Sponsor:	Elpida Therapeutics, a non-profit Social Purpose Corporation
IND #:	Not yet assigned
Product Name:	ELP-02
Indication:	Treatment of patients with Charcot-Marie-Tooth disease type 4J (CMT4J) caused by recessive, loss-of-function mutations in the *FIG4* gene
Request Type:	**Request for Orphan-Drug Designation (this is accompanied with a request for Pediatric Rare Disease designation)**
Submission Date:	30 July 2024

TABLE OF CONTENTS

1. SPONSOR STATEMENT REQUESTING ORPHAN-DRUG DESIGNATION 5

2. SPONSOR CONTACT INFORMATION, PRODUCT NAME AND MANUFACTURER 5

3. RARE DISEASE OR CONDITION FOR WHICH THE DRUG WILL BE INVESTIGATED, THE PROPOSED USE OF THE DRUG, AND THE REASONS WHY SUCH THERAPY IS NEEDED 5
   - 3.1. The Rare Disease or Condition for Which the Drug Will Be Investigated 6
     - 3.1.1. Pathophysiology of CMT4J 6
     - 3.1.2. Natural History and Treatment of CMT4J 8
   - 3.2. Proposed Use of the Drug 9
   - 3.3. Reasons Why Such Therapy is Needed 9

4. A DESCRIPTION OF THE DRUG, ITS PROPERTIES, AND SCIENTIFIC RATIONALE 10
   - 4.1. Product Description 10
   - 4.2. Mechanism of Action 10
   - 4.3. Nonclinical Studies 11
     - 4.3.1. In vivo efficacy study using *FIG4*$^{plt/plt}$ mice (FIG4-deficient) 12

5. PREVIOUSLY APPROVED DRUGS 15

6. TREATMENT OF A SUBSET OF PATIENTS 15

7. REGULATORY STATUS AND MARKETING HISTORY 15
   - 7.1. Regulatory Status 15
   - 7.2. Marketing History 15

8. DOCUMENTATION THAT THE DISEASE OR CONDITION AFFECTS FEWER THAN 200,000 PEOPLE IN THE UNITED STATES 15

9. SUMMARY AND CONCLUSION 16

10. REFERENCES 18

LIST OF TABLES

Table 1 Overview of Clinical Presentation in CMT4J 8

Table 2 Product description for ELP-02 10

Table 3 Nonclinical Studies for ELP-02 Investigations 11

Table 4 Dose extrapolation based on age and brain size 14

LIST OF FIGURES

Figure 1 Predicted structure for FIG4. 7

Figure 2 Deficiency in FIG4 7

Figure 3 Schematic of ELP-02 10

Figure 4 Outline of Preclinical Study Design with *AAV9-FIG4* Vector in *Fig4*$^{plt/plt}$ mice 13

Figure 5 Survival and Average Body Weight for mice treated with AAV9-FIG4 vector. 13

Figure 6 Histopathology (H&E images) of motor cortex, thoracic spinal cord, and dorsal root ganglion (DRG) from AAV9-FIG4 treated mice. 14

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
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)
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 STATEMENT REQUESTING ORPHAN-DRUG DESIGNATION

This application is presented for review to the Office of Orphan Products Development (OOPD) of the United States Food and Drug Administration (USFDA) by Elpida Therapeutics seeking orphan-drug designation for the investigational product ELP-02.

ELP-02 is an adeno-associated virus (AAV9) vector-based gene therapy intended to be used for the treatment of patients with Charcot-Marie-Tooth disease type 4J (CMT4J).

2. SPONSOR CONTACT INFORMATION, PRODUCT NAME AND MANUFACTURER

Sponsor	Elpida Therapeutics
Primary Contact	Terry Pirovolakis
Address:	16501 Ventura Blvd, Suite 400 Encino, California, USA 91436
US Regulatory Agent	Diane Balderson, Regulatory Affairs Consultant
Telephone Number	[redacted]
Email	[redacted]

Name(s) of Drug (including all available names: Trade, Generic, Chemical, or Code): ELP-02, AAV9/FIG4

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

Research grade product for use in nonclinical studies was produced by University of North Carolina Vector Core (UNC-VC), Chapel Hill, North Carolina. The drug substance and drug product will be manufactured at Viralgen Vector Core S.L. (San Sebastián, Spain).

