Clinical Study Protocol

Title	A Prospective Natural History and Outcome Measure Discovery Study of Charcot-Marie-Tooth Disease, Type 4J
Study Sponsor	Elpida Therapeutics SPC 12643 Rancho Bernardo Rd San Diego, CA 92127
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Protocol Version and Date	**Version 1 (6-July2023)**

SIGNATURE PAGE/STATEMENT OF COMPLIANCE

Title:	A Prospective Natural History and Outcome Measure Discovery Study of Charcot-Marie-Tooth Disease, Type 4J
Protocol No:	TBD

Elpida Therapeutics _____ _____
Terry Pirovolakis Date
CEO & Founder

The trial will be conducted in accordance with the International Conference on Harmonisation (ICH) E6 and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). Except where necessary to eliminate an immediate hazard(s) to the trial subjects, the Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____ _____
Signature Date

Name: _____
(Print)

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LIST OF ABBREVIATIONS AND ACRONYMS

ADL	Activities of Daily Living
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BUN	blood urea nitrogen
BUN/Cr	BUN/creatine ratio
CBC	complete blood count
CIDP	chronic inflammatory demyelinating polyneuropathy
CMT	Charcot-Marie-Tooth disease
CMT1A	Charcot-Marie-Tooth disease, type 1A
CMT4J	Charcot-Marie-Tooth disease, type 4J
CMT-FOM	CMT Functional Outcome Measure
CMTHI	CMT Health Index
CMTNSv2	CMT Neuropathy Score, second version
CMTPedS	CMT Pediatric Scale
CRF	case report form
CRP	c-reactive protein
CTCAE	common terminology criteria for adverse events
DSMB	Data and Safety Monitoring Board
EDB	extensor digitorum brevis muscle
EOS	end of study
ESR	erythrocyte sedimentation rate
FEF	forced expiratory flow
FEV	forced expiratory volume
FF	fat fraction
FIG4	Factor-induced Gene 4
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
IRB	Institutional Review Board
MFF	muscle fat fraction
MRI	magnetic resonance imaging
NCS	nerve conduction study
ONLS	Overall Neuropathy Limitation Scale
pCMT-QOL	pediatric CMT quality of life
PEDI	Pediatric Evaluation of Disability Inventory
PEDICAT	PEDI Computer Adaptive Test
PedsQL	Pediatric Quality of Life Inventory
PFT	pulmonary function test
PRO	patient-reported outcome
PT/INR	prothrombin time test and international normalized ratio
PTT	partial thromboplastin time test
SAE	serious adverse event
TA	tibialis anterior muscle
TUG	Timed Up & Go

CLINICAL PROTOCOL SYNOPSIS

Study Title	A Prospective Natural History and Outcome Measure Discovery Study of Charcot-Marie-Tooth Disease, Type 4J
Sponsor	Elpida Therapeutics SPC
Trial Phase	Observational
Study Population	Subjects with a genetically confirmed diagnosis of CMT4J will be included.
Investigational Site	4 US sites • University of Texas Southwestern Medical Center /Children's Health • University of Iowa • NIH (National Institute of Neurological Disorders and Stroke) • Stanford School of Medicine
Study Objectives	• To gain a better understanding of the course of illness • To collect data about genotype-phenotype correlations to allow for better prediction of disease progression based on genetic information • To investigate and follow at long term different outcome measurements (e.g., motor, quality of life, radiologic and electrophysiological) • To expedite research and access to new therapies for rare conditions like CMT4J
Study Design	A multicenter, longitudinal, prospective observational natural history study of subjects with a molecular confirmed diagnosis of CMT4J
Eligibility Criteria	<u>Inclusion Criteria:</u> 1. Male or female, all ages 2. A molecularly-confirmed diagnosis of CMT4J (confirmed by a CLIA certified, CE-marked, or equivalent lab): Genomic DNA mutation analysis demonstrating 1) bi-allelic pathogenic and/or likely pathogenic variants (by ACMG criteria) in the FIG4 gene, or 2) bi-allelic variants with one pathogenic and/or likely pathogenic variant in trans with a variant of uncertain significance if laboratory evidence and expert consensus exits in support of loss of FIG4 function exists. 3. Informed consent from patients 18 years or older who are able to provide consent and from caregivers; parent(s)/guardian(s) providing consent for subjects younger than 18 years at Screening and patients older than 18 years unable to provide informed consent 4. Informed assent of patients younger than 18 years at Screening who are able to provide assent 5. Able and willing to comply with the study protocol, including travel to Study Center, procedures, measurements and visits <u>Exclusion Criteria</u>: 1. Any known genetic abnormality, including chromosomal aberrations that confound the clinical phenotype 2. Current participation in an interventional or therapeutic study 3. Receiving an investigational drug within 90 days of the Baseline Visit

	4. Prior or current treatment with gene or stem cell therapy 5. Any other diseases which may significantly interfere with the assessment of CMT4J 6. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion or could interfere with the subject participating in or completing the study
Study Duration	Subject visits will occur every 12 months ± 4 weeks for up to 2 years for the initial period with extension of up to 60 months if feasible. No investigational product will be used during the study.
Assessments	Clinical Assessments: • Electrophysiology • Nerve Conduction Studies (NCS) • Pulmonary Function Tests (PFTs) • Scoliosis series X-ray • Magnetic Resonance Imaging 1. Thigh and calf muscle without contrast 2. Brain without contrast Neuropsychological Assessments: • Vineland Adaptive Behavior Score, 3rd edition • Bayley Scales of Infant and Toddler Development-III • Wechsler Abbreviated Scale of Intelligence Second Edition / Wechsler Preschool & Primary Scale of Intelligence Fourth Edition (WASI-II / WPPSI-IV) • Stanford-Binet V (SB5) Physical Therapy Assessments: • PEDICAT • CMTPedS for subjects 5 to 17 years of age • CMTInfS (< 4 years old) • CMTNSv2 for subjects >18 years of age • CMT-FOM for subjects > 18 years of age • Timed Up and Go Test (TUG) Questionnaires: • PedsQL (2-18 years) • ONLS (18 years and older) • pCMT-QOL PRO (8-18 years) • pCMT-QOL parent proxy (8-18 years) • pCMT-QOL parent proxy (0-7 years) • CMT Health Index (CMTHI) for >18 years of age

	Exploratory Assessments: • Blood collection for exploratory biomarker • Wearable devices • Optional skin biopsy
STATISTICAL CONSIDERATIONS	The sample size of 20 subjects is expected to provide sufficient insights into the natural history of individuals with CMT4J, a rare disease, to provide exploratory and descriptive results and guide the design of future studies of CMT4J. No formal sample size estimation was performed for this study. Parametric and non-parametric tests will be used to analyze possible associations between clinical, radiographic, and laboratory data. The tests will be selected based on the question being asked of the database. This database will be used to analyze multiple medical issues among subjects with confirmed CMT4J.

