Sponsor:	Elpida Therapeutics, a non-profit entity, a Social Purpose Corporation
IND #:	Not yet assigned
Product Name:	ELP-02
Indication:	Charcot-Marie-Tooth disease type 4J and other diseases caused by the FIG4 gene mutation
Request Type:	**Request for Rare Pediatric Disease Designation (this is accompanied with a request for Orphan Drug Designation)**
Submission Date:	30 July 2024

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TABLE OF ABBREVIATIONS

AAV	adeno-associated virus
CBA	CMV enhancer and truncated chicken β-actin 5' UTR
CMT	Charcot-Marie-Tooth
CMT4J	Charcot-Marie-Tooth disease type 4J
CNS	central nervous system
DNA	deoxyribonucleic acid
ExAC	Exome Aggregation Consortium (now gnomAD)
FIG4	factor-induced gene, phosphoinositide 5-phosphatase
FDA	Food and Drug Administration
gnomAD	genome aggregation database
h	human
H&E	hematoxylin and eosin staining
HGMD	Human Gene Mutation Database
I41T	FIG4 protein with change from isoleucine to threonine at residue 41
INC	Inherited Neuropathy Consortium
IND	Investigational New Drug
ITR	inverted terminal repeat(s)
NfL	neurofilament light chain
NIH	National Institutes of Health
OMIM	Online Mendelian Inheritance of Man
OOPD	Office of Orphan Products Development
Opt	optimized
PI(3,5)P2	phosphatidylinositol 3,5-bisphosphate
PND	post-natal day
PNS	peripheral nervous system
RNA	ribonucleic acid
US	Unites States of America
UTSW	University of Texas Southwestern Medical Center
vg	vector genome(s)
WT	wild type

1. SPONSOR NAME AND ADDRESS

Sponsor	Elpida Therapeutics, SPC
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2. PRODUCT NAME

Name(s) of Drug (including all available names: Trade, Generic, Chemical, or Code):

Sponsor Code: ELP-02.

Generic and tradenames have not yet been requested for this product.

3. PROPOSED INDICATION, PREVALENCE AND

The proposed indication is Charcot-Marie-Tooth disease type 4J and other diseases caused by the FIG4 gene mutation".

4. APPLICATION AND DESIGNATIONS FOR RBIO1

There are no applications or designations currently for ELP-02.

Orphan drug designation (ODD) is being requested alongside this request for Rare Pediatric Disease Designation (RPDD).

5. PRODUCT DESCRIPTION

The investigational agent, ELP-02 is an AAV9 gene therapy [redacted]

Table 1 Product description for ELP-02

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6. PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION

ELP-02 will be provided as a sterile clear colorless solution, vialed at a strength to be determined. ELP-02 will be administered as a single one-time administration by intrathecal injection at a dose and volume to be determined from ongoing nonclinical studies.

7. INFORMATION SUPPORTING RARE PEDIATRIC DISEASE DESIGNATION

Per Section 529(a)(3), a rare pediatric disease is required to meet the following criteria:

a. The disease is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children and adolescents, AND

b. The disease is a rare disease or condition, within the meaning of Section 526 of the FD&C act.

Additionally, the product application needs to be for a human drug for the prevention or treatment of a rare pediatric disease where the active moiety has not been previously approved and provides data suggesting that the drug may be effective in the rare pediatric disease.

The following sections provide the information necessary for the determination of this designation; the below bullets summarize the more detailed content that follows:

- CMT4J (OMIM 611228), first described in 2007, is an ultra-rare peripheral neuropathy resulting from recessive inheritance of loss-of-function FIG4 (OMIM 609390) alleles (Chow et al., 2007). CMT4J patients are compound heterozygotes carrying one complete loss of function allele of FIG4 in combination with a partial loss of function missense FIG4 allele (typically p.Ile41Thr) (Chow et al, 2007; Cottenie et al., 2013; Menezes et al., 2014; Nicholson et al., 2011).

- CMT4J, an ultra-rare form of CMT disease, is a rare, debilitating, progressive hereditary motor and sensory neuropathy caused by heteroallelic FIG4 loss of function alleles. It is characterized by progressive motor weakness with sensory involvement resulting in quadriplegia, respiratory failure, and a shortened lifespan.

- CMT4J is estimated to account for 0.3% to 0.4% of all diagnosed Charcot-Marie-Tooth cases (Nicholson et al., 2011; DiVincenzo et al., 2014, Fridman et al., 2015). Based on the 2024 U.S. population of nearly 342 million people and the well-established CMT prevalence of approximately 1 in 2500, the prevalence of CMT4J in the U.S. is estimated to be between 400 and 550 cases.

- This designation request focuses on CMT4J (OMIM 611228). Symptoms and age of onset vary, with pediatric onset disease often characterized by a rapid progression of muscle weakness and atrophy, often leading to the inability to walk by late adolescence. Asymmetric muscle weakness is common, as is localization to only proximal or distal portions of the limbs. Disease severity can range from mild gait difficulties to quadriparesis.

- Recent evidence supports that almost 75% of CMT4J patients are diagnosed before the age of 18 with over half of new patients diagnosed in late adolescence between ages 5 and 10.

- There are no approved treatments for CMT4J, leaving an unmet medical need for this serious and quality of life limiting disease affecting pediatric patients.

- ELP-02 is an AAV9 gene therapy containing codon optimized human (h) FIG4, which has been shown to extend the lifespan of plt mice which are FIG4 deficient from a few weeks to at least a year with near normal behavioral, neurophysiological, and histopathological phenotypes (Presa et al., 2021).

- The therapeutic goal is to treat pediatric patients with a single one-time intrathecal administration of ELP-02, which will provide the FIG4 protein which may potentially prevent further progression of the disease, improving functional outcomes and survival. As with similar pediatric diseases, it is likely that earlier treatment could provide better outcomes for patients (Gray, 2016).

In summary, the data presented in this designation request support the granting of rare pediatric disease designation to ELP-02.

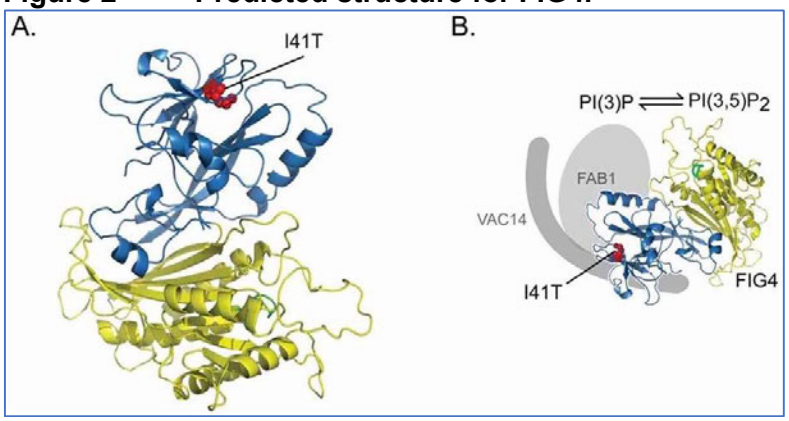
7.1. Description of CMT4J (and FIG4-related diseases)

