# STUDY PROTOCOL

## *Phase I/II study of NORTHERA (DROXIDOPA) for Dysautonomia in Adult Survivors of Menkes Disease and Adults with Occipital Horn Syndrome*

Double-blind Placebo-controlled Randomized Crossover Clinical Trial

**Protocol Version/Date: 1.7 Version** (15MAR2022)

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## 1.0 PROTOCOL SYNOPSIS

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|---|---|
| **Title** | *Phase I/II Study of NORTHERA (DROXIDOPA) for Dysautonomia in Adult Survivors of Menkes Disease or Adults with Occipital Horn Syndrome* |
| **Study ID Number** | 00001113 |
| **Clinical Study Phase** | Phase I/II |
| **Number of Centers** | Single site (Nationwide Children's Hospital) |
| **Study Design** | Double-blind placebo-controlled randomized crossover clinical trial |
| **Patient Population** | Inclusion Criteria<br>1. Adult persons with Menkes disease who survived beyond the expected natural history, attained independent ambulation, attend (or attended) school, and reached adulthood after early CuHis treatment for three years or adults with Occipital Horn Syndrome, who manifest clinical signs and symptoms of dysautonomia, e.g., orthostatic hypotension: specifically, a decrease in systolic or diastolic blood pressure of at least 20 or 10 mm Hg, respectively, within three minutes after standing, and/or chronic diarrhea: production of loose stools with or without increased stool frequency for more than four weeks immediately preceding enrollment.<br>2. History of at least thrice weekly occurrence of dizziness/feeling lightheaded while standing upright and/or thrice weekly episodes of diarrhea or an urgent need to defecate after food ingestion for more than four weeks immediately preceding enrollment.<br>3. Documented mutation in *ATP7A*.<br>4. Must sign and date an Informed Consent Form (ICF).<br>5. Age ≥ 18 years of age.<br>6. Ability to adhere to the prescribed oral *Northera (Droxidopa)* regimen.<br>7. Willingness to comply with all study visits and procedures.<br>Exclusion Criteria<br>1. Pre-existing liver (e.g., hepatitis, biliary atresia, cirrhosis) or kidney disease (i.e., calculated glomerular filtration rate <30 ml/min).<br>2. History of hypertension, anti-hypertensive therapy, heart failure (or decreased ejection fraction), cardiac arrhythmia, or bleeding diatheses.<br>3. Any disease or condition that, in the opinion of the Investigator, has a high probability of precluding the subject from completing the study or where the subject cannot or will not appropriately comply with study requirements.<br>4. Any alpha-1 adrenoreceptor agonist, beta-blocker, DOPA decarboxylase inhibitor, midodrine, ephedrine, or any triptan medication as a concomitant medication. |
| | Provide *Northera (Droxidopa)* treatment in a dose titration schedule (100mg, 200mg, 300mg po b.i.d. for adults and a blinded placebo control crossover to evaluate safety and assess clinical (hemodynamic and gastrointestinal effects) and plasma neurochemical responses and effect on symptoms during a six-week period. Please see Protocol Schema p18 for detailed description of all study procedures. |
| **Primary Outcome** | Safety and Tolerability |
| **Secondary Outcomes** | 1. Improved plasma neurochemical levels<br>2. Improved systolic blood pressure<br>3. Improved gastrointestinal symptoms<br>4. Improved performance on tests of physical exertion |
| **Exploratory Outcome** | Improved scores on the Orthostatic Hypotension Symptom Assessment Questionnaire |
| **Study Duration** | 13 to 18 weeks per Subject (depending on cumulative visit interval) |

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| **Sample Size** | Six to 10 adult subjects |
| **Statistical Analysis** | The safety and effect(s) of *Northera (Droxidopa)* treatment will be assessed in a double blind, placebo-controlled, two-period, randomized, crossover design by comparing baseline to treatment and placebo-treatment data using paired *t* tests or a linear mixed-effects model. |
| **Long-term follow-up** | After participation in this study, subjects will be followed up by their local physicians under a normal standard of care, and also will be seen annually in the NCH Menkes Disease Clinic. Subjects may also be followed by phone and/or medical records. |

## 2.0 Introduction

Menkes disease is an X-linked recessive disorder of human copper metabolism with a predicted minimum birth prevalence of 1 in 34,810 live male births based on loss-of-function variant frequencies in the Genome Aggregation Database (gnomAD) [1] for *ATP7A*, which encodes an essential copper-transporting ATPase [2-4]. Abnormal plasma neurochemical levels due to deficiency of a copper-requiring enzyme, dopamine-β-hydroxylase, are diagnostic in affected Menkes newborns [5]. A brief window of therapeutic opportunity exists in the newborn period during which medical intervention can prevent the inexorable downhill course otherwise expected for this illness, as demonstrated with Copper Histidinate (CuHis) treatment [5,6]. Another emerging approach, adeno-associated virus-mediated *ATP7A* gene therapy, appears highly promising, demonstrating a synergistic treatment effect with CuHis in the Menkes mouse model [7,8].

Survivors of the profound central nervous system (CNS) effects of this illness, spared by their early diagnosis and successful responses to early subcutaneous CuHis treatment (daily injections for the first three years of life), sometimes develop symptoms of dysautonomia, including dizziness, lightheadedness, syncopal episodes, low blood pressure, and chronic diarrhea. This reflects a persistent defect in Cu delivery into the secretory pathway of cells, including sympathetic (dopaminergic) neurons that regulate the autonomic nervous system, resulting in diminished DBH activity and deficiency of norepinephrine (**Fig. 1**).

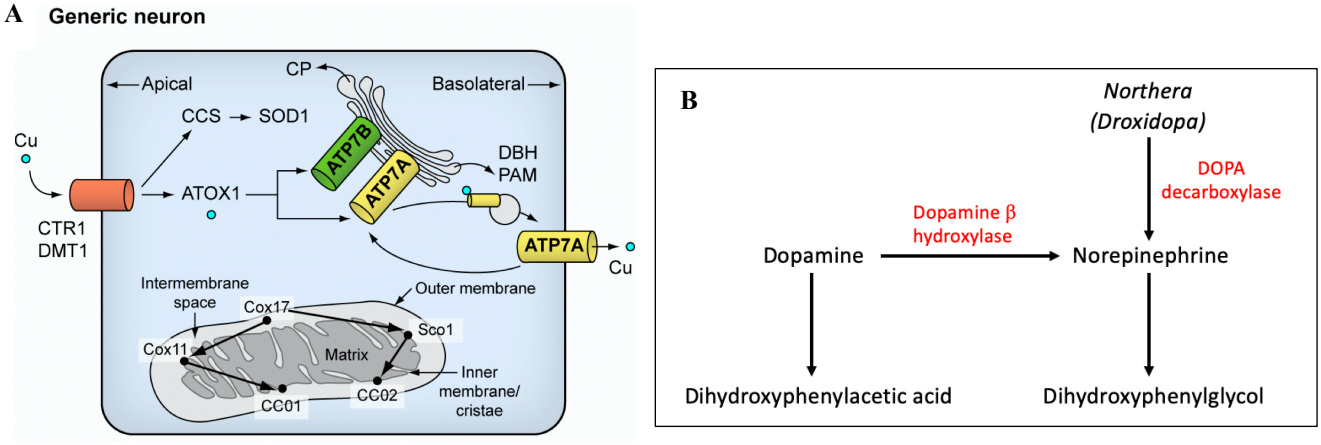


**Figure 1. Normal neuronal copper transport and catecholamine biosynthesis. A)** In neuronal cells, Cu uptake is mediated by CTR1 and DMT1 and ferried to various intracellular destinations by a set of copper chaperones (CCS, ATOX1, Cox17, Cox11 and Sco1). The copper transporting ATPases ATP7B (Wilson disease) and ATP7A (Menkes disease, Occipital Horn syndrome) are both localized at the *trans*-Golgi network and required for maturation of ceruloplasmin (CP), and dopamine-β-hydroxylase (DBH) and peptidylglycine-α-amidating monooxygenase (PAM), respectively. Details of cytochrome c oxidase (CCO) subunit metalation are illustrated here. With an increase in Cu levels, ATP7A normally traffics from the somatodendritic to axonal (basolateral) region. **(**From Kaler SG. *Nat Rev Neurol* 2011). **B)** In dopaminergic neurons, the catecholamine biosynthetic pathway requires DBH to convert dopamine

to norepinephrine. Since DBH acquires its copper co-factor based on the activity of ATP7A, subjects with Menkes disease and Occipital Horn syndrome have diminished DBH activity. In contrast, DOPA decarboxylase converts L-DOPS (*Droxidopa*) to norepinephrine and is not Cu-dependent.

Early treatment with CuHis enhances delivery of copper to the developing brain in Menkes disease patients, who have all the other proper Cu-transport machinery, except for ATP7A. Without ATP7A, however, correction of DBH (and PAM, a cuproenzyme responsible for amidation of various neuropeptides) deficiency is not possible in Menkes disease subjects, whether or not under treatment with CuHis. The importance of CuHis in Menkes subjects is to enhance Cu delivery across the blood-CSF and blood-brain barriers. This facilitates restoring the activities of brain cuproenzymes such as SOD1 and CCO during the critical first three years of life, when brain growth and development is particularly rapid (**Fig. 2**). Our Phase I/II and Phase III studies limited CuHis treatment to three years based on this fact, as well as benefit-to-risk considerations related to potential renal toxicity (NCT00001262, NCT00811785). Importantly, three years of daily CuHis treatment was adequate to prevent premature death in a large majority of classic Menkes disease subjects treated from early infancy who now range in age from 3 to 27 years. In addition to prolonged survival, these individuals manifest impressive neurodevelopmental and neurocognitive outcomes. They have all attended school, including college in some instances, and are socially active. Some have learned to drive, voted in US national elections, and joined the work force.