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Introduction and Purpose

Charcot-Marie-Tooth (CMT) disease is a group of inherited peripheral neuropathies, affecting 1 in 1,214 (1) to 2,500 (2). CMT can affect both females and males of all ethnicities.

CMT is classified according to the type of nerve damage (demyelinating vs. axonal) and its type of inheritance (autosomal recessive, dominant or X-linked). Mutations in more than 80 genes cause CMT. Most of the CMT neuropathies are demyelinating, especially CMT1A which comprises 60 to 65% of cases.

CMT4J is a rare autosomal recessive, peripheral motor demyelinating neuropathy caused by biallelic pathogenic variants in the FIG4 gene. CMT4J is characterized by childhood onset gait abnormalities and balance difficulties, that rapidly progress to muscle weakness and muscle atrophy during the teen or adult years. Onset can be acute or sub-acute, mimicking an acquired neuropathy and often misdiagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP), or a subacute presentation of Guillain-Barre Syndrome. Involvement can be asymmetric and can affect distal as well as proximal musculature. Although sensory symptoms are minimal, examination may reveal decreased response to touch, pin prick, or vibration distally. Bulbar and cranial nerve functions are often spared; intellect is often normal.

This study is designed to investigate the clinical characteristics and natural history of CMT4J. We aim to follow subjects with a molecularly confirmed diagnosis of CMT4J longitudinally to collect standardized clinical data to evaluate epidemiological characteristics, clinical course, and to identify potential outcome measures which may be used in future clinical trials. Clinical data collection will include medical history and physical exam, hematology and biochemical analyses, calf muscle imaging, nerve conduction studies, pulmonary function testing and neuropsychological assessments.

The study will be conducted in accordance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.2 Background and Rationale

There is no causative treatment available for CMT, but therapeutic clinical trials for the most common types of CMT, like CMT1A, are ongoing. Most recently, animal models have demonstrated the possibility of treating some types of CMT, like CMT4J, with gene transfer therapy through viral vectors. To be able to understand the condition over time and evaluate these therapies at long term, natural history studies are indispensable. This study investigates the natural history of CMT4J.

1.3 Concise Summary of Project

This is a multicenter, longitudinal, prospective observational natural history study of subjects with a molecularly confirmed diagnosis of CMT4J. We plan to enroll 20 subjects of any age into a uniform protocol for follow-up and evaluations. We will obtain demographic and medical history information. Natural history data will be collected prospectively on an annual basis and may include physical/neurological exams, standard laboratory tests, CMT outcome and disability measures, neuropsychological tests, nerve conduction studies (NCS), and imaging studies (muscle MRI). Pulmonary function test (PFT) and scoliosis series x-ray Subject visits will occur every 12 months

± 4 weeks for up to 2 years. Subjects who terminate from the study prior to Visit 3 will undergo an early termination/end of study visit (EOS) if possible. The early termination/end of study visit is comprised of the Visit 3 assessments. If needed, the Investigator may conduct unscheduled visits with Sponsor's approval. No investigational product will be used during the study.

Since CMT4J is a rare disease, there is a high likelihood that both national and international families may be interested in study participation.

OBJECTIVES

1.4 Study Objectives

- To gain a better understanding of the CMT4J disease course and phenotypic spectrum.
- To explore CMT4J genotype-phenotype correlations to allow for better prediction of disease progression based on genetic information.
- To evaluate candidate clinical trial outcome measures related to motor function, quality of life, radiology, and electrophysiology. To expedite research and access to new therapies for rare conditions like CMT4J.

2 STUDY ELIGIBILITY, ENROLLMENT AND CONSENTING

2.1 Target and Study Population

Subjects with a prior diagnosis of CMT4J will be included. CMT4J diagnosis will be made by both clinical manifestations and a confirmed genetic confirmation. Examples of clinical manifestations consistent with CMT4J, include but are not limited to, childhood onset gait abnormalities, poor balance, and accelerated, most commonly asymmetric, limb weakness and muscle atrophy, involving distal and proximal musculature.

2.2 Subject Inclusion Criteria

Inclusion Criteria:

1. Male or female, all ages
2. A molecularly-confirmed diagnosis of CMT4J (confirmed by a CLIA certified, CE-marked, or equivalent lab): Genomic DNA mutation analysis demonstrating 1) bi-allelic pathogenic and/or likely pathogenic variants (by ACMG criteria) in the FIG4 gene, or 2) bi-allelic variants with one pathogenic and/or likely pathogenic variant in trans with a variant of uncertain significance if laboratory evidence and expert consensus exits in support of loss of FIG4 function exists.
3. Informed consent from patients 18 years or older who are able to provide consent and from caregivers; parent(s)/guardian(s) providing consent for subjects younger than 18 years at Screening and patients older than 18 years unable to provide informed consent
4. Informed assent of patients younger than 18 years at Screening who are able to provide assent

5. Able and willing to comply with the study protocol, including travel to Study Center, procedures, measurements and visits

Exclusion Criteria:

1. Any known genetic abnormality, including chromosomal aberrations that confound the clinical phenotype
2. Current participation in an interventional or therapeutic study
3. Receiving an investigational drug within 90 days of the Baseline Visit
4. Prior or current treatment with gene or stem cell therapy
5. Any other diseases which may significantly interfere with the assessment of CMT4J
6. Have any other conditions, which, in the opinion of the Investigator or Sponsor would make the subject unsuitable for inclusion or could interfere with the subject participating in or completing the study

2.3 Recruitment Methods

We plan to enroll up to 20 subjects into the study. The gender, race, and ethnic distribution of the accrued study population may not be representative of the general population but is expected to reflect those affected with the disease under study. Patients who currently seek medical care at a study site may be approached to participate in the study. For those patients who are followed at a study site, their treating physician will inform the patient and/or family of the study. Should the patient/family be amenable to learning more about the study, then a member of the research staff will speak with them about study participation. The patient/family will be given ample time to review the consent form and ask questions. The patient may enroll into the study at any time during their care.

