Sponsor:	CureSPG50, a non-profit entity
IND #:	028202
Product Name:	MELPIDA (scAAV9-UsP-hAP4M1opt)
Indication:	Treatment of patients with Spastic Paraplegia Type 50 (SPG50) caused by the AP4M1 gene mutation
Request Type:	**Resubmission of Request for Orphan-Drug Designation**
Submission Date:	16 September 2022

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TABLE OF ABBREVIATIONS

AAV	adeno-associated virus
AP	Adaptor Protein
ATG9A	Autophagy Related 9A
BCH	Boston Children's Hospital
BGH	Bovine growth hormone
CNS	central nervous system
DAPI	4′,6-diamidino-2-phenylindole
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
GFP	green fluorescent protein
h	human
HSP	Hereditary spastic paraplegia
IND	Investigational New Drug
IRNHS	International registry Natural History Study
ITR	inverted terminal repeat(s)
kg	kilogram
MOI	Multiplicity of Infection
NIH	National Institutes of Health
opt	optimized
OOPD	Office of Orphan Products Development
sc	self-complimentary
SPG50	Spastic Paraplegia 50
RNA	ribonucleic acid
TGN	Trans-Golgi network
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 is a resubmission of the original ODD #20-7740 with modifications to update the existing data and include the in vivo nonclinical data obtained in a mouse model of SPG50.

A request for an extension was submitted and granted to 19 October 2022.

This second application is presented for review to the Office of Orphan Products Development (OOPD) of the United States Food and Drug Administration (USFDA) by the non-profit group CureSPG50 seeking orphan-drug designation for the investigational product MELPIDA.

MELPIDA is an adeno-associated virus (AAV9) vector-based gene therapy intended to be used for the treatment of patients with Spastic Paraplegia Type 50 (SPG50).

2. SPONSOR CONTACT INFORMATION, PRODUCT NAME AND MANUFACTURER

Sponsor	CureSPG50
Primary Contact	Terry Pirovolakis
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Name(s) of Drug (including all available names: Trade, Generic, Chemical, or Code):

MELPIDA (scAAV9-UsP-hAP4M1opt).

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

Drug Product (GMP) was manuractured by Viralgen Vector Core (VVC), San Sebastian, 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:

- Spastic Paraplegia Type 50 (SPG50) is one of a group of 4 genetic disorders (SPG47, SPG50, SPG51 and SPG52) involving a mutation that results in the production of an abnormal adaptor protein complex 4 (AP-4); all 4 subtypes present with the same clinical phenotype (Behne et al, 2020; Ebrahimi-Fakhari et al, 2018).

- SPG is an ultra-rare autosomal recessive disease with ~156 patients identified worldwide for all phenotypes and 59 identified with SPG50. There are ~9 patients with SPG50 in North America (AP4M1, OMIM #612936) (source: Ebrahimi-Fakhari et al, unpublished).

- Without new-born screening identification, patients are often 8 to 10 years of age before they are correctly diagnosed although symptoms start within infancy (Table 2). Patients are usually paralyzed by spasticity paraplegia within their first decade and tetraplegic and severely mentally delayed later on in life; epilepsy is also a key symptom (Ebrahimi-Fakhari, Behne et al, 2018). Only a few patients are identified over the age of 30 years (Figure 2) (Ebrahimi-Fakhari et al, under review);

- There are no approved treatments for SPG50, leaving an unmet medical need for this serious and quality of life limiting disease affecting pediatric patients.

- MELPIDA is a self-complimentary (sc) AAV9 gene therapy containing codon optimized human (h) AP4M1, which has been shown to rescue up to 77% of defective fibroblasts from two SPG 50 patients in vitro. In an in vivo model of heterozygous and homozygous Ap4m1 knock-out (KO) mice dosed intrathecally at post-natal day (PND) 7 to 10 or PND 90 with either no treatment, vehicle, low (1.25E11), mid (2.5E11) or high (5E11) doses of MELPIDA, improvements in Hindlimb clasping and total Maze distance were noted 8 months post dosing, suggesting MELPIDA generates benefits when dosed at the early-symptomatic stage in patients (Section 4.3).