7.1.1. Pathophysiology

The *FIG4* (factor-induced) gene (located in chromosome 6q21) (also known as Sac3 [SAC domain-containing protein 3]) encodes a phosphatase that removes the 5-phosphate from the inositol ring of phosphoinositide $PI(3,5)P_2$, a membrane-bound phospholipid that acts as a molecular signal for trafficking and fusion of intracellular vesicles (Figure 2). In cells derived from 13 patients with Charcot-Marie-Tooth disease type 4J (CMT4J), there was a noted decrease in steady-state levels of PtdIns(3,5)P2 and PtdIns5P. This reduction was independent of the onset of disease symptoms, suggesting that the decline in these lipid levels occurs before symptoms appear (Shisheva et al., 2019). CMT4J patients are compound heterozygotes with one null FIG4 allele and one missense FIG4-I41T allele (FIG4-c.122 T>C mutation). The FIG4-I41T mutation, which changes isoleucine to threonine at residue 41 of

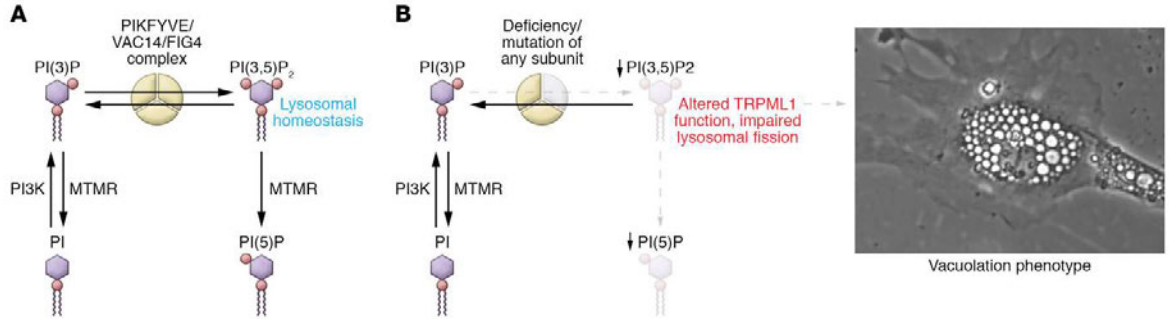
the FIG4 protein, is the most common missense mutation in CMT4J and causes significant functional loss (Beloribi-Djefaflia et al., 2024). This mutation results in an unstable FIG4 protein and leads to the accumulation of swollen endo/lysosomes and disruptions in vesicular organelle transport and function (Hu et al., 2018; Gentil et al., 2017) (Figure 3).

Figure 2 Predicted structure for FIG4.



A. Predicted structure for FIG4 with I41T mutation located near the surface of the N-terminal domain (blue). B. predicted protein in the PI(3,5)P2 biosynthetic complex. I41T reduces interactions with FAB1 (5'-kinase, PIKFYVE) and VAC14 (scaffold protein, ArPIKfyve), resulting in mislocalization of the complex. (Figure courtesy of Lenk et al., 2011)

Figure 3 Deficiency in FIG4.



Although FIG4 is a lipid phosphatase that can convert PI(3,5)P2 to PI(3)P, it exists within a complex with the lipid 5 kinase (PIKFYVE) and VAC14. Deficiency of any of the subunits results in deficiency of PI(3,5)P2 and PI(5)P, which are required for lysosomal homeostasis. (B) The altered TRIPML1 channel function and impaired lysosomal fission likely contribute to the prominent vacuolation phenotype in CMT4J. Similarly, cultured embryonic fibroblasts from Fig4 null mice accumulate large, acidic vacuoles (photograph provided with permission by G. Lenk and M. Meisler).

FIG4 is highly expressed in the brain, endocrine tissues, skin, and respiratory system (Yu et al., 2022). In rat studies, FIG4 was found abundantly in neurons and myelin-forming cells in the CNS and PNS during neural development and is diminished in neurons of the adult CNS (Guo et al., 2012). Mutation in the FIG4 gene results in the deficiency of not only FIG4, but also the complex formed with PIKFYVE and VAC14. This results in a deficiency of PI(3,5)P2 and PI(5)P, required for lysosomal homeostasis. Impaired lysosomal fission likely contributes to the vacuolation phenotype of CMT4J (Figure courtesy of Svaren, 2021).

In mouse mutants with conditional inactivation of FIG4 in either motor neurons or Schwann cells, it was found that FIG4 loss in motor neurons causes neuronal and axonal degeneration, whereas FIG4 loss in Schwann cells resulted in general trafficking impairment, leading to a

defect in autophagy-mediated degradation and demyelination (Vaccari et al., 2015). Further, loss of FIG4 in Schwann cells impaired both myelination and nerve regeneration.

FIG4 is stabilized and protected from degradation by its interaction with VAC14. In the absence of this complex, FIG4 remains unfolded and prone to rapid destruction (Ikonomov et al., 2010). The I41T mutation of FIG4 does not significantly alter the association of FIG4 with VAC14 (at least through coimmunoprecipitation analyses) or affect catalytic activity, but it is possible that the complex affinity is weakened, or local folding is affected and FIG4 is rapidly turned over, disrupting $PI(3,5)P_2$ homeostasis (Manford et al., 2010; Ikonomov et al., 2010).

7.1.2. Natural History of CMT4J

Charcot-Marie-Tooth (CMT) disease is a group of inherited peripheral neuropathies, affecting 1 in 1,214 (Braathen et al, 2011) to 2,500 (Skre, 1974). 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 compromises 60-65% of cases.

CMT4J is a rare autosomal recessive, peripheral motor demyelinating neuropathy caused by mutations 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 as CMT4J is a peripheral neuropathy resulting in progressive muscle weakness. The disease progression varies widely, but common features include muscle weakness, atrophy, scoliosis, sensory deficits, and mobility impairments. Disease severity can range from mild gait difficulties to quadriparesis.

Early-onset severe phenotypes present with reduced nerve conduction velocity (NCV) and motor developmental delay. Later onset phenotypes develop progressive muscle weakness, gait abnormalities, and sensory deficits.

Complications throughout the course of disease and starting in childhood may include scoliosis, pes cavus, hammer toes, and loss of reflexes. Sensory symptoms, including numbness, tingling, and pain may persist or worsen over time.