Participants will be recruited through clinician or self-referral. The study will be posted at clinicaltrials.gov to aid recruitment. An IRB-approved study advertisement will also be made available to patient and professional organizations such as Cure CMT4J and the Inherited Neuropathies Consortium, respectively. The approved advertisement may be posted on patient organization websites/social media accounts and may also be made available at scientific/medical/patient conferences.

Participant selection will be equitable considering the rarity of CMT4J. All ages within the specified range, races, and both sexes will be accepted. There will be no restriction based on geographic location. The study team will enhance retention by sending email reminders to participants prior to scheduled visits and will be available to answer any study-related questions between visits.

If a patient/family contacts the study personnel, they will send a consent form to the patient/family and answer their questions accordingly. If the patient/family is interested in establishing care at a study site, the study staff will connect them with the proper department.

2.4 Consenting Process and Review of Genetic Diagnosis

Documentation of genetic confirmation will be reviewed by the Investigator prior to any on-site visits being arranged, in order to confirm eligibility. Each site will follow their IRB guidelines on consent processes for obtaining genetic test results prior to on-site patient visits.

The Sponsor is using a vendor to manage travel planning and expenses for the site and subjects. The vendor will act as a third-party working with both the site and subject to book travel (including flights, hotels, ground transportation, etc.) The vendor will bill the Sponsor directly for subject travel costs,

and any travel expenses incurred by the subject (e.g., meals, tolls, parking fees, etc.) will be reimbursed to the subject. Only the travel expenses of the subject and up to two caregivers will be covered. The Investigator must confirm eligibility of the subject prior to any travel or on-site visits being arranged. The subject will be asked to sign a vendor-specific data use consent prior to any travel arrangements. Once a potential subject expresses interest in study participation and chooses to travel to the site, the study staff will connect the subject to the vendor coordinator to sign the vendor data use consent and proceed with travel arrangements. This may be done prior to the subject signing the study's informed consent document.

Informed consent will be obtained from all subjects with sufficient capacity or from legal guardians/representatives of subjects with insufficient capacity to consent. Written or verbal assent will be obtained in accordance with Institutional Review Board (IRB) guidelines. Dissent from all subjects will be respected.

2.5 Withdrawal from the Study

2.5.1 Reasons for Withdrawal or Termination

Participation in the study is strictly voluntary. Subjects have the right to withdraw from the study at any time and for any reason, without penalty. Site Principal Investigators and/or designees may, at her/their discretion, withdraw a subject from continuing in the study if it is in the subject's best interest, or if the subject is not willing or able to comply with the study requirements. The reason for withdrawal will be documented.

2.5.2 Handling of Subject Withdrawals or Termination

Every effort will be made to undertake protocol-specified safety follow-up procedures to capture protocol specified assessments. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant non-compliance
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Subject has completed the study follow-up period
- Death
- Screening Failure

The reason for participant discontinuation or withdrawal from the study will be recorded on the discontinuation/withdrawal Case Report Form (CRF).

A participant will be considered lost to follow-up if a follow up visit is missed and the participant is unable to be contacted by the study site staff following at least three attempts (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods).

3 STUDY PROCEDURES AND SCHEDULE

The frequency of the following assessments will be according to the schedule of study procedures in Appendix 1. Not all the following assessments need to be performed at every visit, only those that the subject is able to perform.

1. 4.1 Medical Information

Medical History: Medical history of participating subjects will be recorded in order to obtain the following data: basic demographic information (sex, ethnicity), past medical history, birth history, surgical history, developmental history, medications and family history. We will also collect time of symptoms onset (e.g., motor, language, etc.) and progression, age at diagnosis and genetic results.

Physical and Neurological Examination: At each visit, a physical exam will be recorded including but not limited to evaluation of the ears, nose, throat, heart, lungs, abdomen, back, and extremities, motor and sensory, and vital signs which will include blood pressure (measured in one arm or, if necessary, one leg, after the subject has been seated for approximately 5 minutes), pulse, temperature, height, weight, and head circumference.

A detailed neurological examination including but not limited to evaluation of cranial nerves, muscle tone, muscle strength, sensation, gait, coordination and deep tendon reflex testing will also be performed. Handheld dynamometry will also be performed during clinic visits in muscles of the upper and lower extremities. The examination is anticipated to take approximately 30 minutes.

3.1 Outcome Measures

CMT Pediatric Scale (CMTPedS): The CMTPedS is a clinical tool used to supplement a neurological examination and capture functionally relevant limitations caused by CMT in the pediatric population. It is intended to have broad application in natural history studies and clinical trials of rehabilitative (e.g., orthoses, stretching, strengthening), pharmacological (e.g., curcumin, anti-progesterone) and surgical (e.g., foot and hand tendon transfer, arthrodesis, hip dysplasia) interventions (3). This scale will be used for subjects aged 5 to 17 years 11 months (less than 18 years).

CMT Infant Scale (CMTInfS): The CMTInfS is a validated clinical tool and requires 20 min to administer and is a reliable and sensitive 15-item functional outcome measure for early onset CMT and related neuropathies. The CMTInfS can be implemented in natural history studies to understand the rate of progression at the earliest stages of disease in preparation for therapeutic trials of early interventions. The CMTPedS involves some difficult items that require advanced levels of comprehension, so high variability is seen in children <4 years of age. Therefore, for children aged 3 years, the CMTInfS may be more sensitive to disease severity and clinical impression.

CMT Neuropathy Score, second version (CMTNSv2): The CMTNSv2 is a validated clinical outcome measure developed for use in clinical trials to monitor disease impairment, severity and progression in affected CMT subjects (4). This scale will be used for subjects 18 years of age or older.

CMT Functional Outcome Measure (CMT-FOM): The CMT-FOM is a performance-based outcome assessment which measures limitations in functional abilities in adults with CMT1A (5). It was based on the validated CMTPedS and further developed using review of the literature, patient interviews and a survey of 407 adults with CMT, and subjects 18 years of age or older.