- The therapeutic goal is to treat patients with a single one-time intrathecal administration of MELPIDA, which will provide the AP4M1 protein required to prevent further progression of the disease, improving functional outcomes and survival in these pediatric patients. The intrathecal route has been used with AAV9 as a way to deliver gene therapies to the central nervous system (CNS) (Bailey et al, 2018). As with similar pediatric diseases such as spinal muscular atrophy and aromatic l-amino acid decarboxylase, it is likely that earlier treatment could provide better outcomes for patients (Gray, 2016).

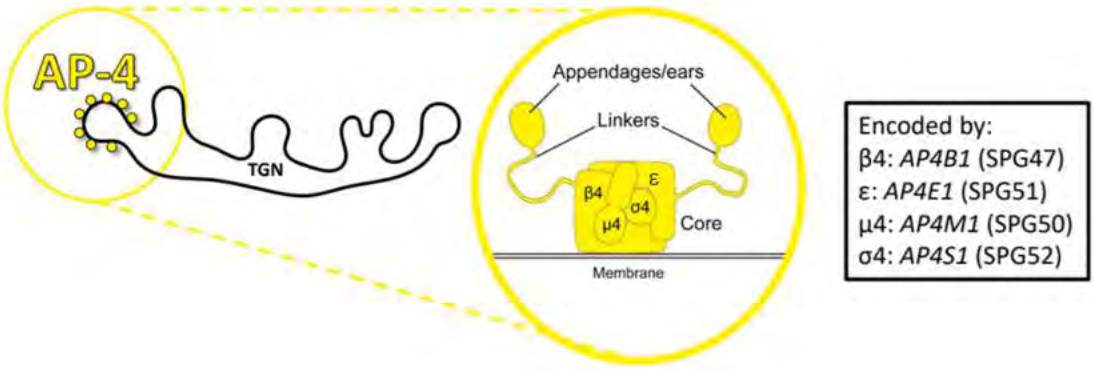
In summary, the data presented in this designation request support the granting of orphan-drug designation to MELPIDA.

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

3.1.1. Pathophysiology of SGP50

SPG50 is one of a collection of adaptor protein complex 4 (AP-4) deficiencies (Figure 1). A homozygous loss-of-function mutation in any of the four AP-4 subunits causes a neurological disorder characterized by spastic paraplegia, developmental delay and intellectual disability (Ebrahimi-Fakhari et al, under review; Ebrahimi-Fakhari et al, 2018).

Figure 1 Schematic of Adaptor Protein complex 4



The four deficiencies are divided into SPG47, SPG50, SPG51 and SPG52 (Table 1).

Table 1 Subtypes of AP-4 deficiencies (Ebrahimi-Fakhari et al, under review)

AP-4 subtype	OMIM	Mutation	Distribution	Male:Female
SPG47	#614066	AP4B1	34%	39% Female
SPG50	#612936	AP4M1	38%	43% Female
SPG51	#613744	AP4E1	13%	33% Female
SPG52	#614067	AP4S1	15%	52% Female

*From International Registry and Natural History Study (IRNHS) of Adaptor-Protein 4-Related Hereditary Spastic Paraplegia database (with 185 identified patients worldwide),

The AP-4 biology and molecular mechanisms of AP-4-hereditary spastic paraplegia (HSP) are not completely elucidated. Available data demonstrated that AP-4 complex consists of four subunits (β4, ε, μ4 and σ4) (Hirst et al, 2013) and has been implicated in trafficking of transmembrane proteins from the trans-Golgi network (TGN) to early (Burgos et al, 2010;

Toh et al, 2017) and late endosomes (Aguilar et al, 2001). More recent cell culture studies have demonstrated that ATG9A, an autophagy protein, is a cargo of AP-4 and loss of AP-4 leads to a mislocalization of ATG9A (Mattera et al, 2017; Davies et al 2018; De Pace et al, 2018; Ivankovic et al, 2020). Characterization of an AP4E1 knockout mouse has revealed widespread axonal pathology that includes reduced axonal development and prominent axonal swellings (De Pace et al, 2018; Ivankovic et al, 2020).