Table 2 Disease Progression of CMT4J

Onset	Age	Characteristics
Childhood	Early infancy (0-1 year)	Delayed motor milestones, such as delayed gait acquisition, and ataxia
	Toddlerhood (1-3 years)	Muscle weakness and hypotonia, leading to decreased crawling and walking

Onset	Age	Characteristics
	Early childhood (3-5 years)	Gait abnormalities with walking difficulties emerging at this time (patients are often diagnosed in early to late childhood)
	Middle childhood (6-12 years)	Progressive muscle weakness leading to difficulty with activities, such as climbing stairs, running, and playing sports. Sensory symptoms, such as paresthesia may also occur.
Teenage Onset	Early Teen years (13-15 years)	Muscle weakness particularly in lower limbs, leading to gait disturbances and difficulty with activities requiring limb strength, such as jumping and running.
	Late Teen years (16-19 years)	Muscle weakness continue to progress, affecting both proximal and distal muscles in the limbs. Sensory deficits may worse, impacting daily living activities.
Adult Onset	Early adulthood (20s-30s)	Progressive weakness and atrophy of muscles, particularly in upper limbs. Respiratory compromise and breathing difficulties may emerge as muscle weakness affects the respiratory muscles.
	Middle adulthood (40s-50s)	Severe weakness affecting both upper and lower limbs. CNS abnormalities may develop in some cases, leading to speech difficulties, tremors, and neurological symptoms.
	Late adulthood (60s and beyond)	Disease progression varies, with some patients experiencing stabilized symptoms, while others deteriorate. Mobility may become severely impaired, necessitating use of assistive devices, such as wheelchairs

Neurogene Inc sponsored a 24-month multi-center prospective natural history study (NHS) in the US and subjects with a CMT4J diagnosis were enrolled (ClinicalTrials.gov NCT03810508) starting in Jan 2019 (Sadjadi et al., 2024). In this study, the aim was to further characterize the CMT4J disease phenotype and evaluate sensitivity and responsiveness of validated CMT related outcome measures to be able to select an appropriate endpoint to track meaningful change in future therapeutic trials. A total of 20 subjects (15 male, 6 female) with a genetically confirmed autosomal recessive FIG4 mutation were recruited by University of Texas Southwestern (11 patients, PI: Dr. Diane Castro) and University of Iowa (9 patients, PI: Dr. Michael Shy). Fifteen patients were from US, 2 from Canada, others from India, Brazil, and the United Kingdom.

Fifteen of 20 (75%) patients were children younger than 18 years of age at the time of recruitment (mean age 11.6±3.8 years, median 13 years [9;15]) and 5 patients were adults (mean 40.6±12.2 years, median 36 years [28.5;55]). Patients were evaluated at screening and subsequently every 6 months. Data were collected on fine and gross motor assessments, cognition and memory assessments, adaptive behavior and quality of life, neurophysiology,

imaging biomarkers, biochemical biomarkers and CMT disease scales using CMTPedS(Burns et al, 2012). Unfortunately, this study was terminated in 2022 due to business decisions by the sponsor, and further natural history data were not collected. Additionally, due to the pandemic, there were limitations to in-person visits and, therefore, longitudinal data were minimal and sporadic for most of the patients.

The CMTPedS consists of standardized measurements of strength, dexterity, sensation, gait, balance, power, and endurance and was collected every 6 months, though only 6/14 pediatric patients had follow-up from baseline. While statistically significant change was not observed, the functionality of this outcome measure shows promise as a marker for following CMT4J patients over time. MRI measurements of calf muscle fat fraction and thigh muscle fat fraction (Morrow et al., 2018; Doherty et al., 2024), both of which correlate with denervation, showed utility as a biomarker, with calf muscle fat fraction correlating with CMTPedS. A limited evaluation of plasma NfL (neurofilament light chain) was performed due to lack of in-person visits, but NfL is a potential biomarker for CMT (Millere et al., 2021).

7.1.2.1. Cases reported in literature:

A detailed description of the clinical features and, in some cases, disease progression, of early onset CMT4J patients and demographic location are published in the literature, see Table 3.

Table 3 Published Cases of Early Onset CMT4J

Study	Patients	Onset Age	Key Clinical Features	Progression/Outcomes	Location
Chow et al. (2007)	5 (4 families)	Early childhood	Severe phenotype, reduced NCV, motor developmental delay, similar to Dejerine-Sottas neuropathy	3 of patients diagnosed by age 5, severe phenotype early, progressive muscle weakness, atrophy	US
Zhang et al. (2008)	2 siblings	Late (adult) with early symptoms in childhood	Early signs in childhood, progressive muscle weakness, arm and leg weakness, atrophy	Progressive to complete loss of movement in limbs, respiratory compromise (death in early 30s for female sibling)	
Nicholson et al. (2011)	11	Early child to 6th decade	Variable onset (5 had early onset in childhood), gait abnormalities, muscle weakness, scoliosis, and fixed flexion deformity	Progressive muscle weakness, use of walking aids, wheelchair, severe weakness in later years	Australia (3)/US (8)
Cottenie et al. (2013)	1	Early childhood	Delayed motor milestones, progressive limb weakness, NCV tests showing demyelination	Progressive muscle weakness in all 4 limbs and use of wheelchair by age 13, rapid progression, loss of arm function by age 24	UK
Menezes et al. (2014)	2 (mother and daughter)	Early childhood	Frequent falls, unsteady gait, difficulty climbing stairs, handwriting issues, severe sensorimotor neuropathy	Daughter: severe neuropathy by age 14; Mother: mild form, symptoms since teens, NCV indicating demyelination	Australia

Study	Patients	Onset Age	Key Clinical Features	Progression/Outcomes	Location
Gentil et al. (2017)	1	Childhood	Mild gait difficulties, clumsiness, poor sport abilities, hammer toes, distal sensory deficits	Progressive weakness and atrophy leading to quadriparesis with sensory symptoms	Canada US
Orengo et al. (2018)	1	Childhood	Slow progressive weakness in distal legs, CNS abnormalities (aphemia, word finding difficulties), hand tremors	Rapid progression in late 40s, CNS abnormalities unique to this patient	Germany
Hu et al. (2018)	12	Birth to teenage	Severe limb paralysis, mental retardation in early onset cases, demyelinating polyneuropathy	Variable progression, some with severe paralysis at birth, others with milder symptoms but progressive weakness	US
Zimmermann et al. (2020)	1	Childhood	Proximal and distal muscle weakness by age 5, gait disturbances, sensory deficits, learning difficulties	Continued progression to severe muscle weakness, able to graduate high school despite early onset	Germany
Tafontaine et al. (2021)	3	Childhood	Severe clinical neuropathy symptoms, distal axon loss, scoliosis, amyotrophy, gait disturbance	No clinical evolution over decades, able to walk unaided though running or jumping not possible	France
Suarez et al. (2023)	4	Childhood	Frequent falls, slow running, pes cavus, sensory symptoms, proximal and distal limb weakness, demyelinating polyneuropathy	Paresthesia, balance difficulties, subacute motor impairment in late adolescence. Stable over follow-up period (~5 years), able to walk without assistance	Chile
Beloribi-Djefaflia et al. (2024)	8	Childhood to adult	Pure CMT4J or CMT with parkinsonism, distal amyotrophy, loss of reflexes, severe phenotype in some with early parkinsonism	Progressive muscle weakness, some stable over decades, CNS involvement in some cases with parkinsonism	France

Patients described in Table 3 generally have CMT4J disease (without CNS anomalies) associated with the most common compound heterozygote in which one FIG4 allele is null and the other encodes a missense FIG4-I41T allele. The less common heterozygote with a missense FIG4-L17P in place of I41T has only been noted once (Nicholson et al., 2011), while other less common mutations present with similar CMT4J disease.

7.1.2.2. Survey study to capture disease burden:

To capture the disease burden in patients with CMT4J, Elpida Therapeutics sent out surveys to caregivers (15 patients with CMT4J, Elpida Therapeutics, unpublished 2024) to obtain unique insights into the daily challenges and overall impact of rare disease symptoms. The goal was to understand the array of symptoms and how improved treatment options would

impact quality of life for those affected by CMT4J. Among the survey were 2 open ended questions relating to the most impactful symptoms of daily life and the caregiver responses shown below.