CMT Health Index (CMTHI): The CMTHI is a disease-specific, patient reported outcome measure designed to capture the disease burden of inherited neuropathies, in the context of a clinical trial (6). This scale will be used for subjects 18 years of age or older.

Vineland Adaptive Behavior Scale, 3rd Edition: The caregiver interview form will be used to evaluate communication, socialization, and daily living skills of subjects to assess their overall adaptive

functioning. The items in the Vineland Adaptive Behavior Scale requires the caregiver to be familiar with the subject's day-to-day functioning in areas of communication, socializing, and daily living skills. As such, for subjects who reside independently, the rater who administers the assessment should determine if the caregiver, if he/she is available during the visit, has sufficient knowledge of the subject's day-to-day functioning to be able to complete the interview. If the caregiver is not familiar with the subject's day-to-day functioning skills, then the assessment should not be completed. The motor subdomain will be administered to those up to age 9 years. This assessment is an interview of the caregiver by a qualified rater (8). The semi-structured interviews will be recorded in a standardized manner.

Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III): The comprehensive tool has 5 developmental domains, of which we will utilize 4: Cognitive Scale, which assesses attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play, Language Scale, which focuses on recognition of objects and people, following directions, and naming objects and pictures, Motor Scale, which assesses gross and fine motor skills such as grasping, sitting, stacking blocks, and climbing stairs, and Social-Emotional Scale, which measures a child's ability to engage with others socially, self-calm and takes part in age-appropriate play. We will not make use of the Adaptive Behavior Scale to avoid duplication of the same information. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to determine the child's performance compared with norms taken from typically developing children of their age (in months). The Bayley-III will be performed through 42 months of age.

Wechsler Abbreviated Scale of Intelligence Second Edition / Wechsler Preschool & Primary Scale of Intelligence Fourth Edition (WASI-II / WPPSI-IV): A test of intellectual functioning comprised of verbal and visual reasoning subtests as well as tasks of working memory and processing speed.

Stanford-Binet Fifth Edition (SB5): The Stanford-Binet test V is an examination meant to gauge intelligence through five factors of cognitive ability. These five factors include fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing and working memory. Both verbal and nonverbal responses are measured. Each of the five factors is given a weight and the combined score is often reduced to a ratio known commonly as the intelligence quotient, or IQ. For children ages 2 to 5, use the early SB5.

Timed Up & Go Test (TUG): The Timed Up and Go Test (TUG) is a measure of mobility. Patients are asked to sit in a regular chair and upon command rise from the chair, walk at their normal pace to a line on the floor 10 feet (3 meters) away from the chair, return to the chair and sit down again. The time required by the patient to complete the assessment is measured and recorded. The TUG should be performed in triplicate at each visit and the best performance will be used for analyses. The TUG is administered by a Physician, a Physical Therapist, or designee familiar with the test. Every attempt should be made that the same assessor is administering the TUG in a given patient throughout the study. TUG will be administered to ambulatory patients in this Study.

Pediatric Evaluation of Disability Inventory-Computer Adaptive Test (PEDICAT): PEDI, originally published in 1992 by Haley et al. and revised as a computer adaptive test (CAT) – the PEDI-CAT, is a parent/clinician functional test that measures abilities in 4 content domains: daily activities, mobility, social/cognitive, responsibility. It will be completed by the caregiver with support from a qualified study center staff, for subjects younger than 20 years of age (9).

Pediatric Quality of Life Inventory (PedsQL)-Family Impact Module: Measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry (10). The Module

also measures parent-reported family daily activities and family relationships. This assessment will be used in subjects between 2 and18 years of age.

Overall Neuropathy Limitation Scale (ONLS): The scale was derived by modifying the Overall Disability Sum Score (ODSS) slightly to avoid the ceiling effect. Its inter-rater reliability was found to be high, as was its correlation with the ODSS (11). It is used to assess the limitations of subjects with immune-mediated peripheral neuropathies. It focuses on upper and lower limb functions and consists of a checklist for interviewing subjects. This scale will be used in subjects 18 years of age or older.

Pediatric CMT-specific Quality of Life Patient-reported Outcome Measure (pCMT-QOL PRO) and parent proxy (pCMT-QOL parent proxy): Measures patient-reported physical (symptoms, function, social activities) and social (feelings, cognition, and social skills) domains specific for children with CMT (12). This scale will be used in subjects 8 to 18 years of age.

Pediatric CMT-specific Quality of Life Parent-proxy Outcome Measure (pCMT-QOL [0 to 7 years parent-proxy]): Measure parent-reported physical (symptoms, function, social activities) and social (feelings, cognition, and social skills) domains specific for children with CMT (13). This scale will be used in subjects 7 years of age or younger.

3.2 Procedures

Magnetic Resonance Imaging (MRI): An MRI scan (without contrast) of the bilateral thigh and calf muscles will be performed to characterize the pattern of muscle involvement and evaluate the muscle fat fraction (MFF). Three-point Dixon MRI of leg muscles will be performed to generate fat fraction (FF) maps as described in the detailed CMT47 Imaging protocol. All MR imaging will be supervised by an attending pediatric neuroradiologist to ensure acquisition of complete, high-quality scans. MR imaging will be acquired at baseline and at multiple time points. The data will be transferred to a central site for quality control and analysis.

Nerve Conduction Study (NCS): NCS is an electrophysiological test to evaluate the sensory and motor responses in the upper and lower extremities. The specific measurements include distal latency, amplitude and conduction velocity. Serial measurements can show progression of the disease, as in axonal and demyelinating conditions. Ideally, NCS will be performed on the left arm and left leg. The same limbs will be assessed at every visit. The following nerves will be studied: median motor, radial sensory and peroneal motor response at the extensor digitorum brevis (EDB) and the tibialis anterior (TA).

Pulmonary Function Test, sitting and lying (PFT): The primary purpose of pulmonary function testing is to identify the severity and progression of pulmonary impairment. The specific measurements are lung volumes (Forced Vital Capacity-FVC, Forced Expiratory Volume-FEV and Forced Expiratory Flow-FEF) and maximal respiratory pressures (inspiratory and expiratory). PFTs will be performed in subjects older than 5 years of age based on the evaluator's assessment of subject's compliance and/or ability to follow instructions. The evaluator should complete the seated PFT prior to the supine PFT.