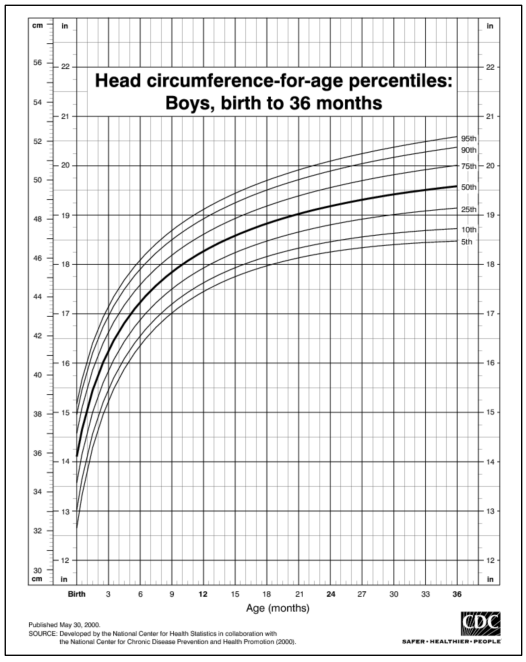


**Figure 2**. Growth velocity of head circumference in first 3 years of life is steep especially in year 1. Head growth reflects underlying brain growth.

However, troubling symptoms of dysautonomia consistent with DBH deficiency and typically beginning at 7 to 10 years of age as they grew taller, has inconvenienced the lives of these Menkes survivors. They often experience dizziness, lightheadedness, syncopal or near-syncopal episodes, and chronic diarrhea, all symptoms reported in adults with congenital absence of DBH, an autosomal recessive disorder not associated with any neurodevelopmental problems in infancy or early childhood [9-11]. Menkes disease survivors typically first manifest these symptoms in mid-late childhood or early adolescence, when they grow taller. Advancing linear growth in children necessitates higher blood pressure to overcome gravity and enable adequate brain perfusion [12].

Occipital horn syndrome (OHS) is a milder allelic variant of Menkes disease in which the neurologic phenotype is far less severe; the diagnosis of occipital horn syndrome is not evident until late childhood or early teenage rather than during infancy [13-17]. Many subjects with the OHS phenotype at these ages also manifest dysautonomia in the form of frequent syncopal episodes [14-17] and chronic diarrhea [13-17]. A recent review [18] indicated that symptoms of dysautonomia, including chronic diarrhea, temperature instability, and orthostatic hypotension are present in almost 90% (13/15) of OHS patients and can be disabling. These symptoms reflect impaired sympathetic noradrenergic function related to DBH deficiency.

Sympathoneural ablation with hydroxydopamine, and blockade of vesicular uptake with reserpine produce diarrhea in experimental animals [19,20]. The loose stools and chronic diarrhea in Menkes disease survivors appears to reflect increased gastrointestinal motility and poor rectal sphincter control caused by unopposed parasympathetic stimulation and are also reported in individuals with isolated DBH deficiency (21) and in OHS [17,18].

## 2.1 Background

The synthetic amino acid L-threo-3,4-dihydroxyphenylserine (L-DOPS, *Droxidopa*) is highly effective in reversing neurogenic orthostatic hypotension and correcting abnormal neurochemical levels in patients with autosomal recessive congenital absence of dopamine-β-hydroxylase (DBH) [22-24]. DBH deficiency is, in fact, one of the labelled indications for *Northera (Droxidopa)* (**Appendices 1, 1A**, Full Prescribing Information). *Northera (Droxidopa)* is metabolized by the enzyme DOPA decarboxylase, which does not require copper to produce norepinephrine, bypassing the DBH enzymatic defect [22]. Individuals with the copper transport disorders Menke disease and occipital horn syndrome (OHS), an *ATP7A*-related variant of Menkes, have partial deficiency of DBH, show distinctive neurochemical abnormalities [5,13,25-27], and frequently symptoms of dysautonomia, such as syncope, dizziness, orthostatic hypotension, and bowel dysfunction (chronic diarrhea) [13-18]. As in patients with congenital absence of DBH [22,23], these problems in autonomic nervous system function seem potentially responsive to restoration of normal neurochemical levels by *Northera (Droxidopa)* treatment.

Menkes disease is an X-linked recessive disease caused by diverse loss-of-function mutations in the gene encoding a copper-transporting ATPase, *ATP7A* [2-6,28]. One function of ATP7A is the delivery of intracellular copper to the *trans*-Golgi network (TGN) for incorporation into specific enzymes within the secretory pathway of cells. Dopamine-β-hydroxylase (DBH), the enzyme catalyzing the conversion of dopamine to norepinephrine (NE) is one such copper-dependent enzyme processed in the TGN. Patients with *ATP7A* mutations (Menkes, OHS) therefore show evidence of partial DBH deficiency [5,25-27].

Affected Menkes disease infants appear healthy at birth and develop normally for 6 to 8 weeks, after which hypotonia, seizures, failure to thrive, and connective tissue abnormalities occur, leading to premature death, often by three years of age [3]. Neonatal diagnosis, sometimes via neurochemical evidence of DBH deficiency, and early treatment with copper injections may improve survival and clinical outcomes [5,6].

The complete pathophysiologic impact of decreased DBH activity in Menkes disease and OHS remains unknown. Mice with knockout of the DBH gene die *in utero*, implying a vital role of NE in neural development [29]. In contrast, humans with autosomal recessive congenital absence of DBH have no major neurodevelopmental consequences but manifest signs of autonomic dysfunction including syncope, dizziness, and orthostatic hypotension, symptoms which are relieved by oral L-DOPS (*Droxidopa*) treatment [22-24]. Furthermore, the abnormal neurochemical levels in these patients are improved by this treatment.

### 2.1.1 Name of the Drug

*Northera*™ (*Droxidopa*) (Treatment A; label known only to the NCH Pharmacy Investigational Drug Service) (please see **Appendices 1, 1A**) will be provided to adult subjects as a capsule with with

100mg, 200mg, or 300mg of *Northera (Droxidopa)* contained within gelatin color capsules (sky blue and white, size 0). These are physically indistinguishable from the Treatment B (placebo) capsules. The synthetic amino acid L-threo-3,4-dihydroxyphenylserine (*Northera (Droxidopa)*) is highly effective in reversing neurogenic orthostatic hypotension and correcting neurochemical abnormalities in patients with autosomal recessive congenital absence of dopamine-beta-hydroxylase (DBH) [22-24].

*Northera (Droxidopa)* is metabolized by the enzyme DOPA decarboxylase to produce norepinephrine, thus bypassing the DBH enzymatic defect. Individuals with the copper transport disorders Menkes disease and occipital horn syndrome (OHS), have partial deficiency of DBH, which is copper-dependent, and show distinctive neurochemical abnormalities and sometimes symptoms of dysautonomia, such as syncope, dizziness, orthostatic hypotension, and chronic diarrhea. As in patients with congenital absence of DBH, these problems in autonomic nervous system function seem potentially responsive to restoration of normal neurochemical levels.

*Placebo* (Treatment B; label known only to the NCH Pharmacy Investigational Drug Service): Empty gelatin color capsules (sky blue and white, size 0) filled with cellulose microcrystalline and physically indistinguishable from Treatment A capsules.

## 2.0 Clinical Information

### 2.1. Clinical Trial and Principal Investigator

This clinical trial will evaluate the safety of *Northera (Droxidopa)* treatment in young adults who survived the major neurodegenerative and neurocognitive effects of Menkes disease via early CuHis treatment. We hypothesize that *Northera (Droxidopa)* treatment in Menkes disease survivors with dysautonomia will improve blood neurochemical levels, raise systolic blood pressure, reduce diarrhea, improve performance on tests of physical exertion, and enhance overall quality of life. **We will test this hypothesis, in six to 10 adult Menkes disease survivors or OHS patients, with symptoms of dysautonomia, by evaluating *Northera (Droxidopa)* treatment in a dose-ascending schedule (100 mg to 300 mg p.o. b.i.d) with a power of 95% at the proposed sample size** [30]**.** Please also see *Statistical Analysis Plan*, **Appendix 5**). Primary outcome will establish safety and tolerability, and secondary outcomes will evaluate plasma norepinephrine and DHPG levels, systolic blood pressure, and performance on tests of physical exertion. We seek to understand whether *Northera (Droxidopa)* will engender a favorable effect on dysautonomia symptoms during a six-week period in comparison to a placebo treatment. Using a double-blind, placebo-controlled randomized crossover design, we will gain a clear delineation of safety and tolerability, as well as preliminary efficacy data for *Northera (Droxidopa)* in this population. Since the half-life of *Northera (Droxidopa)* is approximately 2.5 hours [24], (**Appendices 1, 1A**) after peaking at approximately 3 hours following a p.o. dose, carryover effects when transitioning between the drug and placebo arms are not anticipated, especially when a 7-10 day washout between periods is included. We expect to complete this pilot study within five years.

The principal investigator has long-term experience and interest in Menkes disease, human copper metabolism, and conduct of clinical trials (please see NIH Biosketch for details specific to this project).

## 2.2. Rationale for Using Drug(s) for indication

The synthetic amino acid L-threo-3,4-dihydroxyphenylserine (*Northera (Droxidopa*) is effective in reversing neurogenic orthostatic hypotension and correcting neurochemical abnormalities in patients with autosomal recessive congenital absence of dopamine-beta-hydroxylase (DBH) [22-24]. *Northera (Droxidopa)* is metabolized by the enzyme dihydroxyphenylalanine (DOPA) decarboxylase to produce norepinephrine, thus bypassing the DBH enzymatic defect [22]. Individuals with the copper transport disorder Menke disease who survive beyond early childhood due to very early diagnosis and three years of daily CuHis injections [5,6,28] often have evidence of persistent low DBH activity, with distinctive neurochemical abnormalities and symptoms of dysautonomia, such as syncope, dizziness, orthostatic hypotension, and gastrointestinal dysfunction. These subjects harbor a variety of *ATP7A* mutation types, including deletion/duplication, nonsense, splice junction, and missense (**Table 1**).