3.1.2. Natural History and Treatment of SPG50

Due to the rarity of the condition, limited data are available on the natural history of AP-4 deficiency. Ebrahimi-Fakhari et al, (under review) reports on 156 patients from 101 families that have registered. Subsets of patients have provided information on The Spastic Paraplegia Rating Scale (SPRS) (N=37), The Modified Ashworth Scale (MAS) (N=28), A SPATAX-EUROSPA Disability score (N=39) and a Four Stage Functional Mobility Score (N=85). This is the most extensive data available on these patients.

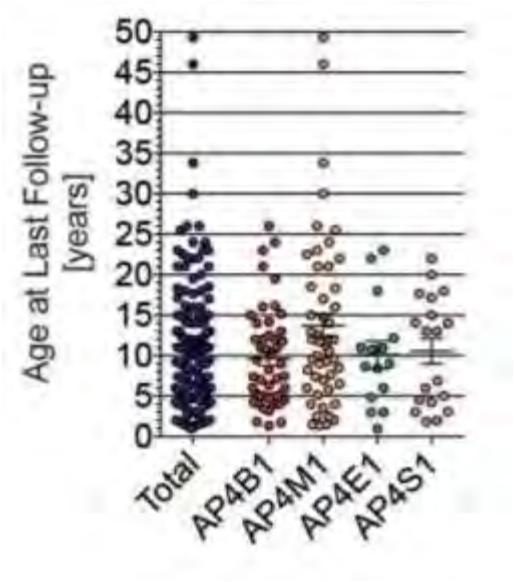
Onset of symptoms is typically prior to 1 year of age, with diagnosis often occurring 10 years later (Table 2). Often patients are initially misdiagnosed with cerebral palsy (Jameel et al, 2014).

Table 2 Key demographic data for 156 AP-4 deficient patients from Ebrahimi-Fakhari et al, (under review)

AP-4-HSP Subtype	Age at onset, years	Age at diagnosis, years	Age at last visit, years	Consanguinity	Familial case
AP4B1-HSP: *n* = 53	0.6 ± 0.4 (*n* = 34)	7.8 ± 6.9 (*n* = 31)	9.6 ± 6.1 (*n* = 48)	60% (*n* = 50)	55% (*n* = 53)
AP4M1-HSP: *n* = 59	0.9 ± 0.8 (*n* = 42)	11.7 ± 10.0 (*n* = 44)	13.7 ± 10.6 (*n* = 50)	77% (*n* = 52)	78% (*n* = 59)
AP4E1-HSP: *n* = 21	0.7 ± 0.3 (*n* = 6)	10.3 ± 6.7 (*n* = 14)	10.1 ± 6.6 (*n* = 15)	90% (*n* = 20)	86% (*n* = 21)
AP4S1-HSP: *n* = 23	0.8 ± 0.5 (*n* = 11)	10.4 ± 7.3 (*n* = 13)	10.6 ± 6.8 (*n* = 19)	47% (*n* = 19)	48% (*n* = 23)
Total: *n* = 156	0.8 ± 0.6 (*n* = 93)	10.2 ± 8.5 (*n* = 102)	11.4 ± 8.3 (*n* = 132)	69% (*n* = 141)	67% (*n* = 156)

There are relatively few adult patients for all phenotypes (Figure 2) (Ebrahimi-Fakhari et al, under review).