Scoliosis Series X-ray: The scoliosis X-ray includes the thoracic spine (upper back) and the lumbar spine (lower back). The scoliosis X-ray will not be completed on subjects older than 17 years of age.

Pregnancy Test- (individuals of childbearing potential only) Urine pregnancy test for females of child-bearing potential (Subject has experienced onset of menses and is not postmenopausal) will be collected. Results of urine pregnancy test must be reviewed and confirmed to be negative prior to

proceeding with any assessments involving radiation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If the subject's urine or serum pregnancy test is positive, assessments involving radiation should not be performed.

3.3 Skin Biopsy (Optional)

An optional skin sample will be taken for exploratory research purposes. If the participant consents, the neurologist will take a small skin sample via punch biopsy (approximately 3-4mm). Lidocaine cream will may be applied 30 mins prior to the area to be biopsied to anesthetize the skin. The skin sample will be sent to specialized laboratory for fibroblast culturing and subsequently the participants fibroblasts will be stored for future use.

3.4 Subject Withdrawal

Subjects may be withdrawn from the study for any of the following reasons:

- Withdrawal of the informed consent
- Lost to follow-up
- Withdrawal at the investigator's discretion

Subjects should be withdrawn at any time if the investigator concludes that it would be in the subjects' best interest for any reason. Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason. Protocol deviations should not lead to subject withdrawal unless they indicate a significant risk to the subject's safety. If premature subject withdrawal occurs for any reason, the investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information on the case report form (CRF). For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show due diligence by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. In the case of death, a subject will be considered withdrawn.

Subjects who terminate from the study prior to Visit 3, if they agree, will undergo an early termination/end of study visit if possible. The early termination/end of study visit is comprised of the Visit 3 assessments. Subjects can voluntarily withdraw from participation in this research study at any time. They may also request that their information be removed and destroyed from the study and that their data not be used in the analysis, evaluation or publication of this research study. That request would need to be in a written format, directed and submitted to the Principal Investigator.

3.5 Unscheduled Visit(s)

Subjects who experience any serious adverse effects (per21cFR312.32) or severe adverse events (CTCA>grade3) or experience another event of concern to the site Principal Investigator can be scheduled for an additional visit for further evaluation. If an unscheduled visit occurs, a member of the clinical study team (PI, sub-investigator, nurse coordinator, or clinical nurse) will evaluate the subject to determine the cause of the visit and provide care as needed. All procedures and/or sample collections should be documented within in unscheduled visit CRF.

4 POTENTIAL RISKS

Medical History and Record Review: There may be psychological distress associated with providing medical and family history. Frequent breaks or even cessation of the interview may be taken to reduce

risk of distress. There is a risk of potential loss of confidentiality and personal health information. Every effort will be made to keep the subject's information confidential; however, this cannot be guaranteed.

Physical and Neurological Examination: There is a small risk of mild pain or discomfort from positioning, activities, equipment, and procedures for the neurologic examination.

Neuropsychological Tests and Quality of Life Measures: These tests do not involve any medical procedures and have no inherent risks. However, subjects may experience mild frustration or nervousness due to cognitively challenging tasks. Subjects and parents may experience mild levels of psychological discomfort when completing rating forms on topics including school performance, mood, and quality of life.

NCS: Electrical stimulation may cause muscle contraction that may be uncomfortable. Also, there may be mild muscle soreness after muscle testing. This may last for one to two days. Subjects may experience some slight discomfort from having to lay or sit still during the procedure.

MRI: Subjects are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips, metallic prostheses, permanent eyeliners, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. Individuals will be screened for these conditions and implants before having any scan, and if they have any, they will not receive an MRI scan (or per the clinical judgement of a certified radiologist and radiology staff, may have a modified MRI that is deemed safe). In addition, all magnetic objects must be removed before entering the MRI scan room. We do not plan to administer gadolinium contrast as part of this imaging protocol.

Subjects with fear of confined spaces may become anxious during an MRI. Those with back problems or significant contractures may have pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing. Everyone having an MRI scan will be fitted with hearing protection. There are no known long-term risks of MRI scans.

X-Ray: This is a relatively painless and safe study. Subjects are exposed to a minimal amount of radiation during the scoliosis series X-ray to create detailed images of the spine.

Pulmonary Function Tests: There are no known risks. Subjects may feel tired after the procedure due to the respiratory effort.

Physical therapy assessments: The outcome measures (CMTPedS and CMTNSv2) carry a very small risk of mild pain, fatigue or discomfort from positioning, activities and equipment.

Blood collection: Subjects may experience minor pain and bruising during routine phlebotomy. All proper precautions will be taken, and only qualified individuals will perform blood draws.

Loss of confidentiality: There is a risk that confidentiality may be breached during the study. These risks are mitigated by anonymizing data and using secure servers and databases. If there is a confidentiality or data breach, the subject will be informed as soon as it is discovered.

Unforeseen risks: A previously unknown problem could result from participation in this observational study. It is not possible to estimate the chance of such problems or how serious problems could be.

Procedures and Risks	Description	Risk	Mitigation measures
Neurology Clinic Visit	Vital signs, anthropometrics, history of present illness and interim information will be obtained. Physical examination including general, neurological exam (including MMT) and hand-held dynamometry	Discomfort or psychological stress.	Subjects allowed to take breaks.
CMT Specific Scales - CMTPedS for subjects 5-17 years of age - CMTInfS < 4 years of age - CMTNSv2 for subjects >18 years of age - CMT-FOM for subjects > 18 years of age - CMT Health Index (CMTHI) for >18 years of age	Validated clinical outcome measures to monitor progression of sensorimotor function, disease-burden and quality of life in CMT subjects	No known risks. May experience mild frustration or fatigue with challenging tasks. May experience mild psychological discomfort when completing rating forms on topics including school performance, mood, and quality of life.	Subjects allowed to take breaks.
Electrophysiology Nerve Conduction Studies (NCS)	Evaluates sensory and motor responses in the upper and lower extremities including distal latency, amplitude and conduction velocity.	Risk of discomfort with muscle contraction from stimulation. Mild muscle soreness and fatigue. Discomfort from staying still during the procedure.	Procedure expectations will be communicated with the subjects and time will be given between stimulations.
Magnetic Resonance Imaging of the thigh and calf muscle without contrast Brain MRI without contrast	MRI scan of the thigh and calf muscle to characterize the structural abnormalities in CMT4J. MRI scan of the brain.	Risk for injury from the MRI magnet if present: pacemakers or other implanted electrical devices, brain stimulators, some dental implants, aneurysm clips, metallic prostheses, permanent eyeliners, implanted delivery pump, magnetic devices (such as	Individuals are screened to ensure MRI safety procedures are met before a scan Hearing protection for risk of hearing damage

