

## **Niemann Pick Type C Clinical Trials**

This is an exciting and enviable time for the NPC community with several clinical trials currently being discussed. It can be a confusing time too as families try to decipher all of the available information to understand what the trials are about and whether their loved ones a) are eligible, b) whether they want to be involved and c) whether it will be available in their country/location.

Below is a document that is divided into two sections; the section “Clinical Trials” explains what a clinical trial is and provides a list of potential questions to ask as part of your research into the trials, and the section “Clinical Trials Comparison” provides a table comparing the current trials in Niemann Pick Type C.

I would also strongly recommend you read the articles titled “Clinical Trials” and “NPC Trials – My Perspective”, by Dr. William Evans, a parent of a child with NPC and a Niemann Pick UK Trustee. The articles can be found at <http://www.niemann-pick.org.uk/wp-content/uploads/Wills-posts-re-clinical-trials.pdf> and <http://www.niemann-pick.org.uk/wp-content/uploads/NPC-Trials-My-Perspective-Dr-Will-Evans-June-20151.pdf>. It provides a wealth of information about the trials and explains the mechanism in which each drug works. It is well worth your time.

### **Disclaimer**

The "51 and Done" is a committee composed strictly of parents dedicated to providing information and knowledge to the Niemann Pick Type C community on ALL upcoming and future clinical trials. The intent is to ensure parents have objective and relevant information and knowledge to help them decide on the path to take for their loved ones affected by NPC. Please note that the “51 and Done” committee does not engage in the practice of medicine or claim to have medical knowledge. The main purpose of this committee is to provide information and knowledge from publicly available sources.

All material contained in this document is for educational and informative purposes only. It is not intended to substitute medical or professional services nor replace the relationship that exists between patients, their physicians and other health care providers. No action, treatment, independent entities or persons are endorsed and all information is provided without warranty. Any questions should be referred to your physicians and in particular, any changes in treatment or care should be made in conjunction with your medical team.

Since information on the critical trials are under constant revision, it is recommended that you refer to the links provided below for the latest and more complete information about the trial including updates on inclusion/exclusion criteria for trial participation.

If you have any further questions, please call Harry Koujaian at 847 922 2493 or send an email to [NPC51andDone@yahoo.com](mailto:NPC51andDone@yahoo.com).

## **II. Clinical Trials Comparison**

Below is a list of the currently announced clinical trials for Niemann Pick Type C.

<b>Company/ Drug name</b>	<b>NIH/Vorinostat</b>	<b>Orphazyme/ Arimoclomol</b>	<b>Vtesse/VTS-270/Cyclodextrin</b>
<b>Official Trial</b>	Phase 1/2 Study of Vorinostat Therapy in Niemann-Pick Disease, Type C1  <a href="#">NCT02124083</a>	A Prospective Non-therapeutic Study in Patients Diagnosed With Niemann-Pick Disease Type C in Order to Characterise the Individual Patient Disease Profile and Historic Signo-symptomatology Progression Pattern  <a href="#">NCT02435030</a>	A Phase 2b/3 Prospective, Randomized, Double-Blind, Sham-Controlled 3-Part Trial of 2-hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) in Subjects With Neurologic Manifestations of Niemann-Pick Type C1 (NPC1) Disease  <a href="#">NCT02534844</a>
<b>Purpose</b>	Study whether Vorinostat can be repurposed to treat patients with NPC1. Our primary objective is to determine the safety and tolerability of Vorinostat in NPC1 disease.	This is a prospective non-therapeutic observational study in NP-C patients. The aim is to characterize the individual patient disease progression profile through the historical and 6 months prospective evaluation of clinical, imaging, biological(biomarkers) and quality of life data.  Patients will be offered enrollment into a Phase II/III study on arimoclomol at the end of the study.	This study evaluates the efficacy and safety of 2-hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) in patients with neurologic manifestations of Niemann-Pick Type C1 (NPC1) Disease. Approximately two-thirds of patients will receive the study drug, 2-hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD), while the remaining study participants will receive a sham control.
<b>Current Phase</b>	1/2	2/3	2/3
<b>Study Type</b>	Interventional  (A study in which participants	Observational  (A study in which participants	Interventional  (A study in which participants are