**Table 1.** Adult Menkes Disease Survivors and OHS Subjects at Risk for Dysautonomia

| **Current Age** (Years) | ***ATP7A* mutation** | **Diagnosis** | **Age enrolled in CuHis treatment trial [Reference]** |
|---|---|---|---|
| 19 | G666R | Menkes | 10 days [5] |
| 20 | IVS9; DS, +6, t>g | Menkes | 9 days [5] |
| 25 | R201X | Menkes | 8 days [6] |
| 27 | IVS8; AS, dup5 | Menkes | 8 days [6] |
| 31 | IVS14 DS, +4, a>g (c.2917-4a>g) | OHS | Not enrolled [18] |
| 41 | IVS11; DS, -2, A>G (S833G) | OHS | 11 years [6,13] |

The occipital horn syndrome (OHS) is a neurologically milder allelic variant of Menkes disease [13]. This condition takes its name from the wedge-shaped calcifications that form bilaterally within the trapezius and sternocleidomastoid muscle tendons at their point of attachment to the occiput in affected individuals, generally by the second decade of life. Such protuberances can be palpated in some patients and are demonstrable radiographically on lateral and Towne's view skull X-rays or appropriate sagittal images from CT or MRI [4,13,16,18]. OHS shares the hair and connective tissue abnormalities observed in classic Menkes disease, which are attributable to a lysyl oxidase deficiency [14]. However, since the neurological phenotype in OHS is mild (slight generalized muscle weakness, and dysautonomia that includes syncope, orthostatic hypotension and chronic diarrhea), affected individuals often escape detection until mid-childhood or later. Patients with this variant of Menkes disease manifest low-normal levels of serum copper and ceruloplasmin, and distinctively abnormal plasma and CSF catecholamine levels [13,27], reflecting deficiency of DBH activity, as in Menkes disease. We treated one OHS individual with CuHis [6,13] (**Table 1**) who has reached adulthood. A number of other adult OHS patients may be available for recruitment to this study from academic departments of medical genetics, neurology, and gastroenterology [18].

As in patients with deficiency of DBH unrelated to copper metabolism, these problems in autonomic nervous system function seem potentially responsive to restoration of normal neurochemical levels via *Northera (Droxidopa)* treatment [22-24]. Therefore, there is prospect of direct benefit from this treatment for adult Menkes survivors and adults with OHS.

## 2.3. Preliminary Clinical Data

One 11-year-old Menkes disease survivor with a large deletion (exons 2-19) in the *ATP7A* gene (which contains 23 exons) detected by DNA microarray in the first month of life who was referred for enrollment in the phase 3 early CuHis treatment protocol (NCT00811785) has experienced significant dysautonomia for the past six years. This young man attained normal gross motor, fine motor, personal-social, and language development, and attends school in normal classes. A significant issue affecting this patient's life, however, is the need to stop and squat after walking short distances. After a few seconds squatting, he is able to resume walking before having to squat again. These episodes are attributed to orthostatic hypotension. He has also had numerous episodes of syncope and lightheadedness, especially on rising from prone or seated positions, as well as chronic diarrhea, all known manifestations of dysautonomia attributable to reduced DBH activity and NE deficiency [9,10,21].

This Menkes disease survivor was evaluated at 10 years of age in July 2019 at New York University Center for Dysautonomia (Jose-Alberto Palma MD PhD, a colleague of this project's PI). During a two-day assessment, the following preliminary data were obtained before and after a 50 mg **(1.9mg/kg)** dose of *Northera*: Blood pressure in the supine position was 103/78 mmHg with a heart rate of 83 bpm. Fluctuations in heart rate in response to deep paced breathing were within the normal range for age, indicating preserved parasympathetic innervation of the heart. After 1-min of head-up tilt the blood pressure dropped to 47/32. After 3-min of head-up tilt blood pressure was 36/33 mmHg. During this tilt table exercise, plasma concentration of norepinephrine was 122 pg/ml in supine position and increased only to 130 when tilted (normal pediatric range: 500-1,056 pg/ml [25]), indicating impaired baroreflex-mediated sympathetic activation. Epinephrine concentration remained stable at <10 pg/ml, and dopamine was high at 22 pg/ml in the supine position and increased to 37 in the head-up tilt position (normal pediatric range 0-22 pg/ml [25]).

One hour after the 50 mg trial dose of *Northera* (measured by estimating 50% of the contents of a 100 mg capsule of the drug, Lundbeck Pharmaceuticals, Inc.), the patient's blood pressure in the supine position rose to 126/95 mmHg. After 1-min of head-up tilt, his blood pressure was 73/66. After 3-min of head-up tilt, his blood pressure was 54/42 mmHg. After 6-min of head-up tilt, his blood pressure was 63/48 mmHg. After *Northera*, the plasma concentration of norepinephrine substantially increased to 237 pg/ml in supine position and 313 when tilted, consistent with conversion of *Northera* to norepinephrine. Off the tilt table, the patient demonstrated improved ability to remain standing, improved duration of walking, and an improved overall sense of well-being.

In summary, this subject's evaluation indicated impaired autonomic reflexes and impaired norepinephrine release with severe, symptomatic neurogenic orthostatic hypotension. After 50

mg of *Northera*, his systolic blood pressure rose, plasma norepinephrine levels increased, and his gross motor function and capacity, and psychological outlook all improved.

## 3.0 Other Preliminary Data

### 3.1 Proof of Principle Studies

In the *mottled-brindled* mouse model of Menkes disease, we previously documented that L-threo-dihydroxyphenylserine (L-DOPS), the active ingredient in *Northera (Droxidopa)*, crosses the blood-brain barrier and corrects brain neurochemical abnormalities, including norepinephrine concentration [31].

In a single human subject (also mentioned in Section 2.3) who survived the most devastating neurodegenerative effects of Menkes disease through early diagnosis and CuHis treatment, a trial dose of *Northera* was associated with increased plasma norepinephrine levels, higher blood pressures, and improved clinical symptomatology. The subject was exquisitely sensitive to 50 mg doses of *Northera* however, and the drug was discontinued due to severe headaches and difficulty in precise measurement of doses from the commercially available 100mg, 200mg and 300mg capsules (Lundbeck Pharmaceuticals, Inc.)

### 3.2 Safety of drug treatment

*Northera*, approved by the FDA in 2014 and approved in Japan for orthostatic hypotension since 1989, is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease), multiple system atrophy, and pure autonomic failure), **dopamine beta-hydroxylase deficiency**, and non-diabetic autonomic neuropathy. Headache and supine hypertension are known side effects of this product. The product may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure (please see **Appendix 1**, Full Prescribing Information). *Droxidopa,* a generic version of *Northera*, was also approved in 2014.

## 4.0 Research

### 4.1. Study Population

The study population is comprised of six to ten adult survivors of classic Menkes disease or adult subjects with occipital horn syndrome, aged 18 to 50 years, who have signs and symptoms of dysautonomia including neurogenic orthostatic hypotension and chronic diarrhea. These represent subjects with Menkes disease or Occipital Horn Syndrome who completed three years of subcutaneous CuHis treatment in the Phase 1/2 clinical trial previously conducted by the PI at the NIH Clinical Center through the intramural research programs of NINDS and NICHD. The Menkes disease subjects were enrolled in this trial within 8 to 10 days after birth, based on family histories of classic severe Menkes disease and one OHS patient began CuHis at age 11 years (**Table 1**). These subjects all completed three years of CuHis treatment with no significant adverse effects identified (5,6). Additional OHS Subjects may be referred from departments of Neurology, Gastroenterology, Genetics, or Metabolism,

at US or international academic medical centers. The study will be registered and posted on ClinicalTrials.gov website.

## 4.2. Pre-Treatment Assessment:

### A) Inclusion Criteria

1. Adult persons with Menkes disease who survived beyond the expected natural history, attained independent ambulation, attend (or attended) school, and reached adulthood after early CuHis treatment for three years or adults with Occipital Horn Syndrome, who manifest clinical signs and symptoms of dysautonomia, e.g., orthostatic hypotension: specifically, a decrease in systolic or diastolic blood pressure of at least 20 or 10 mm Hg, respectively, within three minutes after standing, and/or chronic diarrhea: production of loose stools with or without increased stool frequency for more than four weeks immediately preceding enrollment.
2. History of at least thrice weekly occurrence of dizziness/feeling lightheaded while standing upright and/or thrice weekly episodes of diarrhea or an urgent need to defecate after food ingestion for more than four weeks immediately preceding enrollment.
3. Documented pathogenic mutation in *ATP7A*
4. Must sign and date an Informed Consent Form (ICF).
5. Age ≥18 years.
6. Ability to adhere to the prescribed oral *Northera (Droxidopa)* regimen.
7. Willingness to comply with all study visits and procedures.

### B) Exclusion criteria

1. Pre-existing liver (e.g., hepatitis, biliary atresia, cirrhosis) or kidney disease (i.e., calculated glomerular filtration rate <30 ml/min).
2. History of hypertension, anti-hypertensive therapy, heart failure (or decreased ejection fraction), cardiac arrhythmia, or bleeding diatheses.
3. Any disease or condition that, in the opinion of the Investigator, has a high probability of precluding the subject from completing the study or where the subject cannot or will not appropriately comply with study requirements.
4. Any alpha-1 adrenoreceptor agonist, beta-blocker, DOPA decarboxylase inhibitor, midodrine, ephedrine, or any triptan medication as a concomitant medication.

## 4.3. Dosing Plan

The present study will evaluate the safety and efficacy of *Northera (Droxidopa)*, in adult Menkes disease survivors or adults with Occipital Horn syndrome, who have symptoms of dysautonomia, by providing *Northera (Droxidopa)* treatment and assessing the neurochemical response (plasma catechol levels) and effect on hemodymanic and gastrointestinal symptoms, and exercise tolerance during a six-week period while receiving the study drug, or a placebo control.