Figure 2 Age at last follow-up for 156 patients with AP-4 deficiency (from Ebrahimi-Fakhari et al, under review)



All phenotypes present with serious and quality of life limiting symptoms. From Ebrahimi-Fakhari et al, (2018) GeneReview using data from the International Registry and Natural History Study of Adaptor-Protein 4-Related Hereditary Spastic Paraplegia database (updated 5-20-18 with 68 identified patients worldwide), characteristic clinical findings include:

- Progressive spastic paraplegia with progression to tetraplegia in the later stages (94%, 58/62)
- Early-onset developmental delay (100%, 68/68)
  - Delayed motor milestones (100%, 54/54)
  - Failure to achieve or loss of independent ambulation (93%, 41/44)
  - Impaired or absent speech development (98%, 51/52)
- Neonatal/infantile hypotonia (usually mild) (100%, 41/41)
- Postnatal microcephaly (77%, 47/61) (usually in -2 StDev to -3 StDev range)
- Early-onset seizures including frequent febrile seizures (42%, 25/59)
- Thinning of the corpus callosum (with prominent thinning of the posterior parts) (88%, 37/42)
- Delayed myelination and nonspecific loss of the periventricular white matter (69%, 29/42)
- Ex-vacuo ventriculomegaly, often with prominent enlargement of the posterior horns of the lateral ventricles (60%, 24/40)

When categorized by age, the following is a typical progression of motor function:

- 6 months: Microcephaly and low muscle tone become pronounced; MRI results show thinning of the corpus callosum.
- 1 year: Delays become evident, low muscle tone is more evident and microencephaly progresses such that head circumference becomes <2 StDev from age related mean.
- 2 years: Children are usually placed in multiple forms of therapy yet are unable to walk independently or speak. Spasticity begins to present in the ankles, calves and in some cases thighs.
- 3-5 years: Children exhibit greater spasticity, their ability to walk is severely impaired and a walker along with braces is used to keep children mobile. Botox injections have been used by many families as an intervention for spasticity. Some children develop a limited ability to speak a few words.
- 5-10 years: Children experience progressive spasticity and usually wheelchair-dependent. Typically, disease has not progressed to upper extremities yet. Some children are able to speak sentences, but others remain non-verbal.
- 10-15 years: Children are mostly wheelchair-dependent and many begin exhibiting spasticity in upper extremities.
- 15-20+ years: Children present with spasticity in all extremities and associated complications. Not much more is known beyond 15+ as there are very few patients in this category.

Published data from the 156 patients with AP-4 deficiency described by Ebrahimi-Fakhari et al, (2020) support earlier findings that symptoms are severely debilitating and manifest prior to adulthood (Table 3). Motor milestones were often missed or delayed and although some patients were able to sit and walk independently, these abilities were lost as the patients aged; the mean age of wheelchair dependency was 13.4 ± 9.8 years. Loss of previously acquired skills or development regression and cognitive decline was reported in 41% of patients.

Table 3 Clinical and Radiographic features of AP-4 deficiency (from Ebrahimi-Fakhari et al, (under review)

Principal clinical features of AP-4-HSP	
Developmental delay / intellectual disability	100%
Motor delay	100%
Speech delay	99%
Mild neonatal or infantile hypotonia	89%
Spasticity	97%
Spastic diplegia	54%
Spastic tetraplegia	43%
Hyperreflexia	92%
Babinski sign	88%
Contractures	50%
Drooling	70%
Postnatal microcephaly	83%
Dysmorphic facial features	78%
Foot deformities	69%
Febrile seizures	62%
Epilepsy	66%
Episodes of stereotypic laughter	56%
Principal radiographic features of AP-4-HSP	
Thin corpus callosum	90%
Ventriculomegaly	65%
White matter loss / changes	68%

There are no approved treatments for SPG50.