	are assigned to receive one or more interventions so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes).	identified as belonging to study groups are assessed for biomedical or health outcomes. The investigator does not assign participants to specific interventions).	assigned to receive one or more interventions so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes).
<b>Primary outcome measure</b>	To assess the safety and tolerability of oral Vorinostat therapy in Niemann Pick Disease, type C1. Please refer to the official trial website (link provided below) for the complete list.	The primary endpoint of the study is disease progression rate including, change in NP-C Clinical Severity scale, change in the Quality of life, changes in the size and/or characteristics of the liver and spleen. Please refer to the official trial website (link provided below) for the complete list.	NPC Clinical Severity Score. Data for NPC score rating will be provided to a centralized independent and blinded rater who will analyze all NPC information for all subjects and assign the NPC Clinical Severity Score. Please refer to the official trial website (link provided below) for the complete list.
<b>Estimated Enrollment:</b>	15	46	51
<b>Study Start Date</b>	April 2015	September 2015	September 2015
<b>Estimated Primary Completion Date</b>	June 2017	March 2016 (Observational Phase), March 2017 Interventional phase	December 2016
<b>Name of Drug</b>	Vorinostat	Arimoclomol	VTS-270 (Cyclodextrin)
<b>Trial Design</b>	This study will enroll up to 12 NPC1 patients and test the safety of two dose levels (200 and 400 mg). Drug will be administered on a 3 days on/4	<i>Stage 1:</i> An observational study, which is a 6 month study used to map the individual patient's baseline	Part A: Three (3) different HP- $\beta$ -CD lumbar intrathecal doses (900 mg, 1200 mg, and 1800 mg) administered IT every 2 weeks for 8 weeks in 9 subjects; 3 subjects will receive sham

	<p>days off schedule for 3 months at each dose level. Patients will be evaluated at the NIH Clinical Center at 0, 3 and 6 months. Safety will be assessed by adverse events (AEs), clinical laboratory tests and physical examinations. Biochemical efficacy will be assessed by measurement of serum and cerebral spinal fluid biomarkers. Clinical efficacy will be evaluated by audiologic testing, assessment ataxia, and swallowing studies.</p>	<p>disease progression rate. The patients stay on current standard of care (including Zavesca and/or symptom management). The stage 1 will provide a baseline of each individual patient that will increase the likelihood of documenting a robust effect of Arimoclomol within the following period of 12 months.</p> <p>Every patient completing the observational study is offered entry to Stage 2.</p> <p><i>Stage 2:</i> The interventional study. Starting immediately after completing stage 1, is a double-blind, controlled study, where patients will receive either Arimoclomol or placebo in addition to their ongoing standard of care treatment for a 12-month period. Patients will be randomized 2:1, which means that two patients will receive Arimoclomol for every one patient receiving placebo. Neither the patients nor the treating physicians will know during the 12 months whether they are receiving placebo or Arimoclomol (i.e., 'double-blind').</p> <p>After completing the 12-month intervention study every patient will be offered Arimoclomol.</p>	<p>treatment. Dose for Part B to be selected for the remainder of the study.</p> <p>Part B: Approximately 51 subjects, including 12 from Part A, will receive lumbar intrathecal infusions of HP-<math>\beta</math>-CD or sham (randomized 2:1) every 2 weeks for a total of 52 weeks.</p> <p>Part C: Open-label extension with IT treatment every 2 weeks.</p> <p>All subjects (sham and drug-treated) with clinically defined worsening following &gt; 6 months of treatment in Part B will be eligible to enter Part C.</p> <p>All subjects who complete Part B will be eligible to enter Part C.</p>
<b>Location</b>	United States. National Institute of Health (NIH)	Denmark, France, Germany, Italy, Poland, Spain, Switzerland, UK.	USA, UK, Germany (Centres in other countries may be added)

