TransportNPC

Perspectives on the TransportNPC Trial

TransportNPC is the largest and most advanced clinical trial underway to develop a treatment for NPC and every member of the Cyclo Team is dedicated to advancing this development program as rapidly as possible.

Dear Niemann-Pick C Community,

October is Niemann-Pick Disease Awareness Month, an important opportunity to join together to raise awareness of the impact of this devastating disease and to help bring patients and families more of the support and services they need. It is also an opportunity to spotlight the advances in research that can bring hope for a new treatment and better health for patients in the years ahead.

We are pleased to share with you an update on our efforts to develop a treatment for Niemann-Pick disease type C at Cyclo Therapeutics. In this issue, Dr. Caroline Hastings, a renowned specialist in NPC patient care, shares insights about clinical trials. In addition, Dr. Lise Lund Kjems, Cyclo's new Chief Medical Officer, talks about her decision to join Cyclo and the impact she hopes our work will have for the NPC Community. As we work to continue our progress with the TransportNPC clinical trial, we are very grateful to the patients and families around the world who are joining in this important research effort. TransportNPC is the largest and most advanced clinical trial underway to develop a treatment for NPC and every member of the Cyclo Team is dedicated to advancing this development program as rapidly as possible.

We look forward to continuing to update you on our progress. If you would like any additional information about the TransportNPC trial, please visit clinicaltrials.gov.

Sincerely,

The Cyclo Therapeutics Team

Caroline Hastings, MD

Dr. Caroline Hastings is a hematologist-oncologist and neuro-oncologist at the University of California San Francisco who works with children with blood diseases including blood cancers. In addition, she cares for adults with lysosomal storage disorders and metabolic diseases including Niemann-Pick disease type C. She works on clinical trials for drugs that show promise for treating NPC and serves on related advisory boards, including with foundations dedicated to those affected by the disease.

Insights about Clinical Trials from Dr. Caroline Hastings

Most people, and especially patients and families affected by rare diseases, have heard the term "clinical trials." These are the research programs used to help determine if a drug is safe and effective. There are many factors associated with clinical trials that can be confusing. For example, why do they often take many years to complete? Why are some patients treated with placebo instead of the drug? We invited Dr. Caroline Hastings, a researcher and oncologist at the University of California San Francisco, to share some helpful information about clinical research and what it is like to participate in a trial. Dr. Hastings has worked extensively in research related to Niemann-Pick disease.

Q: How long does it generally take to complete a clinical trial?

Clinical trials are designed with input from statisticians and researchers to determine how many patients need to be included in a study to determine a potential difference in outcome due to the drug effect. They also determine the optimal length of treatment to measure this effect or change. Diseases that progress slowly will often need patients to participate in a trial for a longer period of time compared to diseases that progress quickly. Rarer diseases may require longer periods of time to reach full enrollment due to difficulty in identifying eligible patients. Many clinical trials in rare diseases last one-to-two years for each patient, but it is not uncommon for some trials to last up to four years.

A: What is a placebo control? Why is it so common for many clinical trials to have a placebo control? How is this structured in the TransportNPC trial?

A placebo-controlled trial is one in which patients are randomized to receive the study medication or an inactive substance (called the *placebo*). Neither the patient nor the clinician knows who is being treated with drug or placebo. These types of trials can help to limit bias or influence in interpreting the results and help researchers confirm when safety concerns or clinical changes in the disease can be attributed to the drug (or not).

In the TransportNPC trial there is a placebo control group. Two thirds of patients will be randomly assigned to the study drug and one third will be assigned the placebo. All patients and their clinical teams will be blinded, so no one will know who is receiving the drug or placebo. The study drug is mixed in saline and administered intravenously (IV) while the placebo will be just the saline in the IV. Study participants will undergo all the same assessments, regardless of whether they are receiving study drug or placebo, and all will be treated in the same manner. Clinical outcomes will be carefully monitored. The study will aim to answer questions including whether the study drug prevents or diminishes disease progression, and patients will be enrolled for two years. There is an opportunity mid-way through the trial to assess the outcomes. There will be an independent review board conducting this assessment and making a determination as to whether the trial has shown efficacy at the mid-way point or if the study should continue for another year, based on previously set criteria.

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Q: The TransportNPC trial will administer treatment intravenously. What should patients understand about therapies that are administered via IV to treat NPC?

Drugs that are given through an IV (intravenous) are typically administered by a nurse. They can be administered in a hospital or clinic setting or even in the home with a visiting nurse. It requires placing an IV into a vein in the arm and setting up a pump to deliver drug over a set amount of time. The length of the infusion is based on factors including the volume of fluid used to dilute the drug and the potential for side effects. During the infusion, the site of the IV is periodically checked to make sure the medication is going safely into the vein. IV is a very common way to receive medication and the technique is safe with experienced providers. There are many benefits of IV drug infusion, including assurance the entire drug dose is given (no problem with swallowing medications or not tolerating them in the stomach), not having to keep track of taking medications, and less frequent dosing. Drugs given through IV may also reach higher blood concentrations and have better penetration into certain tissues such as the central nervous system.

Q: Why is it important to have clear eligibility criteria in clinical trials and what are the options for patients who are not eligible to participate in a trial? What about the option of an expanded access program?