Question 1: "What symptoms of your CMT4J most impact your daily quality of life?"

- Mobility (73%)
- Balance/Standing (67%)
- Fatigue (67%)
- Arms/Hands (50%)
- Pain (47%)
- Sensory loss (27%)
- Respiratory/Vocal/Swallowing (13%)

Question 2: "What specific aspects of daily life are most challenging because of CMT4J?"

- Work/School (67%)
- Exercising (60%)
- Using Hands (47%)
- Caring for Self (47%)
- Hobbies (40%)
- Communicating (20%)
- Driving (13%)

7.1.3. Incidence and prevalence of CMT4J

CMT affects an estimated 126,000 individuals in the US (1 in 2500) (Nam and Choi, 2019). CMT4J is one of many subgroups belonging under the umbrella of CMT and currently the estimated US prevalence is 1 per 1,000,000 (ranging between 0.2% of CMT patients and 0.3% [of those genotyped] of a large cohort of individuals with genetic neuropathy); significantly below the level required for orphan designation.

The prevalence of a disease should be established using authoritative peer-reviewed references based on the U.S. population therefore a PubMed literature search was conducted (17 May 2024) without limit of publication date using the following search terms:

- "CMT4J" (N=42 publications),
- "Charcot-Marie-Tooth type 4J" (N=42),
- "FIG4" (N=175),

- "FIG4 mutation" (N=107)
- "Charcot-Marie-Tooth" (N=6,309)

Within each of these searches, "incidence," OR "prevalence" was added.

As previously discussed, no publications were identified that spoke specifically to the incidence of CMT4J in the US. Most of the limited information available was related to allelic frequency of the FIG4-I41T allele and frequency of CMT4J among CMT disease patients.

Table 4 Data Supporting Prevalence of CMT4J

Data Source	Key data
Chow et al. (2007)	• Screened FIG4 in 95 individuals diagnosed with CMT disorder but lacking mutations in known genes (US cases) • Identified 5 patients – null/I41T FIG4 heterozygous
Nicholson et al. (2011)	• 8 Patients CMT4J out of 4000 sent for CMT disease gene panel testing (0.2%) (Athena Diagnostics in US) • 3 patients CMT4J identified from 6 CMT disease patients negative for CMT disease genes (Australian families) • Frequency of I41T heterozygotes in 5769 Northern European Controls was calculated as 0.001 allelic frequency (13/5769)
Saporta et al. (2011)	• Identified 2/527 (0.4%) CMT4 patients among CMT patients with a genetic diagnosis (from 1024 patients evaluated at a clinic between 1997 and 2009 at Wayne State University, Detroit, MI)
DiVincenzo et al. (2014)	• 0.3% FIG4 mutations (10/3216) of cohort of 17,780 patients sent for commercial testing from 2009 to 2013, Athena Diagnostics for 14 CMT-related disease
Fridman et al. (2015)	• CMT4J was identified in 4 patients (0.24%) from 1652 patients in a natural history cohort for CMT from 2009 to 2013 that included 13 Inherited Neuropathy Consortium sites (including 10 in the US)
Lafontaine et al. (2021)	• Identified 1.57% (12/764) French patients with CMT that had I41T mutation. Among these, 3 had homozygous I41T.
Sadjadi et al., 2024) in press	• Neurogene CMT4J NHS (NCT03810508) included 16/20 patients with CMT4J from the US (2019-2022)
Elpida Therapeutics CMT4J Natural History Study	• Elpida Therapeutics CMT4J NHS (NCT06151600) will enroll 20 patients with CMT4J at 4 sites in the US (expected 2024). Among those that have contacted Elpida Therapeutics interested in participating, 21/26 are from the US

7.1.4. Standard of Care

There is no treatment for CMT4J (or any of the other phenotypes associated with mutation in the *FIG4* gene). Standard of care for CMT4J patients is limited to symptom management and

supportive care, including physical and occupational therapy, assistive devices, surgeries for deformities, and pain management (McCorquodale et al., 2016). Although these interventions may help improve daily functioning and quality of life, they do not address the underlying genetic cause of the disease, allowing disease progression to continue.

Elpida Therapeutics is developing ELP-02 to treat CMT4J. The therapeutic goal of ELP-02 is to reverse and/or prevent progressive symptoms of CMT4J in patients with a single one-time intrathecal administration, resolving or preventing the serious manifestations, and providing patients the opportunity to experience an improved quality of life. In addition, a study is designed to investigate the clinical characteristics and natural history of CMT4J. The aim is 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, biochemical analyses, calf muscle imaging, nerve conduction studies, pulmonary function testing and neuropsychological assessments.

7.2. Mechanism of action of ELP-02

Efficient transduction of neurons in the PNS and CNS by intrathecal delivery with ELP-02 (AAV9 vector expressing the normal FIG4 gene) is expected to positively impact the normal course of disease progression in FIG4 patients. The mode of action of ELP-02 is to express the normal FIG4 gene in the targeted cells, restoring normal function. Primary cellular targets proposed for the treatment of FIG4 are lower motor neurons, as CMT4J is predominantly a peripheral nervous system (PNS) disorder, though the route of administration may also target the CNS. FIG4 expression in the cytoplasm is found in most tissues, with high expression in the brain, endocrine tissues, skin, and respiratory system, so the targeting of any other cell types within the body is also desired. The AAV9 vector utilized is expected to deliver the FIG4 gene to these primary targets (Bailey et al., 2018). The introduced cDNA should exist primarily as an episome following transfer of ELP-02 and express a normal version of functional human FIG4 protein continuously, which should prevent/slow the onset of CMT4J.

Nonclinical proof-of-concept has been established from an in vivo mouse study that supports PNS and CNS targeting using the proposed clinical route of administration (intrathecal injection). These data are described in Section 7.3.

7.3. Non-clinical Proof of Concept studies supporting ELP-02's usefulness to treat CMT4J

The following nonclinical study provides proof of concept that ELP-02 provides promise for the clinical treatment of CMT4J:

- In vivo administration of ELP-02 to homozygous *plt* (pale tremor) F1 hybrid C57BL/6J x C3HeB/FeJ mice, *FIG4*-deficient mice, dose dependently improved outcomes including survival and was more effective when mice were treated one day after birth compared to day 4, 7 or 11 days after birth.

- FIG4$^{+/+}$ mice treated with ELP-02 showed 100% survival and no differences in growth, suggesting the vector was well-tolerated.
- hFIG4opt mRNA expression was found in whole brain and spinal cord at 6 months after ELP-02 treatment supporting the mechanism of action.
- Control mice survived at least 1 year, with largely normal gross motor performance and little sign of neuropathy compared to demyelination, loss of motor neurons, and vacuolization in many regions of the nervous system and just 23 days survival for untreated *plt* mice.

