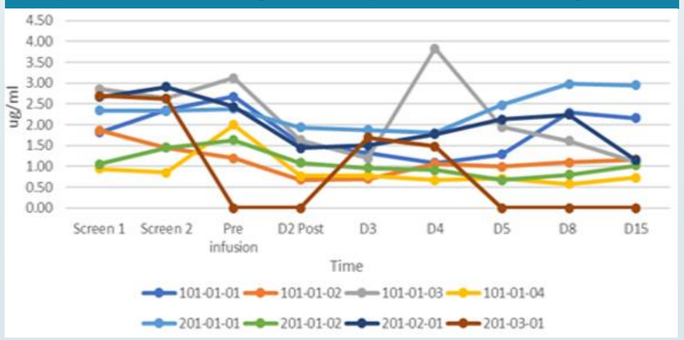


Individual Patient Values for Serum 27-hydroxy cholesterol

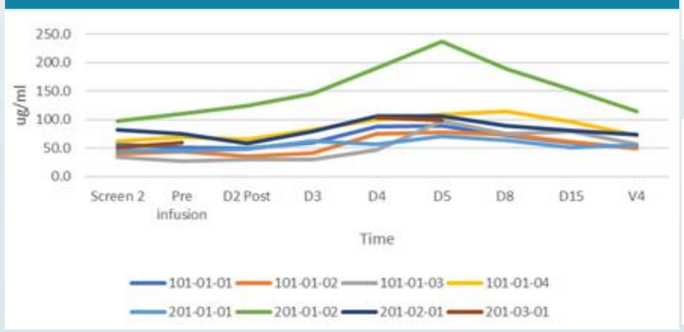


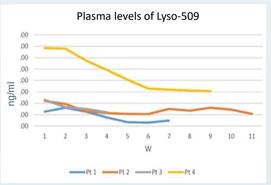


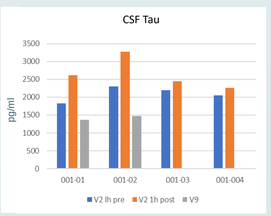
Individual serum levels of Lathosterol at each visit from 4 subjects in the 101 study and 4 subjects in the 201 study



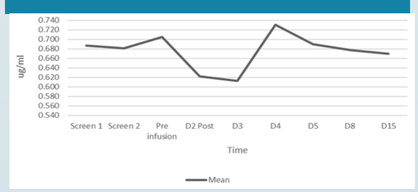
Individual Patient Values for Serum 4B-hydroxy cholesterol



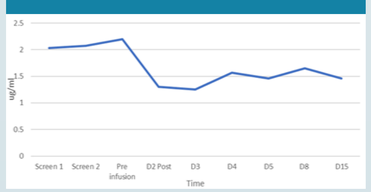




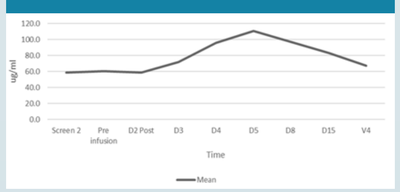
Mean serum levels of Desmosterol (n=8)



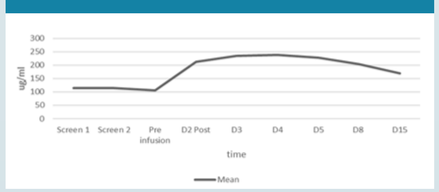
Mean serum levels of Lathosterol



Mean Values for Serum 4B-hydroxy cholesterol



Mean Values for Serum 27-hydroxy cholesterol



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 CSF at levels ranging from 30 ug/ml to 45 ug/ml.

Two biomarkers of NPC disease, lyso-sphingomyelin 509 and tau, show decreasing trends with successive administration of the study drug.

Liver ultrasound and elastography data for the first four subjects were inconclusive. Cholesterol fractionation and histology will be completed at the end of the study and correlated with ultrasound and elastography data.

Initial data on safety, pK, serum biochemistry and biomarkers 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 with FDA. We also acknowledge partners across Boyd Consultants, especially Professor Alan Boyd, Medpace, Centogene, Accenture, ProductLife, and Emmes. We thank Professor David Begley, Kings College, for critical review of pK data.

UCSF Benioff Children's Hospitals

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