3. RARE DISEASE OR CONDITION FOR WHICH THE DRUG WILL BE INVESTIGATED, THE PROPOSED USE OF THE DRUG, AND THE REASONS WHY SUCH THERAPY IS NEEDED

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

- 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. 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.

- 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 debilitating 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 (FIG4-deficient, more severe than the genetic heterozygous allelical combinations found in most CMT4 patients) (Presa et al., 2021).

- The therapeutic goal is to treat 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 orphan-drug designation to ELP-02

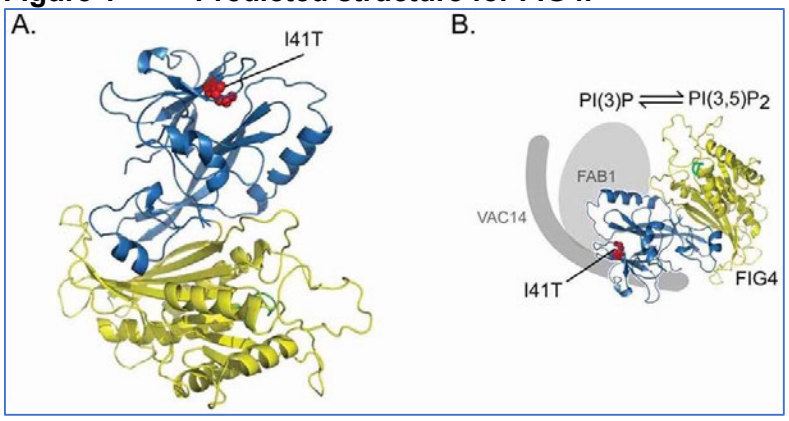
3.1. The Rare Disease or Condition for Which the Drug Will Be Investigated

3.1.1. Pathophysiology of CMT4J

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

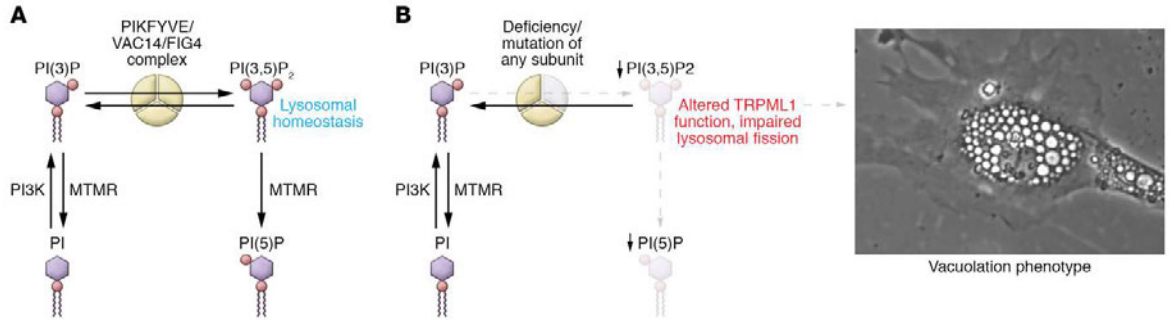
inositol ring of phosphoinositide PI(3,5)P_2, a membrane-bound phospholipid that acts as a molecular signal for trafficking and fusion of intracellular vesicles (Figure 1). In cells derived from 13 patients with Charcot-Marie-Tooth disease type 4J (CMT4J), there was a noted decrease in steady-state levels 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 2).

Figure 1 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 2 Deficiency in FIG4.



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).

Table 1 summarizes the clinical presentation of CMT4J patients described in the literature. While disease course can be heterogenous, it appears to be correlated with age of onset (although not uniformly so). The most common missense allele, FIG4-I41T, is present in the population at a frequency of about 0.1% (ExAC Database).

Table 1 Overview of Clinical Presentation in 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
	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

3.1.2. Natural History and Treatment 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% to 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 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.

The current standard of care for CMT4J patients is limited to symptom management and supportive care, including physical and occupational therapy, assistive devices, and pain management. 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.

3.2. Proposed Use of the Drug

ELP-02 is an AAV gene therapy containing codon optimized human FIG4, which has been shown to be able to extend survival time (from median survival of 23 days untreated to more than 12 months treated) of 90% of FIG4 null mice (*plt*) when injected at P1 (Presa et al., 2021) (Section 4.3). The therapeutic goal is to target all types of cells in the central nervous system (CNS) and treat patients with a single one-time intrathecal administration of ELP-02, which will provide the FIG4 protein required to prevent further progression of the disease, improving functional outcomes and survival in these pediatric patients.