There have been 5 nonclinical studies conducted with ELP-02 (Table 5) using either the *Fig4*$^{-/-}$ *or Fig4*$^{+/+}$

Table 5 Nonclinical Studies for ELP-02 Investigations

Study GLP Status	Description	Model, Dose, Delivery Route in Studies	Source
Non-GLP complete	**In Vivo Proof-of-concept (NGL-POC-001)**		
	Fig4-/- mice at PND1 or PND4 terminated at 12 months of age or >15% BW loss maximum	CMT4J Mouse model (*Fig4-/-*) and WT (*Fig4+/+*), (PND1 cohorts N=75; PND 4 cohorts N= 51), ELP-02 or vehicle 5.4E 11 vg/ mouse dose in 2µL via ICV	Jackson Labs
	In Vivo Efficacy and Safety (NGL-ESY-002)		
	Fig4-/- mice at PND7 or PND11 terminated at 120 days of age or >15% BW loss maximum	CMT4J Mouse model (*Fig4-/-*) and WT (*Fig4+/+*), (PND7 cohorts N=28; PND 11 cohorts N= 25), ELP-02 or vehicle 13.5E 11 vg/ mouse dose in 5µL via IT	Jackson Labs
	In Vivo Biodistribution (NGL-BDN-003)		
	Fig4-/- mice at PND1 and PND4 terminated at 180 days of age and PND7 terminated at 90 days of age	CMT4J Mouse model (*Fig4-/-*) and WT (*Fig4+/+*)- For 180-day qPCR assessments, PND1 (N=4) and PND4 (N=4) mice received 5.4E 11 vg/ mouse ELP-02 dose via ICV; and for 90-day assessments, PND 7 mice received 1.35E 11 vg/ mouse ELP-02 dose via IT; PND1 (N=7) *Fig4+/+* mice received 5.4E 11 vg/ mouse ELP-02 dose via ICV	Jackson Labs
	In Vivo Efficacy and Toxicology Safety Assessment (NGL-ETS-004)		
	PND1 ELP-02 treated and untreated *Fig4+/+* mice terminated at 180 days of post-dosing	PND1 treated (N=7) mice receiving ELP-02 5.4E 11 vg/ mouse ELP-02 dose via ICV and untreated (N=6) *Fig4+/+* mice were subjected to histopathology analysis of safety	Jackson Labs

Key: GLP- good laboratory practice; vg- vector genome; vehicle/ reference item- phosphate buffered saline [PBS] pH7.4 containing 5% D-sorbitol and 0.001% pluronic F-68; ICV- intracerebroventricular; IT- intrathecal; PND- post-natal day; WT- Wildtype

7.3.1. In vivo efficacy study using *FIG4*$^{plt/plt}$ mice (FIG4-deficient)

The pale tremor (*plt*) allele is a spontaneous retrotransposon (early transposon 2β) insertion into intron 18 of the Fig4 gene, resulting in a loss-of-function allele. Homozygous *plt* mice have diluted pigmentation and reduced size at 3 days after birth, followed by tremors at 2 weeks and abnormal limb postures by 3 weeks, resulting in muscle weakness or a

"swimming" gait (Chow et al., 2007). Mice have demyelination, loss of motor neurons, and vacuolization in many regions of the nervous system, resulting in a median life span of approximately 35 days in C57BL/6.C3H F1 genetic background mice (survival in either inbred background alone is only a few days) (Presa et al., 2021).

Presa et al. (2021) used the homozygous *plt* mouse (using an F1 hybrid B6;C3Fe-Fig4^{plt}/MmJ that survives up to 35 days) as a model for CMT4J to evaluate gene-therapy treatment with AAV9-delivered FIG4, though they do consider that this model is more analogous to Yunis-Varon syndrome, considering both the symptoms of the disease and the homozygous null FIG4 alleles in the mice.

Administration of the AAV9-FIG4 vector to the homozygous *plt* mice was done by either intracerebroventricular (i.c.v.) (post-natal day, P1 and P4 with 5.4E11 vg) or intrathecal (i.t.) (P7 and P11 with 1.35E12 vg) injection (Figure 4). The i.c.v. delivery at P1 or P4 extended the life span from weeks to at least a year with nearly normal behavioral, neurophysiological, and histopathological phenotypes (Figure 5, C and D). The i.t. delivery at P7 or P11 resulted in an increased median life span of 90 days (P7) or 17 days (P11), with phenotypic changes more pronounced in the P7 than P11 delivery (Figure 5, E and F). Thus, all these treatment paradigms produced benefit except i.t. injection at P11, as indicated by improved survival, improved gross motor function including grip strength, improved peripheral motor nerve conduction, and improved histopathological outcomes in spinal cord and dorsal root ganglia, as well as other parts of the central nervous system.

Figure 4 Outline of Preclinical Study Design with AAV9-FIG4 Vector in Fig4plt/plt mice

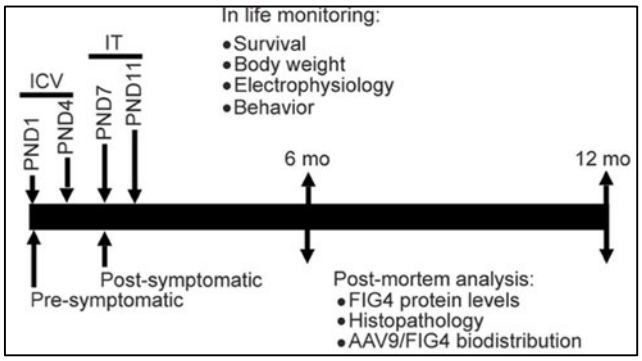
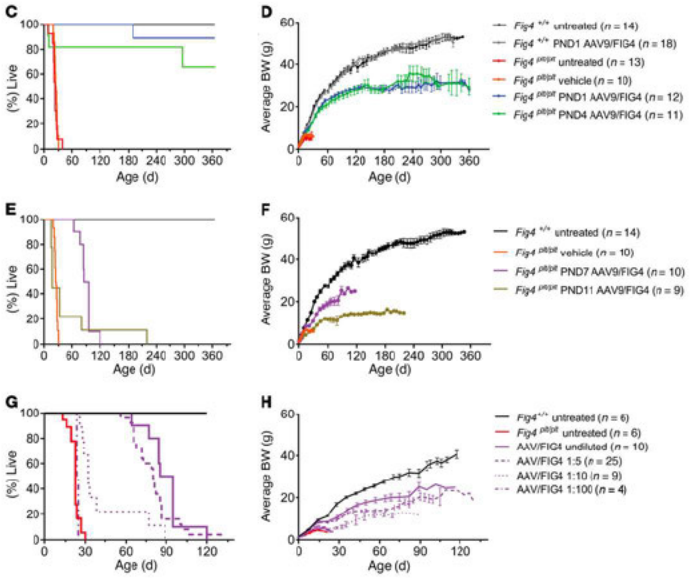


Figure 5 Improvement in survival and growth for mice treated with AAV9-FIG4 vector.



C and D, mice injected with AAV9-FIG4 (5.4e11 vg) ICV (intracerebroventricular) at PND1 (post-natal day) and PND4; E and F, mice injected with AAV9-FIG4 (1.35e12vg) IT (intrathecal) at PND7 and PND11; G and H, mice injected IT at PND7 with AAV9-FIG4 diluted 1:5 (2.7e11 vg), 1:10 (1.35e11 vg), and 1:100 (1.35e10 vg). The success of the treatment was dependent on the age of injection, with greater benefit at early ages (PND1 and PND4), although IT treatment at PND7 also significantly improved survival (PND7-treated vs. untreated Fig4plt/plt mice, $P < 0.0001$) and growth.