**Treatment A**: *Northera*™ (*Droxidopa*) is provided as a tasteless white crystalline powder in capsules of 100mg, 200mg, or 300mg inside unlabeled gelatin color capsules (sky blue and white, size 0), which will accommodate the size 1, 2, and 3 *Northera (Droxidopa)* capsules (plus a variable quantity of cellulose microcrystalline to complete the fill). We will use a ProFill Capsule Filling System (Torpac; Fairfield, NJ) to generate the Treatment A capsules in the NCH Investigational Drugs Service.

**Treatment B**: The placebo control will be approximately 500 mg microcrystalline cellulose in unlabeled gelatin color capsules (sky blue and white, size 0). We will use a ProFill Capsule Filling System (Torpac; Fairfield, NJ) to generate the Treatment B capsules in the NCH Investigational Drugs Service. The Treatment B capsules used are indistinguishable in weight, taste, texture, consistency, and visible characteristics from Treatment A capsules.

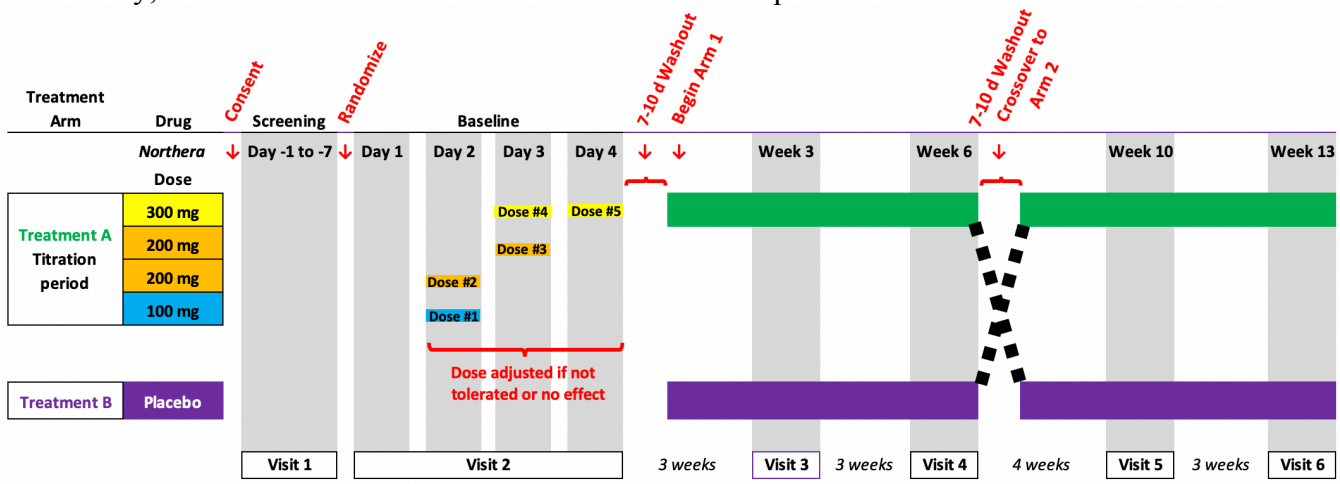


**Figure 3.** *Northera (Droxidopa)* ascending dose schedule. Visit 2 involves an initial open-label dose titration period to identify the ideal *Northera (Droxidopa)* dose for each adult subject.

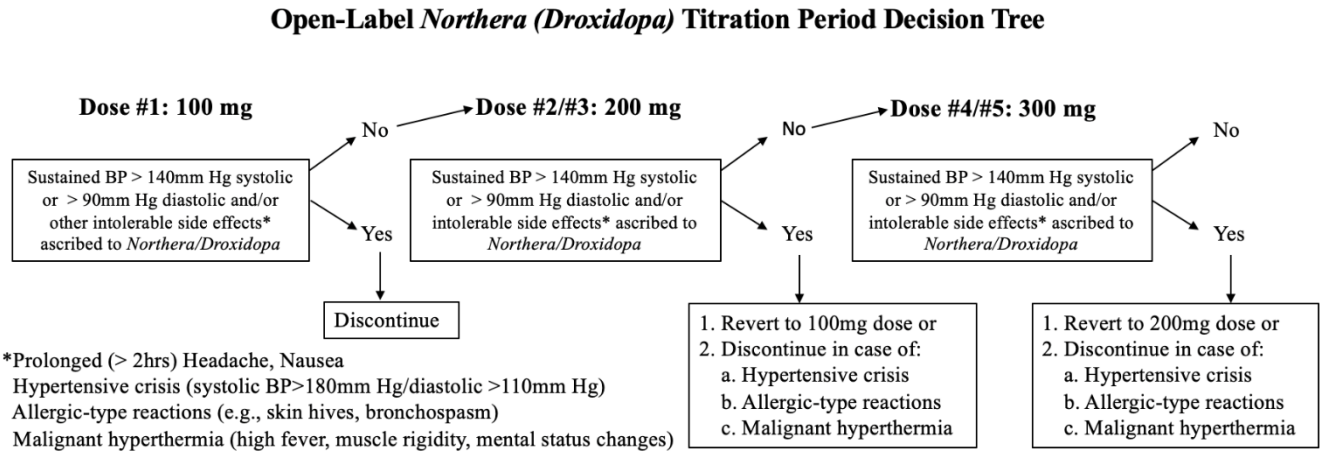


**Figure 4.** Algorithm for determining *Northera (Droxidopa)* dose during open-label dose titration period. Blood pressure greater than 140mm Hg systolic or 90mm Hg diastolic, or headache longer than 2hrs will be grounds to discontinue or lower the *Northera (Droxidopa)* dose. If hypertension persists despite discontinuation of *Northera (Droxidopa)*, conventional medical treatment will be instituted or arranged by the research team in a timely fashion. Signs or symptoms of allergic-type reactions or malignant hyperthermia will be grounds for withdrawing the subject from the study.

**Figures 3 and 4** above, and the **Protocol Visit Schedule** and **Protocol Schema** below illustrate the approach we will take to identify and monitor a safe dose of *Northera (Droxidopa)* for individual subjects in this trial. Each participant will undergo a screening evaluation and, if qualified, will be assigned to Treatment A (*Northera (Droxidopa)*) or Treatment B (Placebo). An open-label dose titration will be used to determine a maximally tolerated dose of *Northera (Droxidopa)* **(Figure 4)**.

Subjects will begin Treatment A or B after a 7-10 day washout period, followed by crossover to the alternative Treatment (A or B) for a second 6-week arm.

In this pilot study, we are testing only the safety, tolerability, and preliminary efficacy of *Northera (Droxidopa)*, and factors such as age, mutation type, or maximum tolerated dose cannot be considered due to the small patient population. Based on preliminary data in one 10 year old Menkes survivor that suggested adrenoreceptor hypersensitivity, and because the safety and effectiveness of *Northera (Droxidopa)* in subjects with Menkes disease has not been established, we will evaluate only adults (≥18 years of age) in this study. Furthermore, the optimal dose identified in the dose-titration period (**Visit 2)** will be used in a b.i.d rather than t.i.d. regimen, to diminish the risk of supine hypertension while sleeping.

As per the product Full Prescribing Information (**Appendix 1**), peak plasma concentration (Cmax) of *Northera (Droxidopa)* are reached by 1 to 4 hours post-dose (mean of approximately 2 hours) in healthy adult volunteers. Cmax was delayed by approximately 2 hours with a high-fat meal. The metabolism of *Northera (Droxidopa)* is mediated by catecholamine biosynthetic pathway (**Figure 1**) and not through the cytochrome P450 system. *Northera (Droxidopa)* is initially converted to methoxylated dihydroxyphenylserine (3-OM-DOPS), a major metabolite, by catechol-O-methyltransferase (COMT), to norepinephrine by DOPA decarboxylase (DDC), or to protocatechualdehyde by DOPS aldolase. After oral dosing in humans, plasma norepinephrine levels peak within 3 to 4 hours but are generally very low (less than 1 ng/mL) and variable with no consistent relationship with dose. The contribution of the metabolites of *Northera (Droxidopa)* other than norepinephrine to its pharmacological effects is not well understood.

The mean elimination half-life of *Northera (Droxidopa)* is approximately 2.5 hours in humans (24). The major route of elimination of *Northera (Droxidopa)* and its metabolites is via the kidneys in both animals and in humans. Studies in animals showed that ~75% of the radiolabeled dose was excreted in urine within 24 hours of oral dosing. There are no known clinically relevant effects of age, body mass index or sex on the pharmacokinetics of *Northera (Droxidopa)*. A population pharmacokinetic analysis suggests that hepatic function, assessed by aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin, does not influence response to *Northera (Droxidopa)*. The controlled clinical trials included patients with mild to moderate renal impairment (GFR>30 mL/min) and did not have a higher frequency of adverse reactions. No dose adjustments are required in patients with mild to moderate renal impairment (*Northera (Droxidopa)* Full Prescribing Information, **Appendix 1**). Statistical comparisons (see *Statistical Analysis Plan*) based on different dose regimens is not currently planned and may be added, if appropriate.

## PROTOCOL DESIGN SUMMARY

Randomization: Schedule established by NCH Investigational Pharmacy (*Statistical Analysis Plan*).

Visit 1: Patients are consented, screened, and randomized blindly to Treatment A (*Northera (Droxidopa)*) or Treatment B (Placebo). Contraception will be discussed with all post pubertal subjects during the informed consent process to ensure that women of child-bearing potential (no female enrollment is anticipated given X-linked recessive inheritance) or sexually active males whose partner is a women of child-bearing potential avoid pregnancy during the study.

Visit 2: Patients have studies performed to test *Northera (Droxidopa)* tolerance and establish dose for clinical trial. Includes four days of testing, followed by assignment to Treatment A (*Northera*

*(Droxidopa))* versus Treatment B (Placebo) based on prior randomization. Patients, their parents, the clinical staff, and the statistician will be blinded. Randomization codes will stored in sealed envelopes. A 7-10 day washout period will precede the start of the Arm 1 treatment period at home.

Visit 3: Mid-way point of Arm 1.

Visit 4: Conclusion of Arm 1; Washout period (7-10 days) and Crossover to Arm 2.