		magnetic spine growing rods) or shrapnel fragments. Risk of discomfort from laying on hard surface or anxiety if fear of confined spaces or loud noises	
Neuropsychological and Physical therapy Assessments	A series of performance-based activities to assess psychomotor functioning and quality of life. This includes: • Vineland Adaptive Behavioral Scale • PEDICAT • PedsQL • ONLS • pCMT-QOL • Bayley-III, • WASI-II, WPPSI-IV • Stanford-Binet test V • TUG	Discomfort or psychological stress and tiredness.	Subjects allowed to take breaks.
Pulmonary Function Tests (PFTs)	PFTs to identify severity and progression of pulmonary dysfunction. Lung volume measurements: Forced Vital Capacity-FVC, Forced Expiratory Volume-FEV, and Forced Expiratory Flow-FEF. Pressure Measurements: maximal inspiratory and expiratory.	No known risks. May feel tired after the procedure.	Subjects allowed to take breaks.
Scoliosis series X-ray	Scoliosis series X-ray includes the thoracic spine (upper back) and the lumbar spine (lower back) to identify areas of spine curvature.	Exposure to minimal amount of radiation.	Adherence to the minimum exposure to radiation as permittable.
Blood collection	Exploratory blood draw	Minor pain and bruising	Adherence to maximum blood volumes permitted in

			pediatric subjects
Skin biopsy (optional)	Small punch biopsy for future exploratory use	Exposure to lidocaine cream and a small irritation to the skin for the punch biopsy	Only trained individuals can perform a skin biopsy

5 SUBJECT SAFETY AND DATA MONITORING

This study will not involve an investigational drug and does not require a DSMB.

Clinical data collected will be entered into a 21CFR11-compliant database by each study site. CRFs will be associated with each scheduled visit and all protocol-related research assessments.

As part of the consent process, subjects will be informed that their de-identified data will be shared with various third parties, including Regulatory Authorities, IRBs or other academic researchers and collaborating biotechnology companies without future consent requests. Future use of data and samples, including sharing with third parties (e.g., regulatory authorities), will be governed by each site's local informed consent form.

6 PROCEDURES TO MAINTAIN CONFIDENTIALITY

Subjects enrolled in the natural history study will be given a unique identifier that includes the project (disease), a site number that corresponds to the site, and a sequentially assigned subject number (ex: CMT4J-001-001).

Collaboration with other institutions and/or researchers may occur. In this case, all subject information shared with collaborators will be de-identified. Identifiable information may be shared with other studies if approved by the IRB or other regulatory body.

Study records are confidential, and they will be kept in a secure environment and protected to the full extent of the law.

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the site Principal Investigators, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within an electronic data capture system which is 21 CFR11 compliant. The electronic case report form will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number.

7 POTENTIAL BENEFITS

Participation in this research study may not provide a direct benefit to participants. This study may expand our knowledge about the genotype range and phenotypic expression of CMT4J. It will also

yield information about other system involvement and the frequency of this in the CMT4J/FIG4 population. The long-term objective is to be able to provide information about natural history and outcome measure validity, which is essential for future therapeutic clinical trials.

8 PROTOCOL DEVIATIONS

A major protocol deviation is a deviation that may adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data or may affect the subject's willingness to have consented in the study. "May" in this paragraph refers to a "reasonable possibility" of having such an effect; it does not require that such an effect has unequivocally occurred.

Major protocol deviations include but are not limited to: enrolment of ineligible subjects, factors that may confound measurement or interpretation of key outcome measures (e.g., a final study endpoint or several smaller "during study" outcome measures), safety or efficacy assessments not performed, or a pattern or frequency of "minor" deviations that together meet criteria described herein for a major deviation.

A minor protocol deviation is a deviation that is unlikely to adversely affect the rights, safety or well-being of the subjects and/or the compromise the quality and integrity of data or affect the subject's willingness to participate in the study. An example of a minor protocol deviation would be a missed laboratory test or a missed study visit.

9 SAFETY

9.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject after administration of an investigational vaccine and that does not necessarily have a causal relationship with the investigational vaccine. As this study is an observational study with no investigational product, any medical condition or diagnosis that is present at the time before the subject is consented will be recorded as Medical History. Any new or worsening of any chronic medical condition that is expected in the course of the disease occurring after consent will not be reported as an AE but recorded as ongoing medical history. Any significant event that emerges as a result of participation in this study, that is not a symptom or condition related to the natural course of the disease, will be reported as an adverse event.

9.2 Definition of Serious Adverse Event (SAE)

A SAE is any AE that results in any of the following outcomes:

1. Death. A death that occurs or that comes to the attention of the investigator.
2. A life-threatening event. A life-threatening event is any adverse experience that, in the view of the investigator, places the study subject at immediate risk of death from the reaction as it occurred. (Note: This does not refer to an event that could hypothetically have caused death had it been more severe).
3. An inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as an inpatient admission, regardless of length of stay.
4. Persistent or significant disability/incapacity.
5. Congenital anomaly/birth defect.
6. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent

one of the outcomes listed above. (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.)

Regardless of the relationship of the AE to the study, the event will be reported to the sponsor as an SAE if it meets any of the above definitions.

Events not considered to be serious adverse events are hospitalizations for:

- A procedure for protocol/disease-related investigations. However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- A procedure that is planned (i.e., planned prior to the starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable serious adverse event.
- An elective treatment of or an elective procedure for a pre-existing medical condition that does not worsen.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

9.3 Collecting, Recording, and Managing Adverse Events

9.3.1 Identifying Adverse Events

Any AE that occurs from the moment the subject has signed the consent form until the end of the study visit or the final assessment at the time of dropout or discontinuation from the study visit will be recorded and is reportable.