To optimize understanding of how a drug works and the safety issues associated with its administration, it is important to design clinical trials precisely to address these questions. Eligibility criteria are created to ensure patients come into the trial in a generally healthy state so that changes in their health can be attributed to the effect of the study drug. It is also very important to keep study patients safe and ensure (as best as possible) that no underlying medical conditions worsen during the treatment or lead to confusion if a safety issue arises. Patients should be similar with respect to the diagnosis, effects of the disease on their body systems and advancement of the disease. Again, this is to ensure the effects of the study drug can be accurately measured and compared among participants.

For patients that do not qualify for participation in a clinical trial, access to the drug through an expanded access program may be an option. It is important to enroll as many patients as possible into the trial. This benefits future patients by increasing our knowledge of the use of a medication in a disease. In the case of rare diseases in which few if any options are available and where certain patients do not meet eligibility criteria for a clinical trial, perhaps due to age or degree of disease progression, having access to a drug through an expanded access program can be an important option. Patients who participate in these programs need to be evaluated for safety just like the clinical trial participants. However, no studies measuring drug concentrations, assessing mechanism of action such as testing biomarkers, or extensive outcome assessments are likely to be part of these programs. Another critical difference between clinical trials and expanded access programs is the cost to the patient. Trials typically cover all costs related to drug administration and assessments, whereas only the drug is provided for

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free in most expanded access programs. All other medical costs associated with drug administration and safety assessments will likely need to be covered by the patient or their insurance.

Q&A with New Cyclo Chief Medical Officer Lise Lund Kjems

Lise Lund Kjems, MD, PhD

We are pleased to announce that we have expanded the leadership team at Cyclo Therapeutics with the addition of Lise Lund Kjems, MD, PhD, our new Chief Medical Officer. Originally from Denmark, Lise received both her MD and PhD from the University of Copenhagen Medical Faculty. She currently lives in the United States and has devoted her professional career to bringing treatments to market for chronic, rare and ultra-rare diseases with high unmet medical needs. Most recently, she led the development program for a treatment for an ultra-rare pediatric liver disease that has now been approved in both the U.S. and Europe. Among her many responsibilities, Lise will be focused on the development of Trappsol® Cyclo™ and our ongoing Phase 3 TransportNPC™ study for the treatment of Niemann-Pick disease type C. Lise will be participating in community events and is looking forward to engaging with many members of the NPC Community. Below she shares some thoughts about her role with Cyclo.

Why did you want to join Cyclo?

In my professional life, it is important that my work make a real difference in peoples' lives. I am drawn to roles that help me make a positive impact on the lives of patients and their families. As the community knows better than anyone, there is an urgent need for approved therapies to treat NPC. I look forward to joining the team in our effort to advance the TransportNPC ™ phase 3 trial as rapidly as possible. I also look forward to engaging with stakeholders including researchers, clinicians and members of the patient community to continue with this important development program. It is a privilege to be working with the team to lead the advancement of this important clinical program and is what inspired me to take on this role.

Why do you believe Cyclo is best positioned to help bring treatment to patients?

It is rare to come across the combination of a proven platform technology with such compelling data and a management team that is as dedicated to developing novel therapies for debilitating diseases and to serving the patient communities. Everyone I have met at Cyclo shares a high level of commitment to improving the lives of those with NPC. We each bring complimentary skills and backgrounds, and a unified focus on our work at hand. The entire team shares the goal of finding a treatment and bringing hope to patients and their families. I will have the opportunity to collaborate closely with Sharon Hrynkow, our Chief Scientific Officer, who has led so much of this drug development program over the past six years, and I look forward to working with Gerry Cox who will remain actively involved in our program as a member of the Cyclo Scientific Advisory Board.

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Every day, I am inspired by the courage and hope of patients living with many different rare diseases. Their strength and resilience in working to improve access to care, disease awareness and research inspire me to do everything in my power to make a positive difference

Are there any updates you can share on the TransportNPC trial?

We are actively enrolling patients at sites in the U.S., and we will update www.clinicaltrials.gov as new site locations become active. If you are interested in enrolling and do not see a site listed near you just yet, please have your treating physician get in touch with us! As a reminder, in the TransportNPC™ study we plan to enroll 93 pediatric and adult patients with NPC1. Eligible patients will be randomized 2:1 to receive investigational drug (Trappsol® Cyclo™) or placebo. The study will last 96 weeks and include an interim analysis at 48 weeks. We understand that 96 weeks can feel like a long time. If we see definitive results at the 48-week mark, that may enable us to accelerate our timelines and switch those from placebo onto study drug earlier than planned.

What inspires you?

Every day, I am inspired by the courage and hope of patients living with many different rare diseases. Their strength and resilience in working to improve access to care, disease awareness and research inspire me to do everything in my power to make a positive difference. I can already see the amazing dedication and unity of the NPC community and I am thrilled I get to be a part of it.

What do you like to do for fun? Where is your happy place?

I enjoy outdoor activities such as walking, biking and gardening. I also enjoy classical music and cooking. I love to go off the beaten path when traveling and learn about new customs and cultures. My family is my happy place.

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