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 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, 2000 mg/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 (1 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- to 9-hour IV infusion, every two weeks for a period of 48 weeks of treatment (24 doses).

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 8 KHz) 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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (Mild)</td>
<td>42</td>
</tr>
<tr>
<td>Grade 2 (Moderate)</td>
<td>12</td>
</tr>
<tr>
<td>Grade 3 (Severe)</td>
<td>5</td>
</tr>
<tr>
<td>Grade 4 (Life-Threatening)</td>
<td>2</td>
</tr>
</tbody>
</table>

Results

Mean serum levels of Lathosterol and Mean values for serum 4B-hydroxy cholesterol are shown below. Trappsol® Cyclo™ in CSF plasma also contains L501 trial data.

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 µg/ml to 450 µg/ml: the drug enters the CSF.

Two biomarkers of NPC disease, lysosphingomyelin 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

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