3.3. Reasons Why Such Therapy is Needed

CMT4J is a rare, debilitating, progressive hereditary motor and sensory neuropathy caused by heteroallelic FIG4 loss of function alleles. CMT4J is a disease with a severe phenotype including motor developmental delay, slow nerve conduction velocities, rapidly progressive paralysis, quadriplegia, respiratory compromise resulting in pneumonias, respiratory failure,

and premature death. CMT4J can present as a devastating early-onset disease in children that occasionally interferes with developmental milestones. The disease has been described as a severe combined axonal and demyelinating neuropathy based on electrophysiologic criteria. Later-onset patients have a more variable disease course, with some experiencing mild initial symptoms lasting years, while others have a rapidly progressive disease course that is reminiscent of and diagnosed as amyotrophic lateral sclerosis and can lead to premature death within two years of diagnosis (Nicholson et al., 2011; Zhang et al., 2008).

While genetic testing is available (e.g., Prevention Genetics, part of Exact Sciences) for patients with autosomal recessive CMT, sporadic CMT and no mutations in the genes most commonly associated with CMT, and reproductive partners of individuals that carry pathogenic variants of FIG4, there are no available treatments. Patients face a severely diminished quality of life or shortened lifespan.

4. A DESCRIPTION OF THE DRUG, ITS PROPERTIES, AND SCIENTIFIC RATIONALE

4.1. Product Description

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

4.2. Mechanism of Action

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.

4.3. Nonclinical Studies

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

- In vivo efficacy study using homozygous plt (pale tremor) F1 hybrid C57BL/6J x C3HeB/FeJ mice, FIG4-deficient mice, The Jackson Laboratory (Bar Harbor, Maine) in conjunction with Dr. Steven Gray's Lab at UTSW Medical Center (Presa et al., 2021). Control FIG4+/+ mice treated with AAV9-FIG4 showed 100% survival and no differences in growth, suggesting the vector was well-tolerated. The key information to support mechanism of action of ELP-02 from this study is that hFIG4opt mRNA expression was found in whole brain and spinal cord at 6 months after AAV9-FIG4 treatment. Furthermore, 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 3) using either the Fig4-/- or Fig4+/+

Table 3 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)		

Study GLP Status	Description	Model, Dose, Delivery Route in Studies	Source
	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			

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

Administration of the AAV9-FIG4 vector to the CMT4J mouse model was done by either intracerebroventricular (ICV) (post-natal day, PND1 and PND4) or intrathecal (IT) (PND7 and PND11) injection (Figure 4). All these treatment paradigms produced benefit except injection at PND11, 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.

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 to provide the most effective treatment. 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.

The CMT4J mouse model is considerably more severe than the target CMT4J patient phenotype, namely in the case of the decreased survival and development of spongiform-like brain pathology (Figure 6). The preclinical finding at 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 4 Outline of Preclinical Study Design with *AAV9-FIG4* Vector in *Fig4*$^{plt/plt}$ mice