Visit 5: Mid-way point of Arm 2.

Visit 6: Conclusion of Arm 2

Unblinding and Data Analysis: After all subjects have completed both Arms.

**Time Table**

Year 1: Enroll initial subjects and complete both Arms. IRB annual review. FDA annual report.
Year 2: FDA and DSMC evaluation of initial results; Enroll additional subjects and complete both Arms; IRB annual review; FDA annual report.
Year 3: DSMC evaluation of 6 to 10 total subjects; IRB annual review; FDA annual report.
Year 4: Follow-up of all participants. Data analysis and publication of primary results in per-reviewed journal(s). IRB Annual review; FDA annual report.
Year 5: Ongoing data analysis and publication of related information from study, e.g., cardiac findings, validation of Orthostatic Hypotension Symptoms Assessment questionnaire in peer-reviewed journal(s); IRB annual review; FDA annual report. Report results to ClinicalTrials.gov.

**Protocol Visit Schedule:**

**Visit 1**: Screening Visit; **Outpatient**

Informed Consent
OHSA Questionnaire (**Appendix 2**), FDA COA, and IBS-D report form completed
Orthostatics: Blood pressure (BP) and Pulse (P) (supine, sitting, standing)*
History and Physical
Physical Therapy Exercise Tolerance Test (walk-through)
Randomize blindly to Treatment A or Treatment B

*Supine after approx. 5 mins. Sitting and standing: each after approx. 3 minutes. Measured with a DINAMAP PRO 100, or Omron 3 Series oscillometric Upper Arm Blood Pressure Monitor (Model BP7100).

# 1 to 7-day interval

**Visit 2**: Dose determination/Initial Dosing Visit

*Day 1* **Inpatient** Admission for acclimatization and rest/preparation for *Day 2* schedule (below)

History and Physical Exam
EKG/ECHO
Placement of saline lock IV
Baseline laboratory work: CBC with diff/PLTs, CMP, Serum Copper and Ceruloplasmin, Urinalysis, Plasma Catechols (1)
Review Concomitant Meds/Adverse Events
Baseline Physical Therapy Exercise Tolerance Tests*

*Time standing duration; Six-minute walk test; Up and Go test

*Day 2* (All hours and times are estimates)

Morning

8am Tilt Table Testing (WR Medical S1 model; DINAMAP PRO 100 or Omron 3 Series oscillometric Upper Arm Blood Pressure Monitor Model BP7100)
Baseline:
Supine for 5 minutes A) BP/P B) Plasma Catechols* (2)
Head tilt 60˚ for 3 minutes A) BP/P B) Plasma Catechols (3)
Off Tilt Table (Seated): A) BP/P

***NORTHERA (DROXIDOPA)* Dose #1 (100 mg)**
Seated BP/P q15 mins x 4

*Plasma catechols drawn from saline lock IV immediately after BP/P

Repeat Tilt Table (75 to 90 minutes post-*NORTHERA (DROXIDOPA)*)
Supine for 5 minutes A) BP/P B) Plasma Catechols (4)
Head tilt 60˚ for 3 minutes A) BP/P B) Plasma Catechols (5)

Rest off Tilt Table (10 mins)
2h post-dose: Plasma Catechols (6)
Physical Therapy Exercise Tolerance Tests
4h post-dose: Plasma Catechols (7)
6h post-dose: Plasma Catechols (8)

Afternoon (All hours and times are estimates)
2pm ***NORTHERA (DROXIDOPA)* Dose #2 (200 mg)†**
Orthostatics: BP and pulse (supine, sitting, standing)* 1h, 2h, 3h, 4h post-dose
Plasma Catechols 2h post-dose (9)

**†Assumes that previous 100 mg dose was well-tolerated.**

*Supine after approx. 5 mins. Sitting and standing: each after approx. 3 minutes.

Evening (All hours and times are estimates)
6pm Head-elevated (30˚) sleeping position:
Supine BP* and Pulse measured every 3 hours (estimated 9pm, 12am, 3am, and 6am)
Plasma Catechols 12am (≈10h post-dose) (10)
*Measured with Philips Sure Signs VM4 inpatient unit monitor

*Day 3* Morning (All hours and times are estimates)
8am Tilt Table Testing (WR Medical S1 model; DINAMAP PRO 100 or Omron 3 Series oscillometric Upper Arm Blood Pressure Monitor Model BP7100)
Baseline:
Supine for 5 minutes A) BP/P B) Plasma Catechols (11)
Head tilt 60˚ for 3 minutes A) BP/P B) Plasma Catechols (12)
Off Tilt Table (Seated): A) BP/P

***NORTHERA (DROXIDOPA)* dose #3 (200 mg)†**

Seated BP/P q15 mins x 4

Repeat Tilt Table (75 to 90 minutes post-*NORTHERA (DROXIDOPA)*)
Supine for 5 minutes A) BP/P B) Plasma Catechols (13)
Head tilt 60˚ for 3 minutes A) BP/P B) Plasma Catechols (14)

Rest off Tilt Table (10 mins)
2h post-dose Plasma Catechols (15)
Physical Therapy Exercise Tolerance Tests
4h post-dose Plasma Catechols (16)
6h post-dose Plasma Catechols (17)

**†Assumes that previous 200 mg dose was well-tolerated.**

Afternoon: (All hours and times are estimates)

2pm ***NORTHERA (DROXIDOPA)* Dose #4 (300 mg)†**
Orthostatics: BP and pulse (supine, sitting, standing) 1h, 2h, 3h, 4h post-dose*
Plasma Catechols 2h post-dose (18)
**†Assumes that previous 200 mg dose was well-tolerated**

Evening (All hours and times are estimates)

6pm Head-elevated sleeping position
Supine BP* and Pulse every 3 hours (estimated 9pm, 12am, 3am, 6am)
Plasma Catechols 12am (≈10h post-dose) (19)
*Measured with Philips Sure Signs VM4 inpatient unit monitor

*Day 4* Morning (All hours and times are estimates)

8am Laboratory work: Plasma Catechols (20)
Remove saline lock IV
Orthostatics: BP and Pulse measurements (supine, sitting, standing)*
***NORTHERA (DROXIDOPA)* Dose #5 (300 mg)†**
*Supine after approx. 5 mins. Sitting and standing: each after approx. 3 minutes.

**†Assumes that previous 300 mg dose was well-tolerated**
If there is no clinical or biochemical response to the 300 mg dose, the PI and team of Co-Investigators may file a protocol amendment to prescribe a higher dose of *NORTHERA (DROXIDOPA),* based on clinical judgment and emerging data for the individual subject.

Treatment A or Placebo (Treatment B) based on prior randomization
Discharge to home with 1-month supply (60 capsules of *NORTHERA (DROXIDOPA)* or Placebo). Instructions: **100 mg, 200 mg, or 300 mg po b.i.d. (8am, 2pm)** to begin **after 7 to 10 day washout**.

Teaching and practice with the Omron 3 Series Home BP monitoring device: The patients will be taught how to use the BP monitoring device and we will practice with them. The study team and all those that will be teaching and instructing the patients and families will have an in-service on proper usage of device prior to study initiation. The investigators and study team will review proper usage with the patient in a hands-on demonstration. We will demonstrate the proper use and then have patient/subject demonstrate proper use as many times as needed and will review again if necessary. We will also provide written instructions to take home and provide the study team members/investigator contact info for any questions or concerns.

## 3-week interval (+/- 7d)

**Visit 3**: Initial Follow-up; Pill count. Consider Dose adjustment. See Schema for testing planned

**Outpatient** (Default weekday: Any)
History and Physical Exam
Orthostatics: blood pressure (BP) and pulse (supine, sitting, standing)*
EKG
Placement of saline lock IV
Baseline laboratory work: CBC with diff/PLTs, CMP, Urinalysis

Tilt Table Testing (All times are estimates)

| | | |
|---|---|---|
| Supine for 5 minutes | A) BP/P | B) Plasma Catechols |
| Head tilt 60˚ for 3 minutes | A) BP/P | B) Plasma Catechols |

Physical Therapy Exercise Tolerance Tests

*Supine after approx. 5 mins. Sitting and standing: each after approx. 3 minutes. Measured with a DINAMAP PRO 100, or Omron 3 Series oscillometric Upper Arm Blood Pressure Monitor (Model BP7100).

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## 3-week interval (+/- 7d)

**Visit 4**: Final Follow-up (Arm 1). Pill count

**Outpatient**
History and Physical Exam
Orthostatics: blood pressure (BP) and Pulse measurements (supine, sitting, standing)*
EKG/ECHO
Placement of saline lock IV
Baseline laboratory work: CBC with diff/PLTs, CMP, Serum Copper and Ceruloplasmin, Urinalysis

Tilt Table Testing (All times are estimates)

| | | |
|---|---|---|
| Supine for 5 minutes | A) BP/P | B) Plasma Catechols |
| Head tilt 60˚ for 3 minutes | A) BP/P | B) Plasma Catechols |

Physical Therapy Exercise Tolerance Tests

*Supine after approx. 5 mins. Sitting and standing: each after approx. 3 minutes. Measured with a DINAMAP PRO 100, or Omron 3 Series oscillometric Upper Arm Blood Pressure Monitor (Model BP7100).

Reinforce Teaching and practice with the Omron 3 Series Home BP monitoring device
**Washout**: 7-10 day washout period
Cross-over to alternate arm (Treatment B or Treatment A)

## 4-week interval (+/- 7d) includes wash-out period

**Visit 5**: Initial Follow-up (Arm 2)

**Outpatient:**

History and Physical Exam
Orthostatics: blood pressure (BP) and pulse (supine, sitting, standing)*
EKG
Placement of saline lock IV
Laboratory work: CBC with diff/PLTs, CMP, Urinalysis

Tilt Table Testing (All times are estimates)
Supine for 5 minutes A) BP/P B) Plasma Catechols
Head tilt 60˚ for 3 minutes A) BP/P B) Plasma Catechols
Physical Therapy Exercise Tolerance Tests

*Supine after approx. 5 mins. Sitting and standing: each after approx. 3 minutes. Measured with a DINAMAP PRO 100, or Omron 3 Series oscillometric Upper Arm Blood Pressure Monitor (Model BP7100).