Adverse events may be discovered through any of these methods:

- Observing the subject,
- Questioning the subject or caregiver with standardized questions/procedures,
- Receiving an unsolicited complaint from the subject or caregiver,
- An abnormal value or result for a clinical laboratory evaluation.

9.3.2 Recording AE/SAEs

Throughout the study all identified AEs (serious and non-serious) will be recorded on all appropriate source documents and AE or SAE CRF regardless of their severity or relation to the study. SAEs will include a narrative of the event signed and dated by the principal investigator.

A complete description of all AEs will include event description, investigator assessment of severity, relationship to study procedures, diagnosis, date started/stopped, outcome, and treatment required. A change in the severity of the AE will also be documented.

9.3.3 Managing Adverse Events

The site investigator must apply his or her clinical judgment as to whether an AE is of sufficient severity to require that the subject immediately be withdrawn from the study. The investigator must institute any necessary medical therapy to protect a subject from any immediate dangers.

An AE will be followed until any of the following takes place: a) it is resolved, b) subject is stable, or c) a minimum of 30 days after subject is discontinued from the study, whichever comes first.

Adverse events assessed as related to study procedure and serious adverse events will be followed for as long as necessary to adequately evaluate the subject's safety, or until the event stabilizes, is otherwise explained, death occurs, or the subject is lost to follow up. If resolved, a resolution date should be provided.

9.3.4 Grading Criteria

Assessment should include the intensity (severity) of the AE, whether clinical or laboratory, and the relationship to study procedure(s).

The severity of AEs experienced by study subjects will be graded according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version (version 5.0 2017-11-27) unless otherwise indicated. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs. These criteria have been reviewed by the study investigators and the sponsor and have been determined appropriate for this study population.

All AEs whether or not listed in the NCI-CTCAE will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual (A semi-colon indicates 'or' within the description of the grade.):

- Grade 1 = Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 = Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
- Grade 3 = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 = Life-threatening consequences; or urgent intervention indicated.
- Grade 5 = Death.

For additional information and a printable version of the NCI-CTCAE manual, NCI-CTCAE website: http://ctep.cancer.gov/reporting/ctc.html will be consulted).

9.3.5 Definition of Attribution

The attribution of an AE to the study will be determined by the site investigator. The site investigator will record the determination of attribution on the appropriate AE or SAE CRF.

Relationship of an AE or SAE is to be determined by the investigator based on the following definitions:

Descriptor	Definition (guidelines)
UNRELATED CATEGORY	
Unrelated	The AE is clearly not related to the study or to disease progression. The AE is completely related to an etiology other than the study procedures (the alternative etiology must be documented in the study subject's medical record) or disease progression.
Unlikely	The AE is doubtfully related to the study or to disease progression and likely to be related to factors other than study procedures.
RELATED CATEGORIES	
Possible	The AE may be related to a study procedure or to disease progression. There is an association between the event and the study procedures and there is a plausible mechanism for the event to be related to the study procedures; there may be also an alternative etiology, such as characteristics of the subject's clinical status and/or underlying disease.
Probable	The AE is likely related to a study procedure or to disease progression. There is (1) an association between the event and the study procedures, (2) a plausible mechanism for the event to be related to the study procedures, and (3) the event could not be reasonably explained by known characteristics of the subject's clinical status and/or an alternative etiology is not apparent.
Definite	The AE is clearly related to a study procedure or to disease progression. There is (1) an association between the event and the study procedures, (2) a plausible mechanism for the event to be related to the related to the study procedure, and (3) causes other than the study procedures have been ruled out and/or the event re-appeared on re-exposure to the study procedure.

9.3.6 SAE Reporting Criteria and Procedures

The following process for reporting a SAE ensures compliance with the ICH guidelines. When an investigator identifies a SAE, he or she must notify the sponsors within 24 hours of discovering the event. In addition, the investigator must ensure that these events are entered in the electronic data capture platform.

All serious adverse events will be reported through completion of the adverse event eCRF. The Investigator will be responsible for reporting serious adverse events to the central IRB and local IRB (per local IRB policy)

10 STATISTICAL CONSIDERATIONS

Sample Size and Power Calculations: The sample size of approximately 20 subjects is expected to provide sufficient insights into the natural history of individuals with CMT4J to provide exploratory and descriptive results and guide the design of future studies of CMT4J. No formal sample size estimation was performed for this study. Parametric and non-parametric tests will be used to analyze possible associations between clinical, radiographic, and laboratory data. The tests will be selected based on the question being asked of the database. This database will be used to analyze multiple

medical issues among subjects with confirmed CMT4J. All analysis will be considered exploratory in nature.

10.1 Data Management

Quality control audits of all key safety, laboratory, and clinical data in the database will be made after data entry has been completed. Coexistent medical conditions, AEs and other medical events will be coded using MedDRA dictionary. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement of the study team.

11 ETHICAL CONSIDERATIONS (AND INFORMED CONSENT)

11.1 Ethical Standard

The Investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6; 62 Federal Regulations 25691 (1997).

11.2 Institutional Review Board

The local institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate ethics review committee or IRB. Any amendments to the protocol or consent materials must also be approved before they are placed into use unless it is in the best interest of the subjects' safety to implement changes prior to approval. In both the US and in other countries, only institutions holding a current U. S. Federal-Wide Assurance issued by the Office for Human Research Protections (OHRP) may participate.

Prior to enrollment of subjects into this clinical study, the protocol and the informed consent form(s) (ICF) will be reviewed and approved by the appropriate IRB. Any amendments to the protocol or consent materials will also be reviewed and approved by the appropriate IRB. The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this clinical study. If amendments to the protocol are required, the amendments will be submitted to the IRB; an IRB letter of approval of the amendment must be obtained prior to implementing the amendment.