A dose-response experiment was performed with i.t. administration at P7 with full dose (1.35E12 vg) and dilutions, including 1:5, 1:10, and 1:100, to identify the lowest level of vector that would still produce significant benefits (Figure 5, G and H) (Presa et al., 2021). The 1:5 and 1:10 dilutions extended life span with the 1:5 similar to undiluted vector.

These outcomes, along with previous work on the biodistribution of AAV9 and molecular analyses of FIG4 levels, indicate that the affected cell populations can be effectively targeted with this treatment strategy, and that the gene replacement is effective in compensating for the FIG4 loss of function mutation. The results indicate that the benefit is greatest the earlier the AAV9/FIG4 is delivered (Figure 5). Further, the results also indicate a clear dose-response of the treatment up to the maximum feasible dose in PND7 mice, justifying the maximum feasible dose of 1E15 vg total in humans to provide the most effective treatment. Human dose extrapolation based on age and brain size is shown in Table 6. In addition, adverse effects were not observed, either overtly or by histopathological examination, in FIG4 mutant or littermate control mice when treated with the vector.

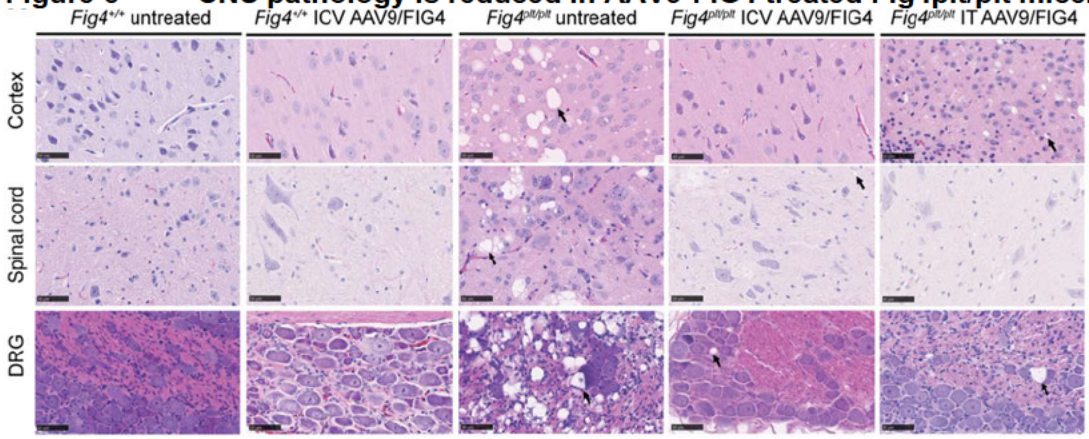
Table 6 Dose Extrapolation Based on Age and Brain Size

Age (years)	Brain Volume (Approx cm3)	Infusion volume (mL)	Total IT High Dose (E14 vg)
4+	1312	10	10
3	1180	9	9
2	1080	8.2	8.2
1	955	7.3	7.3

Age (years)	Brain Volume (Approx cm3)	Infusion volume (mL)	Total IT High Dose (E14 vg)
0.5	525	4	4
Newborn	400	3	3

The CMT4J mouse model is considerably more severe than the target CMT4J patient phenotype (and more similar to YVS), namely in the case of the decreased survival and development of spongiform-like brain pathology (Figure 6). The preclinical finding at i.t. PND7 dosing showed a strong rescue of nerve conduction, grip strength, activity, and peripheral nerve conduction. The more modest survival benefit can be attributed to inadequate delivery of the vector to the brain to rescue that severe aspect of the disease that is specific to the mouse model. Overall, these results predict prospect of direct benefit of this treatment to CMT4J patients (including pediatric subjects) and support our proposed clinical study design.

Figure 6 CNS pathology is reduced in AAV9-FIG4 treated Fig4plt/plt mice.



Histopathology (H&E images) of motor cortex, thoracic spinal cord, and dorsal root ganglion (DRG) from AAV9-FIG4 treated mice. Scale bars: 50 □m. Black arrows indicate cytoplasmic vacuoles.

8. SUMMARY AND CONCLUSIONS

In summary, the details presented in this submission support the following conclusions:

- CMT4J (OMIM 611228), first described in 2007, is an ultra-rare peripheral neuropathy resulting from recessive inheritance of loss-of-function FIG4 (OMIM 609390) alleles (Chow et al., 2007). CMT4J patients are compound heterozygotes carrying one complete loss of function allele of FIG4 in combination with a partial loss of function missense FIG4 allele (typically p.Ile41Thr) (Chow et al, 2007; Cottenie et al., 2013; Menezes et al., 2014; Nicholson et al., 2011).

- CMT4J, an ultra-rare form of CMT disease, is a rare, debilitating, progressive hereditary motor and sensory neuropathy caused by heteroallelic FIG4 loss of function

alleles. It is characterized by progressive motor weakness with sensory involvement resulting in quadriplegia, respiratory failure, and a shortened lifespan.

- CMT4J is estimated to account for 0.3% to 0.4% of all diagnosed Charcot-Marie-Tooth cases (Nicholson et al., 2011; DiVincenzo et al., 2014, Fridman et al., 2015). Based on the 2024 U.S. population of nearly 342 million people and the well-established CMT prevalence of approximately 1 in 2500, the prevalence of CMT4J in the U.S. is estimated to be between 400 and 550 cases.

- This designation request focuses on CMT4J (OMIM 611228). Symptoms and age of onset vary, with pediatric onset disease often characterized by a rapid progression of muscle weakness and atrophy, often leading to the inability to walk by late adolescence. Asymmetric muscle weakness is common, as is localization to only proximal or distal portions of the limbs. Disease severity can range from mild gait difficulties to quadriparesis.

- Recent evidence supports that almost 75% of CMT4J patients are diagnosed before the age of 18 with over half of new patients diagnosed in late adolescence between ages 5 and 10.

- There are no approved treatments for CMT4J, leaving an unmet medical need for this serious and quality of life limiting disease affecting pediatric patients.

- ELP-02 is an AAV9 gene therapy containing codon optimized human (h) FIG4, which has been shown to extend the lifespan of plt mice which are FIG4 deficient from a few weeks to at least a year with near normal behavioral, neurophysiological, and histopathological phenotypes (Presa et al., 2021).

- The therapeutic goal is to treat pediatric patients with a single one-time intrathecal administration of ELP-02, which will provide the FIG4 protein which may potentially prevent further progression of the disease, improving functional outcomes and survival. As with similar pediatric diseases, it is likely that earlier treatment could provide better outcomes for patients (Gray, 2016).

The sponsor considers the data presented in this submission supports the granting of rare pediatric disease designation to ELP-02.

9. REFERENCES

Bailey RM, Armao D, Nagabhushan Kalburgi S, Gray SJ. Development of intrathecal AAV9 gene therapy for giant axonal neuropathy. Mol Ther Methods Clin Dev. 2018;9:160-171.