## 3-week interval (+/- 7d)

**Visit 6**: Final visit (Arm 2); **Outpatient**

History and Physical Exam
Orthostatics: blood pressure (BP) and pulse (supine, sitting, standing)*
EKG/ECHO
Placement of saline lock IV
Baseline laboratory work: CBC with diff/PLTs, CMP, Serum Copper and Ceruloplasmin, Urinalysis

Tilt Table Testing (All times are estimates)
Supine for 5 minutes A) BP/P B) Plasma Catechols
Head tilt 60˚ for 3 minutes A) BP/P B) Plasma Catechols
Physical Therapy Exercise Tolerance Tests

**Detailed Protocol Schema** (Please see next page)

**Daily Home Monitoring Between Visits**

1. Record Blood Pressure and Pulse (supine, after 3 minutes sitting, and after 3 minutes standing) b.i.d. (before and after school or work) via Omron 3 Series Home BP monitor. All times are estimates.
2. Drug Administration/Headache/Other Side Effects Diaries
3. Irritable Bowel Syndrome-Diarrhea Report

**Weekly Home Monitoring Between Visits:**

1. Orthostatic Hypotension Symptom Assessment (OHSA Questionnaire)
2. FDA Clinical Outcomes Assessment (based on the Patient Global Impression of Severity) (**Appendix 3**)
3. Telephone follow-up by a member of the Study Team re:
    a. Daily and weekly monitoring as described
    b. Subject diaries as described
    c. Concomitant medications
    d. Adverse events

## Protocol Schema

| Visit # | Visit 1 | Visit 2 | H | Visit 3 | H | Visit 4 | H | Visit 5 | H | Visit 6 |
|---|---|---|---|---|---|---|---|---|---|---|
| Weekday (Default) | Monday | Tues-Fri | | Any | | Any | | Any | | Any |
| Time from Enrollment | -1 to -7d | 0 | | Approx. 3 weeks ± 7d | | Approx. 6 weeks ± 7d | | Approx. 10 weeks ± 7d | | Approx. 13 weeks ± 7d |
| Purpose | Screening | Open label Dose Titration | | Initial Follow-up First Arm | | F/up 1st Arm; Plan Washout & Crossover | | Initial Follow-up Arm 2 | | Final follow-up, Arm 2; End of Study |
| Informed Consent | ✓ | | | | | | | | | |
| Assent, if < 18yr | ✓ | | | | | | | | | |
| Inpatient | | ✓ | | | | | | | | |
| Outpatient | ✓ | | | ✓ | | ✓ | | ✓ | | ✓ |
| OHSA Questionnaire | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | |
| FDA COA | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | |
| IBS-D report form | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | |
| Randomization | ✓ | | | | | (Crossover) | | | | |
| History and Physical | ✓ | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| EKG | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| Cardiac ECHO | | ✓ | | | | ✓ | | | | ✓ |
| Saline Lock | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| *ATP7A* test (+/-) | ✓ | | | | | | | | | |
| CBC with diff/Plts | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| CMP | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| Copper/CP | | ✓ | | | | ✓ | | | | ✓ |
| Urinalysis | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ |
| Plasma Catechols | | N=20 | | N=2 | | N=2 | | N=2 | | N=2 |
| Tilt Table Test | | ✓(4) | | ✓ | | ✓ | | ✓ | | ✓ |
| PT Exertion tests | Walk-thru | ✓(3) | | ✓ | | ✓ | | ✓ | | ✓ |
| **Orthostatics*<br>*Seated BP/P*<br>*Supine BP/P* | 1 set | 3 sets<br>N=8<br>N=8 | | 1 set | | 1 set | | 1 set | | 1 set |
| Teaching: Med, BP monitoring | | ✓ | | | | ✓ | | | | |
| Omron 3 Series Home BP Log | | | ✓ | | ✓ | | ✓ | | ✓ | |
| Medication Log | | | ✓ | | ✓ | | ✓ | | ✓ | |
| Phone call q wk | | | ✓ | | ✓ | | ✓ | | ✓ | |
| Side Effects Diary | | | ✓ | | ✓ | | ✓ | | ✓ | |
| Total Blood (ml) | 0-4 | 48 | | 8 | | 12 | | 8 | | 12 |

**H**= home; BP= blood pressure; P=pulse; CMP= comprehensive metabolic panel (includes albumin, total bilirubin, calcium, electrolytes, creatinine, glucose, alk phos, AST, BUN, ALT, total protein ; CP=serum ceruloplasmin; OHSA=orthostatic hypotension symptom assessment questionnaire (**Appendix 2**); FDA COA= US Food & Drug Administration Clinical Outcomes Assessment (**Appendix 3**); IBS-D=Irritable Bowel Syndrome-Diarrhea form (**Appendix 4**); N=Number of times tested; PT=Physical Therapy; *Supine after 5 min. Sitting and standing: each after 3 min, measured with a DINAMAP PRO 100, or Omron 3 Series oscillometric Upper Arm Blood Pressure Monitor (Model BP7100). All times are estimates.

Rationale for Study Procedures

*Plasma catechols*: Levels of these neurochemicals and ratios of proximal: distal metabolites (**Figure 1**) are directly influenced by DBH deficiency [9-11] and are distinctively abnormal in Menkes disease patients [25-27]. Preliminary data in one Menkes subject indicated that *Northera (Droxidopa)* treatment raises plasma norepinephrine levels (see p.8), suggesting that plasma catechols represent a rational parameter for serial measurement in this study.

*Plasma L-DOPS levels*: Levels of L-threo-3,4-dihydroxyphenylserine (L-DOPS, droxidopa) may also be measured during Visit 2 for comparison to the known pharmacokinetic (PK) profile of Northera (Droxidopa) (peak level at approximately 3 hrs). The assay for plasma L-DOPS and plasma catecholamines (High Performance Liquid Chromatography with electrochemical detection) is the same [32]. Measurements of L-DOPS may permit correlation between plasma L-DOPS and plasma norepinephrine levels.

*Tilt Table Test*: This testing will enable us to quantify the baseline levels of neurogenic orthostatic hypotension in this unique population. The Tilt Table test is typically used to assess adult and pediatric subjects with dysautonomia of various causes. In February 2020 (before COVID-related travel precautions), the PI visited Jose-Alberto Palma MD PhD, Associate Professor of Neurology at the NYU Dysautonomia Center of NYU Grossman School of Medicine/Langone Health in New York, NY to become acquainted with the procedure and equipment. Tilt Table testing involves gently strapping a patient onto the tilt table with feet resting on footplates. Continuous heart rate and blood pressure monitors are then attached to the subject. The entire table can be tilted to move from 0˚ to 60˚angle in approximately 45s, allowing determination of changes in pulse and blood pressure based on supine (0˚) and standing (60˚) positions.

Tilt Table Stopping Rules: If a subject indicates that fainting is imminent, if measured systolic blood pressure drops more than 90 mm Hg when moved from supine (0˚) to upright (60˚), or if any other untoward medical event, e.g., EKG arrhythmia, seizure, vomiting occurs, the Tilt Table Test will be stopped immediately.

*Routine Laboratory tests*: including CBC with diff/PLTs, CMP and urinalysis will be performed as safety labs to ensure no adverse general hematological or biochemical effects of *Northera (Droxidopa)*. If a subject has not had their *ATP7A* mutation identified, 4 ml of blood will be collected for DNA to perform ATP7A mutation analysis at screening (**Visit 1**).

*Physical Therapy Exercise Tolerance tests*: **These outcome measures will reflect the effect(s) of *Northera (Droxidopa)* on physical activity, e.g., timed duration of standing or walking without the need to change posture due to dizziness or lightheadedness.** Dr. Lowes and her colleagues have extensive knowledge and experience in devising meaningful outcome measures for unique populations based on specific clinical considerations. In conjunction with Dr. Lowes and members of the Menkes survivor community (parents and subjects), we determined that assessing duration of time standing, as well as performance on two formal tests: Six-minute Walk, and Up and Go, will be appropriate endpoints for this study. The duration of time standing will be assessed using a timer. The Subject will rise from a chair and, when standing up straight, the time (minutes: seconds) the Subject can remain standing will be recorded by a member of the study team using a hand-held stopwatch for up to 5 mins. The case report form (CRF) for this component of the study will includes notes to explain delays in performing for tests for specific reasons, e.g., postural hypotension, need to rest, etc.

*EKG and Cardiac ECHO*: A higher than normal rate of congenital heart defects has been reported for Menkes disease [33]. In Menkes disease survivors, the natural history of cardiac function has never been

evaluated formally. Abnormalities including mitral valve prolapse, mitral regurgitation, aortic and pulmonary artery dilatation, RV compression, and wandering atrial pacemaker have been noted in some Menkes survivors. Serial EKGs and ECHOs will primarily contribute to establishing the safety profile of *Northera (Droxidopa)* in Menkes survivors and may also yield information concerning baseline cardiac function in this population. These tests will also be used to screen subjects at Visit 1 for hypertension, heart failure (or decreased ejection fraction), and cardiac arrhythmia (Exclusion criteria).

*Seven to ten day washout period:* Although norepinephrine is rapidly eliminated from the blood (t1/2= 2 to 2.5 minutes), as is *Northera (Droxidopa)* (t1/2= 2.5 hours), dysautonomia experts suggest that cumulative dosing may result in prolonged action of *Northera (Droxidopa)*. Pharmacokinetic studies (in adults) suggest 75% elimination of *Northera (Droxidopa)* in urine within 24 hours (**Appendix 1**). A seven to ten day washout period will eliminate any significant risk of overlap between *Northera (Droxidopa)* and placebo treatments. The 7-10 day window for washout will also facilitate scheduling such that all follow-up visits/assessments occur while Subjects are receiving the study drug or placebo.