<b>Eligibility</b>	Age of Eligibility: 18 to 60 yrs Eligible Genders: Both	Age of Eligibility: 2 to 18 yrs Eligible Genders: Both	Age of Eligibility: 6 to 21 yrs Eligible Genders: Both
<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Aged greater than or equal to 18 and less than or equal to 60 years old at time of enrollment, either gender, and any ethnicity.</li> <li>• Confirmed diagnosis of NPC1</li> <li>• Patients with at least one neurological manifestation of NPC1. For example, but not limited to, hearing loss, vertical supranuclear gaze palsy, ataxia, dementia, dystonia, seizures, dysarthria, or dysphagia.</li> <li>• A patient's cultured skin fibroblasts when treated with 10 M Vorinostat must exhibit a reduction in the filipin lysosomal storage organelle ratio equivalent to 75% of the response measured in NPC1 positive control fibroblasts.</li> <li>• Ability to travel to the NIH Clinical Center repeatedly for evaluation and follow-up.</li> <li>• If taking miglustat, the patient must have been taking a constant dose of the medication for no less than three months prior to</li> </ul>	<ul style="list-style-type: none"> <li>• Written informed consent (and assent if appropriate to local laws and regulations) prior to any study-related procedures.</li> <li>• Males and females aged from 2 years to 18 years and 11 months.</li> <li>• Patient weight <math>\geq</math>15th percentile of body mass index (BMI) for age according to the World Health Organisation (WHO) standards.</li> <li>• Diagnosis of Niemann Pick disease Type C (NP-C), either NPC1 or NPC2.</li> <li>• Presenting at least one neurological symptom of the disease (for example, but not limited to, hearing loss, vertical supranuclear gaze palsy, ataxia, dementia, dystonia, seizures, dysarthria, or dysphagia).</li> <li>• Ability to walk either independently or with assistance</li> <li>• Ability to travel to the corresponding clinical trial site repeatedly (every 6 months) for evaluation and follow-up;</li> <li>• Ability to comply with the protocol-specified procedures/evaluations and scheduled visits;</li> <li>• Willing to participate in all aspects</li> </ul>	<p>Parts A and B:</p> <ul style="list-style-type: none"> <li>• Onset of neurological symptoms prior to 15 years of age.</li> <li>• Confirmed diagnosis of NPC1</li> <li>• Subject or parent/guardian must provide written informed consent and assent (for minors).</li> <li>• Ability to undergo a lumbar puncture (LP) and IT drug administration under conscious sedation or general anesthesia.</li> <li>• An NPC Clinical Severity Scale Score of 1 through 4, inclusive, in two or more of the following on the NPC Severity Scale components: ambulation, fine motor skills, or swallowing and a score of 0 through 4 on the cognition component.</li> <li>• Total NPC Clinical Severity Scale Score of 10 or greater.</li> <li>• If taking miglustat, must have been on a stable dose for past 6 months and be willing to remain on a stable dose.</li> <li>• Agree to discontinue all non-prescription supplements such as Coenzyme Q10, curcumin, cinnamon, fish oil supplements, high dose vitamin D</li> </ul>

	<p>baseline evaluation and must be willing to maintain that dose level for the duration of the trial.</p> <ul style="list-style-type: none"> <li>• Willing to discontinue all non-prescription supplements, with the exception of an age-appropriate multivitamin.</li> <li>• Women of reproductive age must be willing to use an effective method of contraception for the duration of the trial.</li> <li>• Willing to participate in all aspects of trial design including serial blood and CSF collections.</li> </ul>	<p>of trial design including serial blood sampling, skin biopsies and imaging (ultrasonography and MRI/MRS) collections.</p>	<p>(&gt;500(mIU)/day), acetyllecine, or ginkgo biloba at least 1 month prior to first dose (Study Day 0).</p> <ul style="list-style-type: none"> <li>• Agree to discontinue any other investigational treatments for NPC including vorinostat or arimoclomol at least 3 months prior to first dose (Study Day 0).</li> <li>• Females of child-bearing potential (not surgically sterile) must use a medically acceptable method of contraception and must agree to continue use of this method for the duration of the study and for 30 days after participation in the study.</li> </ul> <p>Part C:</p> <ul style="list-style-type: none"> <li>• Subject has completed Part B, or meets the criteria for the Rescue Option.</li> </ul>
<p><b>Exclusion Criteria</b></p>	<ul style="list-style-type: none"> <li>• Aged below 18 or above 60 years of age at enrollment in the trial.</li> <li>• Severe manifestations of NPC1 that would interfere with the patient's ability to comply with the requirements of this protocol.</li> <li>• Neurologically asymptomatic patients.</li> <li>• Patients who have received any form of cyclodextrin or an HDACi in an attempt to</li> </ul>	<ul style="list-style-type: none"> <li>• No written informed consent obtained from the patient or their parent(s)/legal guardian(s) (and assent if appropriate to local laws and regulation) before any study related procedures;</li> <li>• Recipient of a liver transplant or planned liver transplantation;</li> <li>• Patients with uncontrolled severe epileptic seizures</li> <li>• Neurologically asymptomatic patients;</li> <li>• Severe liver insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Exclusion criteria as assessed by NPC Clinical Severity Scale: <ul style="list-style-type: none"> <li>○ Unable to walk, wheelchair dependent (ambulation NPC score=5)</li> <li>○ Needs a nasogastric tube to overcome swallowing difficulties (swallowing NPC score=5)</li> <li>○ Severe dysmetria (fine motor NPC score=5)</li> <li>○ Minimal cognitive function (cognition NPC</li> </ul> </li> </ul>