Beloribi-Djefaflia S, Morales RJ, Fatehi F, Isapof A, Servais L, Leonard-Louis S, Michaud M, Verdure P, Gidaro T, Pouget J, Poinsignon V, Bonello-Palot N, Attarian S. Clinical and genetic features of patients suffering from CMT4J. J Neurol. 2024;271(3):1355-1365.

Braathen G, Sand J, Lobato A, Høyer H, Russell M. Genetic epidemiology of Charcot-Marie-Tooth in the general population. Eur J Neurol 2011;18:39–48.

Chow CY, Zhang Y, Dowling JJ, Jin N, Adamska M, Shiga K, Szigeti K, Shy ME, Li J, Zhang X, Lupski JR, Weisman LS, Meisler MH. Mutation of FIG4 causes neurodegeneration in the pale tremor mouse and patients with CMT4J. Nature. 2007;448(7149):68-72.

Cottenie E, Menezes MP, Rossor AM, Morrow JM, Yousry TA, Dick DJ, Anderson JR, Jaunmuktane Z, Bradner S, Blake JC, Houlden H, Reilly MM. Rapidly progressive asymmetrical weakness in Charcot-Marie-Tooth disease type 4J resembles chronic inflammatory demyelinating polyneuropathy. Neuromuscul Disord. 2013;23(5):399-403.

DiVincenzo C, Elzinga CD, Medeiros AC, Karbassi I, Jones JR, Evans MC, Braastad CD, Bishop CM, Jaremko M, Wang Z, Liaquat K, Hoffman CA, York MD, Batish SD, Lupski JR, Higgins JJ. The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. Mol Genet Genomic Med. 2014;2(6):522-529.

Doherty CM, Morrow JM, Zuccarino R, Howard P, Wastling S, Pipis M, Zafeiropoulos N, Stephens KJ, Grider T, Feely SM, Nopoulous P, Skorupinska M, Milev E, Nicolaisen E, Dudzeic M, McDowell A, Dilek N, Muntoni F, Rossor AM, Shah S, Laura M, Yousry TA, Thedens D, Thornton J, Shy ME, Reilly MM. Lower limb muscle MRI fat fraction is a responsive outcome measure in CMT X1, 1B and 2A. Ann Clin Trans Neurol. 2024;11(3):607-617.

Fridman V, Bundy B, Reilly MM, Pareyson D, Bacon C, Burns j, Day J, Feely S, Finkel RS, Grider T, Kirk CA, Herrmann DN, Laura M, Li J, Lloyd T, Sumner CJ, Muntoni F, Piscosquito G, Ramchandren S, Shy R, Siskind CE, Yum SW, Moroni I, Pagliano E, Zuchner S, Scherer SS, Shy ME, Inherited Neuropathies Consortium. CMT subtypes and disease burden in patients enrolled in the Inherited Neuropathies Consortium natural history study: a cross-sectional analysis. J Neurol Neurosurg Psychiatry. 2015;86(8):873-878.

Gentil BJ, O'Ferrall E, Chalk C, Santana LF, Durham HD, Massie R. A New Mutation in FIG4 Causes a Severe Form of CMT4J Involving TRPV4 in the Pathogenic Cascade. J Neuropathol Exp Neurol. 2017;76(9):789-799.

Gray SJ. Timing of gene therapy interventions: The earlier, the better. Mol Ther. 2016;24(6):1017-1018.

Guo J, Ma Y-H, Yan Q, Wang L, Zeng Y-S, Wu J-L, Li J. Fig4 expression in the rodent nervous system and its potential role in preventing abnormal lysosomal accumulation. J Neuropathol Exp Neurol. 2012;71(1):28-39.

Hu B, McCollum M, Ravi V, Arpag S, Moiseev D, Castoro R, Mobley B, Burnette B, Siskind C, Day J, Yawn R, Feely S, Li Y, Yan Q, Shy M, Li J. Myelin abnormality in Charcot-Marie-Tooth type 4J recapitulates features of acquired demyelination. Ann Neurol. 2018;83(4):756-770.

Ikonomov OC, Sbrissa D, Fligger J, Delvecchio K, Shisheva A. ArPIKfyve regulates Sac3 protein abundance and turnover: disruption of the mechanism by Sac3I41T mutation causing Charcot-Marie-Tooth 4J disorder. J Biol Chem. 2010;285(35):26760-26764.

Lafontaine M, Lia AS, Bourthoumieu S, Beauvais-Dzugan H, Derouault P, Arne-Bes MC, Sarret C, Laffargue F, Magot A, Sturtz F, Magy L, Magdelaine C. Clinical features of homozygous FIG4-p.Ile41Thr Charcot-Marie-Tooth 4J patients. Ann Clin Transl Neurol. 2021;8(2):471-476.

Lenk GM, Ferguson CJ, Chow CY, Jin N, Jones JM, Grant AE, Zolov SN, Winters JJ, Giger RJ, Dowling JJ, Weisman LS, Messier MH. Pathogenic mechanism of the FIG4 mutation responsible for Charcot-Marie-Tooth disease CMT4J. PLoS Genetc. 2011;7(6):e1002104.

Lenk GM, Berry IR, Stutterd CA, Blyth M, Green L, Vadlamani G, Warren D, Craven I, Fanjul-Fernandez M, Rodriguez-Casero V, Lockhart PJ, Vanderver A, Simons C, Gibb S, Sadedin S, Broad Center for Mendelian Genomics; White SM, Christodoulou J, Skibina O, Ruddle J, Tan TY, Leventer RJ, Livingston JH, Mesiler MH. Cerebral hypomyelination associated with biallelic variants of FIG4. Hum Mutat. 2019;40(5):619-630.

Machado RIL, de Souza PVS, Farias IB, Badia BML, Filho JMVA, Lima RJV, Pinto WBVR, Oliveira ASB. Clinical and genetic aspects of childhood-onset demyelinating Charcot-Marie-Tooth's disease in Brazil. J Pediatr Genet. 2022;12(4):301-307.

Manford A, Xia T, Saxena AK, Stefan C, Hu F, Emr SD, Mao Y. Crystal structure of the yeast Sac1: implications for its phosphoinositide phosphatase function. EMBO J. 2010;29(9):1489-1498.

McCorquodale D, Pucillo EM, Johnson NE. Management of Charcot-Marie-Tooth disease: improving long-term care with a multidisciplinary approach. J Multidiscip Healthc. 2016;9:7-19.

Menezes MP, Waddell L, Lenk GM, Kaur S, MacArthur DG, Meisler MH, Clarke NF. Whole exome sequencing identifies three recessive FIG4 mutations in an apparently dominant pedigree with Charcot-Marie-Tooth disease. Neuromuscul Disord. 2014;24(8):666-670.

Michaelidou K, Tsiverdis I, Erimaki S, Papadimitriou D, Amoiridis G, Papadimitriou A, Mitsias P, Zaganas I. Whole exome sequencing establishes diagnosis of Charcot-Marie-Tooth 4J, 1C, and X1 subtypes. Mol Genet Genomic Med. 2020;8(4):e1141.

Millere E, Rots D, Simren J, Ashton NJ, Kuptas E, Micule I, Priedite V, Jurjane N, Blennow K, Gailite L, Zetterberg H, Kenina V. Plasma neurofilament light chain as a potential biomarker in Charcot-Marie-Tooth disease. Eur J Neurol. 2021;28(3):974-981.

