Therapeutic Update

The Cyclo Therapeutics, Inc. team is pleased to provide this update on progress in clinical trials for Niemann-Pick Disease type C (NPC). Cyclo Therapeutics is a clinical-stage biotechnology company that develops cyclodextrin-based products for the treatment of Niemann-Pick Disease Type C1 (NPC1) and Alzheimer's Disease. Our drug development programs are based on intravenous infusions of our proprietary hydroxypropyl beta cyclodextrin product, Trappsol® Cyclo™.

In May 2020, we announced **Top Line data from our Phase I trial** based in the US. This study (NCT02939547) was designed to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of Trappsol® Cyclo™ in NPC1 patients aged 18 years and older, administered by intravenous infusions of either 1500 mg/kg or 2500 mg/kg over 8-9 hours every 2 weeks. The results show a highly favorable safety profile for both doses tested; PK parameters showing that the drug is cleared from the body at expected rates based; evidence of drug in the cerebrospinal fluid several hours after the end of infusions, indicating that it persists for some period (both dose groups); effects on cholesterol synthesis and metabolism for both dose groups; and impacts on tau, a marker for neurodegeneration in the central nervous system. The trend for tau decreased with successive drug administration suggesting a correlation with reduced neurodegeneration (both dose groups). There were 3 hearing-related severe adverse events in the study, all in the high dose group (2500 mg/kg). On cessation of infusions, one patient recovered to baseline hearing levels; one improved but did not return to baseline; and one is awaiting further assessment. According to the investigator, none of the 3 patients nor their families perceived a change in hearing, rather, the changes were detected by audiometry assessments as part of the study's normal screening protocol.

Anecdotally, the treating physician noted that individual patients reported feeling more energetic, more focused, and their families reported greater levels of social engagement and likelihood of initiating activity, including speech. One patient reported specific improvements in speech and swallow. The study was not designed to evaluate efficacy in a short timeframe (14 weeks) but the anecdotal reports are of interest.

The Clinical Study Report for the Phase I trial is expected in August 2020.

All patients who completed the Phase I study opted to participate in the Extension Protocol (NCT03893071) (US-based patients) or to continue on the drug through Compassionate Use programs in their home countries (non-US patients). To date, the adverse event profile in the Extension Protocol is highly favorable. Patients in the Extension Protocol receive the drug every two weeks as in the Phase I study with home-based infusions under the care of qualified health professionals.

In May 2020, Cyclo Therapeutics reported on an **Interim Analysis of our Phase I/II study** (NCT02912793) designed to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and clinical outcomes of Trappsol® Cyclo™ in NPC1 patients aged 2 years and

older. Sites are in the UK, Sweden and Israel. The study drug was administered by intravenous infusions over 8 – 9 hours every two weeks at either 1500 mg/kg, 2000 mg/kg or 2500 mg/kg. The unblinded interim analysis of the Phase I/II study was based on data from 12 patients: four patients had completed the 48-week trial by the cut-off date, two were withdrawn, and six are ongoing. PK results including those related to the drug crossing the blood-brain-barrier were similar to the Phase I study for all dose groups. All three dose groups have shown a favorable safety profile to date as exhibited by AE and SAE profiles: the 2500 mg/kg dose group has no severe adverse events related to hearing in this study. The drug shows similar pharmacodynamic profiles with respect to impact cholesterol synthesis and metabolism as in the Phase I study, and also shows trends toward decreasing levels of tau in the cerebrospinal fluid.

The major efficacy endpoint after 48 weeks of treatment (and as measured at 12-week increments for the interim analysis) is the 17-domain NPC Severity Score (NPCSS). It would be expected that after one year NPC patients with only standard of care and no interventional therapy would worsen their NPCSS by at least 1.5 points. Of the four patients who completed the study at the time of the data cut-off, 3 patients improved in their NPCSS by at least 3 points as compared to baseline while one patient worsened.

Spinocerebellar ataxia, a secondary outcome as measured by the Scale for Assessment and Rating of Ataxia, showed a clear improvement in some patients: the low patient number precluded establishing a dose dependent relationship.

Cyclo Therapeutics Inc. hosted a live webinar to discuss the results from the Phase I trial and interim analysis of the Phase I/II trial. The webinar may be viewed HERE.

The **Phase III Pivotal program** design has been reviewed by both FDA and EMA, and both agencies provided positive feedback. Cyclo Therapeutics is in the final stage of design of the global pivotal protocol, using data from the Phase I and Phase I/II trial to inform dose selection. At the same time, we are actively working to identify clinical sites and investigators to implement the study beginning in the second half of 2020. Physicians interested in learning more should be in touch with Dr. Sharon Hrynkow, Cyclo Therapeutics' Chief Scientific Officer and Senior Vice President for Medical Affairs at Sharon.Hrynkow@cyclodex.com.

Cyclo Therapeutics looks forward to its upcoming virtual participation in the National Niemann Pick Disease Foundation Family Support and Medical Conference (July 11) and the Family Advisory Working Groups (June 28) and hopes to join the Niemann Pick UK annual meeting in September as well as the Australia NPC Disease Foundation meeting, should travel conditions permit.