APPENDIX 1: SCHEDULE OF EVENTS

Study Day	Screening	Baseline	Month 12	Month 24
Windows		*(± 4 wks)*	*(± 4 wks)*	*(± 4 wks)*
Informed Consent	X			
Medical Information		X	X	X
Demographics				
Medical History		X	X	X
Family History		X		
CMT4J Diagnosis and History		X		
Clinical Procedures				
Inclusion/Exclusion Criteria	X			
Vital Signs[a]		X	X	X
Height and Weight		X	X	X
Physical Exam[b]		X	X	X
Neurological Exam[c]		X	X	X
Urine Pregnancy (for female subjects)[d]		X	X	X
Blood Collection for Future Exploratory Analysis[e]		X	X	X
Skin biopsy (optional, any visit, only once)		X	X	X
Adverse Events		X	X	X
Concomitant Medications		X	X	X
CMT Scales*				
CMTPedS[f]	X	X	X	X
CMTInfS[g]	X	X	X	X
CMTNSv2[h]	X	X	X	X
CMT-FOM[h]	X	X	X	X
CMT Health Index (CMTHI)[h]	X	X	X	X
Clinical Studies				
Thigh and Calf MRI without contrast		X	X	X
Brain MRI without contrast		X	X	X
Nerve Conduction Study (NCS)[i]		X	X	X
Pulmonary Function Test (PFT)[j]		X	X	X
Scoliosis Series X-ray[k]		X	X	X
Neuropsychological and Physical Therapy Assessments				
Vineland Adaptive Behavior Scale		X	X	X
PEDICAT[l]		X	X	X
Bailey III		X	X	X
WASI-II or WPPSI-IV		X	X	X
Stanford Binet – V		X	X	X
Timed up and go (TUG)		X	X	X
Wearable devices	X	X	X	X
Questionnaires				
PedsQL[m]		X	X	X
Overall Neuropathy Limitation Scale (ONLS) (18 years and older)		X	X	X
pCMT-QOL PRO (8 to 18 years)		X	X	X
pCMT-QOL (8 to 18 years parent-proxy)		X	X	X
pCMT-QOL (0 to 7 years parent-proxy)		X	X	X

[a] Temperature, pulse, blood pressure measured in one arm or leg after the patient has been seated for ~ 5 minutes.

[b] Exam of heart, lungs, abdomen, back, and extremities; height and weight; head circumference

[c] Includes evaluation of cranial nerves, muscle tone, muscle strength, sensation, gait, coordination and deep tendon reflex testing, handheld dynamometry

[d] Urine pregnancy test for females of child-bearing potential. Results of urine pregnancy test must be reviewed and confirmed to be negative prior to proceeding with any assessments involving radiation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. If the subject's urine or serum pregnancy test is positive, assessments involving radiation should not be performed.

[e] With subject consent, blood and blood products may be stored long-term for exploratory purpose; these samples will be maintained for up to 10 years

[f] Subjects aged 5 to 17 years 11 months (less than 18 years)

[g] Subject < 4 years of age

[h] Subjects aged 18 years and older

[i] Ideally, performed on the left arm and leg, the same limbs will be assessed at each visit

[j] Subjects older than 5 years of age based on the physiotherapist's assessment of subject's compliance and/or ability to follow instructions

[k] Thoracic and lumbar spine

[l] Subjects < 20 years

[m] Subjects 2 to 18 years

*Video capture will be used for some parts of the CMT scales.

12 REFERENCES

1. Braathen G, Sand J, Lobato A, Høyer H, Russell M. Genetic epidemiology of Charcot-Marie-Tooth in the general population. Eur J Neurol. 2011;18(1):39–48.
2. Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clin Genet.1974;6(2): 98-118.
3. Burns J, Ouvrier R, Estilow T, Shy R, Laura M, Pallant JF, Lek M, Muntoni F, Reilly MM, Pareyson D, Acsadi G, Shy ME, Finkel RS. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol. 2012;71(5):642-652.
4. Murphy SM, Herrmann DN, McDermott MP, Scherer SS, Shy ME, Reilly MM, Pareyson D. Reliability of the CMT neuropathy score (second version) in Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2011;16(3):191-198.
5. Eichinger K, Burns J, Cornett K, Bacon C, Shepherd M, Mountain J, Sowden J, Shy R, Shy ME, Herrmann DN. The Charcot- Marie- Tooth Functional Outcome Measure (CMT-FOM). Neurology. 2018;91(15):e1381-e1384.
6. Johnson NE, Heatwole C, Creigh P, McDermott MP, Dilek N, Hung M, Bounsanga J, Tang W, Shy ME, Herrmann DN. The Charcot-Marie-Tooth Health Index: Evaluation of a Patient Reported Outcome. Ann Neurol. 2018;84(2):225-233.
7. Morrow JM, Evans MRB, Grider T, Sinclair CDJ, Thedens D, Shah S, Yousry TA, Hanna MG, Nopoulos P, Thornton JS, Shy ME, Reilly MM. Validation of MRC Centre MRI calf muscle fat fraction protocol as an outcome measure in CMT1A. Neurology 2018;91(12):1125-1129.
8. Sparrow SS, Cichetti DV, Balla DA, Doll E A. (2005). Vineland Adaptive Behavior Scales, second edition manual. Bloomington, MN: PsychCorp.
9. Haley SM, Coster WJ, Dumas HM, Fragala-Pinkham MA, Ni PS, Kramer J, Feng T, Kao YC, Moed R, Ludlow LH. Accuracy and precision of the Pediatric Evaluation of Disability Inventory computer adaptive tests (PEDI-CAT). Dev Med Child Neurol. 2011;53(12):1100-1106.
10. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care. 1999;37(2):126-139.
11. Graham RC and Hughes RAC. A modified peripheral neuropathy scale: the Overall Neuropathy Limitations Scale. J Neurol Neurosurg Psychiatry. 2006;77(8):973-976.
12. Ramchandren S, Wu TT, Finkel RS, Siskind CE, Feely SME, Burns J, Reilly MM, Estilow T, Shy ME, Childhood CMT Study Group. Development and validation of the pediatric Charcot-Marie-Tooth disease quality of life outcome measure. Ann Neurol. 2021;89(2):369-379.
13. Wu TT, Finkel SR, Siskind CE, Feely SM, Burns J, Reilly MM, Muntoni F, Milev E, Estilow T, Shy ME, Ramchandren S, Childhood CMT Study Group of the Interited Neuropathy Consortium. Validation of the parenty-proxy version of the pediatric Charcot-Marie-Tooth disease quality of life instrument for children aged 0-7 years. J Peripher Nerv Syst. 2023;May 11. doi:10.1111/jns.12557.