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):e1125-e1129.

Nicholson G, Lenk GM, Reddel SW, Grant AE, Towne CF, Ferguson CJ, Simpson E, Scheuerle A, Yasick M, Hoffman S, Blouin R, Brandt C, Coppola G, Biesecker LG, Batish SD, Meisler MH. Distinctive genetic and clinical features of CMT4J: a severe neuropathy caused by mutations in the PI(3,5)P2 phosphatase FIG4. Brain. 2011;134(Pt 7):1959-1971.

Orengo JP, Khemani P, Day JW, Li J, Siskind CE. Charcot Marie Tooth disease type 4J with complex central nervous system features. Ann Clin Transl Neurol. 2018;5(2):222-225.

Peddareddygari LR and Grewal RP. Clinical and genetic analysis of a patient with CMT4J. Neurol Int. 2022; 14(1):207-211.

Presa M, Bailey RM, Davis C, Murphy T, Cook J, Walls R, Wilpan H, Bognaik L, Lenk GM, Burgess RW, Gray SJ, Lutz C. AAV9-mediated FIG4 delivery prolongs life span in Charcot-Marie-Tooth disease type 4J mouse model. J Clin Invest. 2021;131(11):e137159.

Sadjadi R, Picher-Martel V, Thedans D, DiCamillo P, Acsadi G, Lloyd TE, Payerson D, Scherer S, Reilly MM, Castro D, Shy ME, Inherited Neuropathy Consortium. Clinical characteristics of Charcot-Marie-Tooth type 4J. 2024. Manuscript submitted for publication.

Saporta ASD, Sottile SL, Miller LJ, Feely SME, Siskind CE, Shy ME. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol. 2011;69(1):22-33.

Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clin Genet 1974; 6: 98–118.

Suarez B, Vargas C, Jofre J, Cortes R, Kleinsteuber K, Castiglioni C. P442 Charcot Marie Tooth disease type 4J and FIG4 compound heterozygous mutation. Neuromuscul Disord. 2023;33(Supplement 1):S189.

Vaccari I, Carbone A, Previtali SC, Mironova YA, Alberizzi V, Noseda R, Rivellini C, Bianchi F, Del Carro U, D'Antonio M, Lenk GM, Wrabetz L, Giger RJ, Meisler MH, Bolino A. Loss of FIG4 in both Schwann cells and motor neurons contributes to CMT4J neuropathy. Hum Mol Genet. 2015;24(2):383-396.

Yu Y, Yin H, Ma C, Jia X, Chen W, Li H and Wu K. Case report and literature review: Novel compound heterozygous FIG4 variants causing both of peripheral and central nervous system defects. Front Pediatr. 2022; 10:1008251.

Zhang X, Chow CY, Sahenk Z, Shy ME, Meisler MH, Li J. Mutation of FIG4 causes a rapidly progressive, asymmetric neuronal degeneration. Brain. 2008;131(Pt 8):1990-2001.

Zimmermann M, Schuster S, Boesch S, Korenke GC, Mohr J, Richbauer J, Kernstock C, Kotzot D, Spahlinger V, Schule-Fryer R, Schols L. FIG4 mutations leading to parkinsonism and a phenotypical continuum between CMT4J and Yunis Varon syndrome. Parkinsonism Relat Disord. 2020;74:6-11.

10. APPENDIX A

10.1. CMT4J patients reported in the literature.

Detail provided includes a patient ID (if given or lead author initial and patient age), age of onset of symptoms (based on best available information in paper), age of patient at the time of clinical examination in the paper, and the FIG4 mutations from both alleles. This list is based on a CMT4J diagnosis and does not include those with CNS involvement (see **Error! Reference source not found.** for this list).

#	Patient ID	Age of onset[3]	Age of exam	FIG4 Genotype (Alleles)	
1	BAB1079[1]	Early	< 5	I41T	F98Gfs*4
2	BAB1161[1]	<5	Unknown	I41T	D348Gfs*11
3	BAB1369[1]	<5	Unknown	I41T	F254Sfs*7
4	BAB1372	34 (maybe 13)	37	I41T	R183*
5	BAB1373	32	35	I41T	R183*
6	S1	14	16	I41T	G264Ffs*13
7	S2	<5	41	I41T	K278Yfs*5
8	S3	5	18	I41T	L458Ffs*4
9	A1[1]	Late	Unknown	I41T	T55GNfs*20
10	A2	54	56	I41T	F254Sfs*7
11	A3	48	56	I41T	T556Nfs*20
12	A4	<3	5	I41T	L458Ffs*4
13	A6	44	46	I41T	E302K
14	A7[1]	Unknown	Unknown	I41T	Deletion
15	A8	<5	11	I41T	R381*
16	A9[1]	Unknown	Unknown	L17P	F254Sfs*7
17	II.1	2	13	I41T	F98fs*38
18	I.1	20's	41	I41T	Exon 2 del
19	C26	< 26 months	26	I41T	K278Yfs*5
20	G48	~13	48	I41T	IVS17-10+'T>G[c]
21	Case 1	12	17	I41T	R432*
22	Case 3	25	25	I41T	c.1184–1186 del
23	Case 4	birth[2]	11	I41T	L458Ffs*5
24	Case 5	birth[2]	8	K278fs*6	IVS21+1G>A

#	Patient ID	Age of onset[3]	Age of exam	FIG4 Genotype (Alleles)	
25	Case 6	14	34	I41T	F98Lfs
26	Case 7	15	16	I41T	W246*
27	Case 8	12	14	I41T	W246*
28	Case 11	birth	6	I41T	Exon8-10 del
29	Case 12	9	10	I41T	I41T
30	Case 5	5	20	I41T	R183*
31	A	<17	37	I41T	I41T
32	B	9 to 10	15	I41T	I41T
33	C	13 months	44	I41T	I41T
34	Index Patient	42	62	I41T	S750Q*10
35	P1	3 months	9	I41T	A396Lfs*
36	P2	childhood	19	I41T	I41T
37	P3	12	30	I41T	K278Wfs*6
38	P4	8	32	I41T	c.289+4A>G
39	P5	12	34	I41T	S750Q*10
40	P6	43	49	I41T	W563X*
41	Pt27	5	17 (now 20)	I41T	R381*
42	Pt28	15	58 (now 61)	I41T	R88*
43	Pt29	13	51 (now 54)	I41T	R88*

[1] No clinical description of the patient was provided, therefore, CMT4J is presumed.
[2] Developmental delays, including brain white matter changes related to other non-FIG4 genes
[3] Age of onset of disease symptoms based on information provided in papers.
Patients 1-5 (Chow et al., 2007), Patients 6-16 (Nicholson et al., 2011), Patients 7-18 (Menezes et al., 2014); Patient 19 (Cottenie et al., 2013); Patient 20 (Gentil et al., 2017), Patients 21-29 (Hu et al., 2018), Patient 30 (Zimmerman et al., 2020), Patients 31-33 (Lafontaine et al., 2021), Patient 34 (Peddareddygari and Grewal, 2022), Patients 35-40 (Beloribi-Djefaflia et al., 2024), Patients 41-43 (Machado et al., 2022).