### 4.4. Clinical Trial Monitoring Plan

The trial will be monitored by a Clinical Research Monitor from the NCH Office of Research Compliance & Integrity, with activities to include: monitoring plan creation, subject record review, pharmacy review, regulatory review, and lab/supplies review.

## 5.0 Study Drug

Please see *Northera (Droxidopa)* Full Prescribing Information (**Appendix 1**)

### 5.1. Storage

Please see *Northera (Droxidopa)* Full Prescribing Information (**Appendix 1**)

### 5.2. Preparation

Please see *Northera (Droxidopa)* Full Prescribing Information (**Appendix 1**) and description of NCH IDS oral suspension (**2.1.1**, page 5)

### 5.3. Drug Accountability and disposal

Subjects and their families will maintain a daily log to record time of dose and will return used bottles and any remaining suspension at time of each follow-up visit.

### 5.4. Risks associated

Please see *Northera (Droxidopa)* Full Prescribing Information (**Appendix 1**)

### 5.5. Randomization

Randomization to either *Northera (Droxidopa)* treatment (A) or placebo (B) will occur at the conclusion or the screening visit (Visit 1). To ensure a balanced allocation of patients to each randomization sequence, the study will employ a permuted block randomization scheme with block sizes randomly alternating between 1 and 2. Block length will be unknown to the clinic personnel. The permuted randomization scheme is designed to effectively conceal the allocation. The technique assures a balanced allocation in the groups and also reduces the chance that testing personnel will be able to discern the next intervention group assignment. After the initial open-label dose titration period and after completion of one treatment arm (Visit 4), subjects will receive no treatment for seven to ten days (washout period).

This is a double-blind study, in which both Menkes survivor participants and the clinical staff conducting the study will be blinded to the treatment administered. Only the NCH IDS Pharmacy staff will be unblinded as to the contents of the Treatment dispensed. The IDS Pharmacy will maintain the codes in sealed envelopes for each participant. At the conclusion of the study, identification of Treatment and Placebo arms for each subject will be revealed to the PI, biostatistician, protocol clinical staff, the subjects, and their families. The code(s) will be revealed sooner only upon request of the Data Safety Monitoring Committee or if there is an emergency indication. The PI will designate a 24hr/7d unblinding contact in case of such an emergency who will have access to the sealed unblinding codes.

## 5.6. Subject Compensation

Subjects in this pilot study will receive a Participant Incentive of $750 ($250 at completion of Visit 2, and $125 after completion of Visits 3 to 6). In addition, travel and lodging expenses for the subjects and one parent will be reimbursed, using the Greenphire ClinCard system.

## 5.7. Study Variables

This study involves specific clinical and neurochemical variables, including systolic blood pressure, plasma norepinephrine and dihydroxyphenylglycol levels, adequate measures of treatment effect on gastrointestinal symptoms, and defined measures of physical exertion, e.g., distance and time able to walk without need to squat or rest.

Quality of life effects will be tracked by scores on the Orthostatic Hypotension Symptom Assessment questionnaire (**Appendix 2**) and the FDA Clinical Outcomes Assessment (**Appendix 3**).

## 5.8. Outcome Measures

The primary outcome of this study will be the safety of *Northera (Droxidopa)* in adult patients with an *ATP7A* genotype predictive of classic Menkes disease and who were spared the severe CNS effects of this illness but now suffer with dysautonomia, or adults with an *ATP7A* genotype predictive of Occipital Horn Syndrome and who suffer with dysautonomia. Safety will be determined by the rates of side effects and adverse events recorded in the treatment and placebo arms.

Secondary outcomes will include: change in plasma norepinephrine and dihydroxyphenyl-glycol levels after *Northera (Droxidopa)* compared to baseline and placebo; changes in systolic blood pressure after *Northera (Droxidopa)* compared to baseline and placebo; changes in gastrointestinal symptoms as reflected in the Irritable Bowel Syndrome-Diarrhea report (**Appendix 4**) compared to baseline and placebo, changes in physical therapy tests of exertion parameters, e.g., time able to stand without need to squat or rest; distance traveled on the 6 min walk test, and time to complete the Up and Go test after *Northera (Droxidopa)* compared to baseline and placebo. Breaks in timed tests will be documented if related to drops in blood pressure, dizziness, syncope or near-syncope, or possible *Northera (Droxidopa)* side effects.

An exploratory outcome involves an improved score on the Orthostatic Hypotension Symptom Assessment questionnaire (**Appendix 2**) for Menkes Disease adult survivors or adult Occipital Horn syndrome subjects after *Northera (Droxidopa)*, compared to baseline and placebo. We

also seek to validate the OHSAQ in this patient population by correlation to the FDA Clinical Outcomes Assessment (**Appendix 3**).

### 5.8.1 Primary Outcome/Anticipated Results

1. Safety and tolerability, as reflected in the type and incidence of serious adverse events in the *Northera (Droxidopa)* treatment versus placebo arms.

### 5.8.2 Secondary Outcomes:

1. Change in level of plasma norepinephrine and dihydroxyphenylglycol after *Northera (Droxidopa)* compared to baseline and placebo

2. Change in systolic blood pressure (mm Hg) Standing, and between supine and head-up tilt table positions after *Northera (Droxidopa)* compared to baseline and placebo

3. Improved gastrointestinal symptoms: Irritable Bowel Syndrome-Diarrhea report

4. Improvement in performance of Physical Exertion tests: Time Standing, Six-minute Walk test, Up and Go test

### 5.8.3 Exploratory Outcome:

1. Change in scores on the Orthostatic Hypotention Symptom Assessment questionnaire (**Appendix 2**) after *Northera (Droxidopa),* compared to baseline and placebo

## 5.9. Statistical Analysis

For analysis of the Primary Outcome, time-to-event and proportions of serious adverse events (SAEs) and adverse events (AEs) between treatment and placebo arms will be compared using paired *t* tests or McNemar's test, and the relative risks and 95% confidence intervals for each type of adverse event will be reported. The planned design in which subjects are treated and followed up for the same period of time will minimize bias in this safety assessment.

For analysis of the Secondary Outcomes, age-matched normal values are available for the neurochemical evaluations planned [25]. The effect of *Northera (Droxidopa)* treatment will be measured by comparing the changes in secondary endpoints between *Northera (Droxidopa)* and placebo using a linear mixed-effects model to account for within- and between-person variability in repeated measurements over time, including patient-specific random intercepts. A similar approach will be applied to assess Treatment/Placebo differences for systolic blood pressure, gastrointestinal symptoms, and performance on the Physical Therapy Exercise Tolerance tests. The reference time point for each treatment period for computation of changes in secondary endpoints will be the time of the baseline assessments (**Visit 1 or 2**). The primary time point for comparison between *Northera (Droxidopa)* and placebo will be at final follow-up (i.e., at **Week 6** +/- 7 d) of each treatment period. If any of the statistical methods described herein prove unsuitable during analysis, more appropriate methods may be applied. All

changes in methodology will be documented in the clinical study report. Additional *ad hoc* analyses may be conducted as deemed suitable.

Power calculation to determine sample size was based on the ability to observe a peak increase in neurochemical levels within three hours of *Northera (Droxidopa)* administration [18]. Based on our previous data on plasma catechol levels in untreated Menkes disease subjects [25], and assigning an absolute effect size of 150 pg/ml between plasma dihydroxyphenylglycol levels pre-treatment versus 6 hours post-treatment, a sample size of six provides 95% power with a two-tailed significance level of 0.05 [30].

For gastrointestinal symptoms, we will follow FDA Guidance for Industry on Irritable Bowel Syndrome and define a positive response as a decrease in weekly average of *worst abdominal pain in past 24 hours* score of at least 30% compared with baseline or placebo, and a decrease at least 50% in the number of days per week with at least one stool with consistency of Bristol Type 6 or 7 compared with baseline (please see **Appendix 4**).

If any of the statistical methods described herein prove unsuitable during analysis, more appropriate methods may be applied. All changes in methodology will be documented in the clinical study report. Additional *ad hoc* analyses may be conducted as deemed suitable.

As an exploratory outcome measure, we will undertake validation of the Orthostatic Hypotension Symptom Assessment questionnaire in a young adult population of Menkes disease survivors using data from this study. The OSHAQ was previously validated in older adults with neurogenic orthostatic hypotension [34]. We will determine whether worsening or improvement in the subjects' secondary outcome measures are associated with commensurate changes in weekly OHSAQ scores. In addition, we will correlate OHSAQ scores with an independent Clinical Outcomes Assessment, the Patient Global Impression of Severity Scale (**Appendix 3**) using Cohen's kappa coefficient, due to that both scores are four to six items on an ordinal scale. Additional correlation analysis such as Spearman's correlation coefficient will be performed but the main validation is through kappa statistic. Hypothesis testing will be conducted at the two-tailed 0.05 significance level. by telephone each week, and compare responses to the OHSAQ.

**Appendix 5** outlines a detailed *Statistical Analysis Plan* for this study and includes a linear mixed-effects model to account for within- and between-person variability in repeated measurements obtained over time.

## 6.0 Dose Limiting Toxicity

In reporting adverse events, we will follow the final regulations issued by the Food and Drug Administration addressing the safety reporting requirements for investigational new drug applications (INDs) found in 21 CFR part 312 and for bioavailability and bioequivalence studies found in 21 CFR part 320. "Safety Reporting Requirements for INDs and BA/BE Studies".

### 6.1. The classification for adverse events to be used is the following:

Grade 1. Mild adverse event; did not require treatment
Grade 2. Moderate adverse event; resolved with treatment

Grade 3. Severe adverse event; inability to carry on normal activities; required professional medical attention
Grade 4. Life-threatening or permanently disabling adverse event
Grade 5. Fatal adverse event

In this grading system, ***severity*** is not equivalent to ***seriousness.*** The definitions to be employed will follow the final regulations issued by the FDA in December 2012 "Safety Reporting Requirements for INDs and BA/BE Studies", and described in section 8.0 of this protocol.