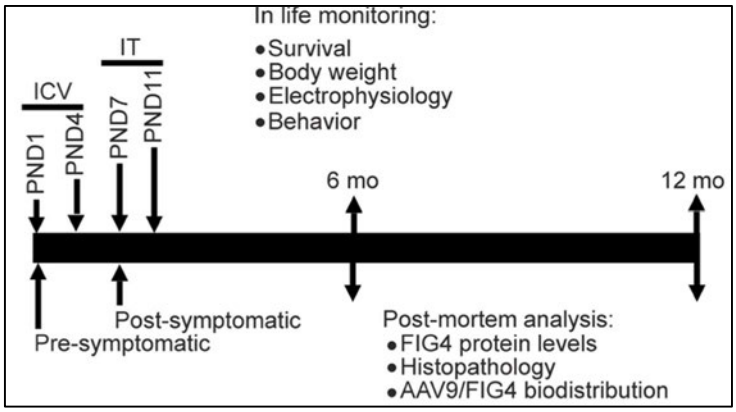
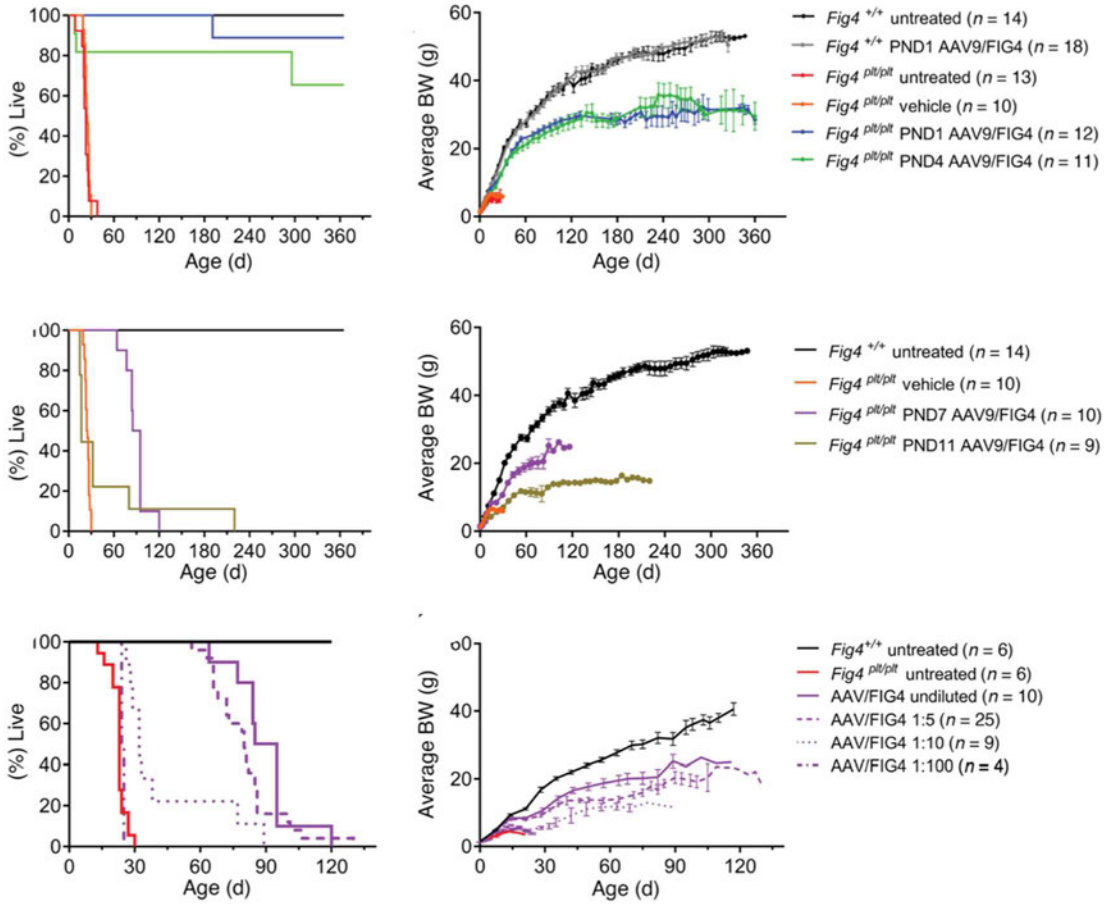
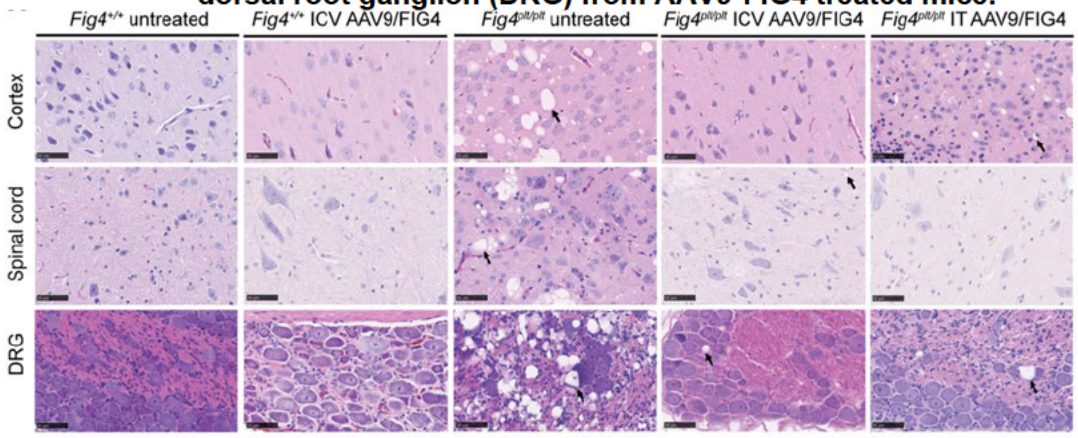


Figure 5 Survival and Average Body Weight for mice treated with AAV9-FIG4 vector.