	<p>treat NPC1.</p> <ul style="list-style-type: none"> <li>• Thrombocytopenia defined as a platelet count less than 75,000 per microliter, or a history of greater than or equal to grade 2 thrombocytopenia (50,000-75,000 platelets/microliter).</li> <li>• Diabetes or a fasting glucose greater than 106 mg/dl.</li> <li>• Active pulmonary disease, oxygen requirement or clinically significant history of decreased blood oxygen saturation, pulmonary therapy, or requiring active suction.</li> <li>• Patients with uncontrolled seizures</li> <li>• Use of another HDAC inhibitor or compounds with established HDAC inhibitory activity.</li> <li>• Patients, who in the opinion of the investigators, are unable to comply with the protocol or have specific health concerns that would potentially increase the risk of participation.</li> </ul>	<ul style="list-style-type: none"> <li>• Severe manifestations of NP-C disease that would interfere with the patient's ability to comply with the requirements of this protocol;</li> <li>• In the opinion of the Investigator, the patient's clinical condition does not allow for the required blood collection and/or skin biopsies as per the protocol-specified procedures;</li> <li>• Current participation in another trial is not permitted unless it is a non-interventional study and the sole purpose of the trial is for long-term follow up/survival data (registry);</li> <li>• Patients will be excluded if there is a confirmed risk linked to the MRI procedure to be performed in the subsequent therapeutic interventional study</li> <li>• Patients will be excluded if there is a confirmed risk linked to the skin punch biopsy procedure like severe thrombocytopenia, at investigator's discretion.</li> </ul>	<p>score=5).</p> <ul style="list-style-type: none"> <li>• Body weight &lt; 15 kg (&lt; 33 lbs)</li> <li>• Prior treatment at any time with HP-β-CD for NPC1 disease.</li> <li>• Uncontrolled seizures, specifically: greater than 1 seizure over a 2-month period (quantified over the 6 months prior to enrollment) or subjects requiring more than 2 antiepileptic medications to control seizures.</li> <li>• Subjects on antipsychotics for treatment of psychosis.</li> <li>• History of hypersensitivity reactions to any product containing HP-β-CD.</li> <li>• Spinal deformity that could impact the ability to perform a lumbar puncture.</li> <li>• Skin infection in the lumbar region within 2 months of study entry.</li> <li>• Thrombocytopenia (platelet count of less than 75 X 10<sup>9</sup>/L).</li> <li>• Recent use of anticoagulants [in past 2 weeks prior to first dose (Study Day 0); re: lumbar puncture safety].</li> <li>• Subjects unable to comply with the study procedures or with a clinical disease or laboratory abnormality that in the opinion of the investigator would potentially</li> </ul>
--	--	--	---

			increase the risk of participation.
<b>Link to website</b>	<a href="https://clinicaltrials.gov/ct2/show/NCT02124083?term=vorinostat+niemann+pick&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT02124083?term=vorinostat+niemann+pick&amp;rank=1</a>	<a href="https://clinicaltrials.gov/ct2/show/NCT02435030?term=Arimoclomol&amp;rank=5">https://clinicaltrials.gov/ct2/show/NCT02435030?term=Arimoclomol&amp;rank=5</a>	<a href="https://clinicaltrials.gov/ct2/show/NCT02534844?term=vtesse&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT02534844?term=vtesse&amp;rank=1</a> <a href="http://www.thenpcstudy.com/">http://www.thenpcstudy.com/</a>

## Links to trials

NIH/Vorinostat

- <https://clinicaltrials.gov/ct2/show/NCT02124083?term=vorinostat+niemann&rank=1>

Orphazyme/ Arimoclomol

- <https://clinicaltrials.gov/ct2/show/NCT02435030?term=orphazyme&rank=1>
- <http://www.orphazyme.com/index.php/news/news-releases/58-clinical-update-orphazyme-announces-update-to-its-niemann-pick-disease-type-c-clinical-programme-aidnpc>

Vtesse/VTS-270 (Cyclodextrin)

- <https://clinicaltrials.gov/ct2/show/NCT02534844?term=vtesse&rank=1>
- <http://www.thenpcstudy.com/>

## References

- Clinical Trials <https://www.nlm.nih.gov/medlineplus/clinicaltrials.html>
- Learn About Clinical Studies <https://www.clinicaltrials.gov/ct2/about-studies/learn>
- Clinical Trials [http://ec.europa.eu/research/health/medical-research/clinical-trials/index\\_en.html](http://ec.europa.eu/research/health/medical-research/clinical-trials/index_en.html)
- Clinical Trials at <http://www.niemann-pick.org.uk/wp-content/uploads/Wills-posts-re-clinical-trials.pdf>

As stated, all material contained in this document is for educational and informative purposes only. It is not intended to substitute medical or professional services nor replace the relationship that exists between patients, their physicians and other health care providers. No action, treatment, independent entities or persons are endorsed and all information is provided without warranty. Any questions should be referred to your physicians and in particular, any changes in treatment or care should be made in conjunction with your medical team.