### 6.2. Dose limiting toxicity (DLT)

DLT is defined as any adverse event that is possibly, probably, or definitely related to the study agent. This would include any grade 3 according to the classification given above. Any treatment dose associated with a **Grade 3, or higher** adverse event toxicity that is **possibly, probably, or definitely related** to the study drug will be reviewed by the responsible physicians and a lower dose substituted, or all treatment stopped.

The PI will fulfill the reporting responsibilities under 21 CFR 312.32(c), to notify the FDA in an IND safety report of potentially serious risks, as soon as possible, but no later than 15 calendar days after the investigator receives the safety information and determines that the information qualifies for reporting. The principal investigator will report to the IRB, FDA, and DSMC before continuing enrollment.

### 6.3. Stopping/Discontinuation Rules

The Principal Investigator (PI) will monitor safety data on a continual basis throughout the trial. The PI, in conjunction with the DSMC (and with IRB approval), can recommend early termination of the trial for reasons of safety. Study enrollment will be halted by the investigators if any subject experiences a **Grade 4, or higher** adverse event that is **possibly, probably, or definitely related** to the study drug. This will include any patient death, important clinical laboratory finding, or any severe local complication related to the study agent. If after review by the IRB and FDA, the decision is made to continue, the study will proceed.

## 7.0 Adverse Event Monitoring and Reporting

### 7.1. Definition of an Adverse Event

As stated above this protocol will follow the final regulations issued by the Food and Drug Administration addressing the safety reporting requirements for investigational new drug applications (INDs) found in 21 CFR part 312.
**Adverse Event (AE)**: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Adverse events will be graded by the investigator accordingly: 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening or debilitating, and 5 = fatal**.**

Association or relatedness to the study agent, study procedures and the subject's pre-existing disease will be graded as follows: 5 = unrelated, 4 = unlikely, 3 = possibly, 2 = probably, and 1 = definitely related.

**Adverse reaction:** An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

**Suspected adverse reaction (21 CFR 312.32(a))** Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### 7.2. Serious adverse event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

To reiterate, an SAE is an event in categories 3, 4, and 5. Category 3 Severe adverse event; inability to carry on normal activities; required professional medical attention Category 4 Life-threatening or permanently disabling adverse event Category 5 Fatal adverse event.

### 7.3. Life-threatening (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. The PI will fulfill the reporting responsibilities to FDA on behalf of Nationwide Children's Hospital, by completing a Form FDA 3500 either online, by fax (1-800-FDA-0178) or calling the FDA at 1-800-FDA-1088.

### 7.4. Obligations of the Investigator

The Principal Investigator will submit a voluntary Form FDA 3500 by one of the methods mentioned above for any serious adverse event that is both unexpected and possibly, probably, or definitely associated with the use of the study drug(s). The Principal Investigator will adhere to any other serious adverse event reporting requirements in accordance with federal regulations, state laws, and the local institutional policies and procedures, as applicable.

The Principal Investigator also will be responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.

## 7.5. Adverse Event Reporting

The investigator or his designee will report all serious and unexpected adverse events to the IRB, according to regulatory requirements described as follows: Any serious adverse event that is unexpected and related/probably related to the study drug(s) will be reported to the IRB within 5 business days from notification.

Any serious adverse event that is fatal or life-threatening, that is unexpected, and associated with the use of the study drug(s) will be reported to the FDA as soon as possible, but not later than 7 calendar days after the sponsor's initial receipt of the information.

Serious adverse events that are unexpected and associated with the use of the study drug(s), but are not fatal or life-threatening, will be reported to the FDA as soon as possible, but not later than 15 calendar days after the sponsor's initial receipt of the information.

If, after further evaluation, an adverse event initially considered not to be associated with the use of the study drug(s) is subsequently determined to be associated, then the event will be reported to the FDA within 15 days of the determination. Relevant additional clinical and laboratory data will become available following the initial serious adverse event report. Any follow-up information relevant to a serious adverse event will be reported within 15 calendar days of the sponsor's receipt of the information. If a serious adverse event occurs after the end of a clinical trial and is determined to be associated with the study drug(s), that event will be reported to the FDA within 15 calendar days of the determination.

### 7.5.1. Serious Adverse Event Reporting: Content and Format

The serious adverse event report will include, but need not be limited to: (1) the date of the event; (2) designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports; (3) clinical site; (4) the Principal Investigator; (5) protocol number; (6) FDA's Investigational New Drug (IND) application number; (7) dosing schedule; (8) a complete description of the event; (9) relevant clinical observations; (10) relevant clinical history; (11) relevant tests that were or are planned to be conducted; (12) date of any treatment of the event; and (13) the suspected cause of the event.

## 7.6. Unexpected Adverse Events

Unexpected adverse events are those which are not previously reported with the study drug(s), commonly not seen in association with the subject's underlying disease or are related to a known toxicity but differ because of greater severity or specificity.

## 7.7. Follow-up of Adverse Events

All adverse events will be followed until resolution or stabilization.

## 7.8. Adverse Event Reporting from Primary Care Physician

Close communication will be established with the primary care physician of all study participants and will be maintained throughout the study. The important hallmarks of the study along with the proposed reporting plan will be explained. We will request that the primary care physician provide information regarding every routine visit and any potential adverse event taking place. Laboratory

reports, hospitalizations, clinical notes and any other relevant medical records will be requested at the time of their occurrence. If non-routine visits are reported to us by the primary care physician, the study investigator will initiate an investigation to determine the possibility of an adverse event related to the study drug(s) and will adhere to the adverse event reporting requirements in accordance with federal regulations, state laws, and the local institutional policies and procedures, as applicable.

## 8.0 Study Reports

### 8.1. Sharing of Results with Subjects:

Visit-to-visit results will be shared with participants verbally by Dr. Kaler and/or other members of the Study Team. Final results, and recommendations, if any, will be given to Subjects in a letter at the end of the study. We will also share the overall results from this study with the participants, including a copy of the medical-scientific paper describing it, if requested.

### 8.2. Final Study Report

The final study report will include data through the final study visit and will not necessarily include long-term follow-up information, such as normal standard of care communications from local physicians, or information from telephone conferences and/or medical records. Information from annual post-study follow-up visits at the NCH Menkes Disease Clinic will be included when available.

### 8.3. Annual Study Reports

Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is completed, the Principal Investigator will submit information set forth in 21 CFR 312.

### 8.4. Safety Monitoring of the Study

The Data and Safety Monitoring Committee (DSMC) will act in an advisory capacity to review participant safety and study progress. The DSMC membership will consist of persons completely independent of the investigator who have no financial, scientific, or other conflicts of interest with the trial. Current or past collaborators or associates of the Principal Investigator must note any conflict of interest before their eligibility to serve on the DSMC is approved.

The DSMC will include experts in or representatives of the fields of: catecholamine metabolism, dysautonomia, Menkes disease/Occipital Horn Syndrome, and DBH deficiency.

Individuals invited to serve on the DSMC as either voting or non-voting members must disclose any potential conflicts of interest, whether real or perceived. Conflicts of interest can include professional, proprietary, and miscellaneous interests as described in the NIH Grant Policy Statement and 45 CFR Part 94. Potential conflicts that develop during a member's tenure on a DSMC must also be disclosed. Written documentation attesting to an absence of conflict of interest is required annually.

<u>DSMC Responsibilities</u>
Responsibilities of the DSMC are to

- Review the research protocol, informed consent documents and plans for data and safety monitoring;
- Evaluate the progress of the trial, including periodic assessments of data quality and timelines, participant recruitment, accrual and retention, participant risk versus benefit, trial site performance, and other factors that can affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on participant safety or the ethics of the trials;
- Review study performance, make recommendations and assist in the resolution of problems reported by the Principal Investigator;
- Protect the safety of the study participants;
- Ensure the confidentiality of the trial data and the results of monitoring; and
- Assist by commenting on any problems with study conduct, enrollment, and sample size and/or data collection.

DSMC Reporting and Meetings

Reports describing the status of the study will be prepared by the PI's staff and sent to the DSMC prior to a meeting, or at the DSMC's request. A meeting (either by teleconference or webcast) with the DSMC will be scheduled prior to study initiation and after three subjects have completed Visit #2, or after one subject has completed three visits.

DSMC reports will include the following:

- A brief narrative of the study status, including the target enrollment, current and projected time to completing enrollment. Any significant events and/or difficulties should be briefly described in this narrative.
- A brief narrative for each participant describing gender, age, race and ethnicity and other relevant demographic characteristics. The narrative for each participant should briefly describe his/her study status (i.e., dose level, visit number, adverse event information);
- A timeline outlining the study progress relative to visit number for each participant, as well as time points for each SAE/Dose Limiting Toxicity. A total for Adverse Events (AEs) for each participant should be included.
- A summary of AEs by severity levels;
- A listing of AE details grouped by participant;
- A listing of SAE details grouped by participant;
- A listing of deaths
- A summary of clinically significant laboratory test results

The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines. The procedures outlined in the protocol and case report forms will be carefully reviewed by the PI and staff prior to study initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care and wellbeing of subjects.

Amendments will be submitted to the Nationwide Children's Hospital IRB for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study subject, the Informed Consent Form will be revised

and if applicable, subject's consent to continue participation will again be obtained. Re-consent may occur at the next study visit or by telephone in the presence of a witness. Prior to a phone consent, the subject will be sent a blank copy of the revised consent document to review and instructed not to sign it until the informed consent process has been completed. After all changes have been explained and all questions answered, and if the subject agrees to give their consent for the changes, the subject will sign and return the consent form to the study team. The witness to the subject's signature and the person obtaining consent will also sign the document. A copy of this fully executed version will be sent to the subject once available.

### 8.4.1. Data Management

All data and observations will be documented and securely stored on REDCap (Research Electronic Data Capture), supported by Research IT R&D (RISI) at Nationwide Children's Hospital. The PI will be responsible for review and evaluation of information relevant to the safety of the drug.

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