(C and D, mice injected with AA9-FIG4 [5.4x10^{11} vg] ICV (intracerebroventricular) at PND1 and PND4; E and F, mice injected with AA9-FIG4 [1.35x10^{12} vg] IT (intrathecal) at PND7 and PND11; G and H, mice injected IT with AA9-FIG4 diluted 1:5 [2.7x1011 vg], 1:10 [1.35x10^{11} vg], and 1:100 [1.35x10^{10} vg]).

Figure 6 **Histopathology (H&E images) of motor cortex, thoracic spinal cord, and dorsal root ganglion (DRG) from AAV9-FIG4 treated mice.**



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 4. 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 4 **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
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.

5. PREVIOUSLY APPROVED DRUGS

There is no product currently approved for the treatment of CMT4J. Elpida Therapeutics is not seeking orphan-drug designation for a drug for which FDA has already granted orphan-drug designation for treatment of CMT4J. This provision is, therefore, not applicable for purposes of the present request for orphan-drug designation.

6. TREATMENT OF A SUBSET OF PATIENTS

Elpida Therapeutics is not requesting orphan-drug designation for an orphan subset.

7. REGULATORY STATUS AND MARKETING HISTORY

7.1. Regulatory Status

ELP-02 has no applications or designations in any region. Orphan-drug and rare pediatric disease designations are being submitted to FDA together for this product which is currently planning for IND enabling studies.

7.2. Marketing History

ELP-02 has not been marketed in any country. Elpida Therapeutics has not previously submitted a marketing application to the FDA for the same active moiety for the same rare disease or condition prior to the submission of this request for orphan-drug designation.

8. DOCUMENTATION THAT THE DISEASE OR CONDITION AFFECTS FEWER THAN 200,000 PEOPLE IN THE UNITED STATES

CMT4J is an ultra-rare autosomal recessive disease with a conservative estimate of 6,714 patients worldwide (as of 2019, 7.7 billion people) based on an approximate 1 in 1 million estimated prevalence. There have been approximately 30 cases identified worldwide in the literature.

Nicholson et al. (2011) reported the frequency of CMT4J among patients presenting with CMT disease to be 0.2% (8 out 4000 patients sent to Athena Diagnostics for CMT disease gene panel testing), equivalent to approximately 20% of recessive CMT disease and 0.4% of all CMT disease. Based on genotyping of 5769 Northern European Controls, the population frequency of the I41T allele of FIG4 was found to be 0.001 (13 heterozygotes).

The international Inherited Neuropathy Consortium (INC) analyzed data from 1652 patients with a natural history of CMT in 13 INC centers and identified only 4 patients with CMT4J (0.24% of total), 0.4% among those with a genetic diagnosis (Fridman et al., 2015). INC centers included 10 in USA, and 1 each in UK, Italy, and Australia.

DiVincenzo et al. (2014) analyzed the frequency of CMT4J among 17,377 individuals (commercial testing from 2009 to 2013 in US) referred to diagnostic testing for 14 CMT-related genes (including FIG4). CMT4J was found in 0.3% of the individuals (Peddareddygari and Grewal, 2022).

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.

ELP-02 may be administered to patients only following diagnosis of CMT4J, therefore, prevalence is the appropriate epidemiological parameter to report when describing the treatment or prevention of a disease or condition in this case.

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 (31 July 2024) without limit of publication date using the following search terms:

- “CMT4J” (N=42 publications),
- “Charcot-Marie-Tooth type 4J” (N=42),
- “FIG4” (N=176),
- “Charcot-Marie-Tooth”, (N=6,360)

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

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.

9. SUMMARY AND CONCLUSION

This submission provides the information necessary for the determination of orphan designation, and concludes the following:

- 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 orphan-drug designation to ELP-02.

10. 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.

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.

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.

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.

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, Mesiler 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.

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.

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.

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

Presa M, Baily RM, Davis C, Murphy T, Cook J, Walls R, Wilpan H, Bodanik 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.

Svaren J. Adeno-associated virus gene therapy to the rescue for Charcot-Marie-Tooth disease type 4J. J Clin Invest. 2021; 131(11):e149492.

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.