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-, 25S-, 27S-, and 48S-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 24th dosing were reduced on average of 30% while two other biomarkers of neuroinflammation, TNF-alpha and GFAp, were below limits of detection at baseline and after the 24th dose. Results on liver ultrasound and elastography taken at baseline and after the 24th 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 varied degrees of benefit in individual compassionate use patients to liver, lung, spleen and the neurologic system. The current trial is a randomized, double-blinded, multicenter, 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).

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). Lyso sphingomyelin-509 was detected 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 II study (NCT02912793) are included. All data are blinded with respect to dose.

Results

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 ng/ml to 45 ng/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.