3.2. Proposed Use of the Drug

MELPIDA is a self-complimentary (sc) AAV gene therapy containing codon optimized human AP4M1, which has been shown to be efficacious through the various non-clinical studies discussed in this document in (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 MELPIDA, which will provide the AP4M1 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

SPG50 is a serious and life-threatening disease affecting pediatric patients. Natural history data indicates age at onset is during infancy with diagnosis occurring towards the end of the

first decade (Ebrahimi-Fakhari et al, 2018). Patients initially present with hypotonia, developmental delay, microcephaly with spasticity and paralysis in the lower limbs; as the disease progresses paralysis increases to the hands and upper extremities and degradation of mental capacity is increased (Ebrahimi-Fakhari et al, 2018).

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

4.1. Product Description

The investigational agent, MELPIDA is a self-complimentary (sc) AAV9 gene therapy containing a mutant AAV2 inverted terminal repeat (ITR) with the D element deleted, the UsP promoter, codon-optimized human AP4M1 cDNA coding sequence, Bovine growth hormone (BGH) polyadenylation signal, and wild type (WT) AAV2 ITR (Figure 3; Table 4).

Figure 3 Schematic of MELPIDA

Promoter = USP; Poly A = BGHpA

Table 4 Product description for MELPIDA

Vector Genome Structure	AAV2 mutant ITR	UsP promoter	Optimized human AP4M1 transgene	BGH poly A sequence	AAV2 ITR
Size	100 bp	328 bp	1362 bp	250 bp	145 bp
Function	Encapsidation, self-priming, self-complementing	Recruitment of transcription factors for AP4M1 transcription	Encoding human AP4M1 protein more efficiently	Provides stability of AP4M1 transcript	Encapsidation, self-priming

4.2. Mechanism of Action

Efficient transduction of the CNS is expected to positively impact the normal course of disease progression in SPG50 patients. The mode of action of MELPIDA is to target all types of cells in the CNS after a single one-time intrathecal injection. Primary cellular targets proposed for the treatment of SPG50 are neurons and glia throughout the CNS. AP4M1 is a ubiquitous intracellular housekeeping gene, so the targeting of any other cell types within the body is also desired. The AAV9 vector utilized is expected to deliver the AP4M1 gene to these primary targets (Bailey et al, 2018). The introduced cDNA should exist primarily as an episome following transfer of MELPIDA and express a normal version of functional human

AP4M1 protein continuously, which should prevent/slow the onset of SPG50 if treated presymptomatic, or halt/reverse the progression of SPG50 if treated after symptom onset.

4.3. Nonclinical Studies

The following nonclinical studies provide proof of concept that Melpida provides promise for the clinical treatment of SPG50:

- Study 1: in vitro efficacy study using patient-derived fibroblasts in Dr. Juan Bonifacino Lab at NIH: Patient-derived fibroblast lines transduced with Melpida result in phenotype rescue without any toxicity even with the higher MOI group (the capsid used here was AAV2 due to transfection issues in vitro, but the transgene and promoter were identical). These results further provide strong proof-of-concept for benefit in SPG50 patient cells. This study has been repeated twice with very similar conclusions.
- Study 2020-06: An in vivo efficacy study is ongoing in WT, heterozygous and homozygous Ap4m1 knock out (KO) mice dosed intrathecally at post-natal day (PND) 7 to 10 or PND 90 with no treatment, vehicle, low (1.25E11), mid (2.5E11) or high (5E11) doses of MELPIDA and assessed for potential phenotypic rescue. Interim results at 8 months post dose indicate the high dose of 5E11 vg provided maximal pharmacological effects on Hindlimb Clasping whether administered early on PND7-10 or later on PND90 in male mice. For the Maze total distance, female mice had a less robust response when dosed at PND90 compared to PND7-10. The mid dose of 2.5E11 vg provided some pharmacological effects on Hindlimb Clasping when administered PND90 in male mice, suggesting MELPIDA may also generate benefits when dosed at the early-symptomatic stage.

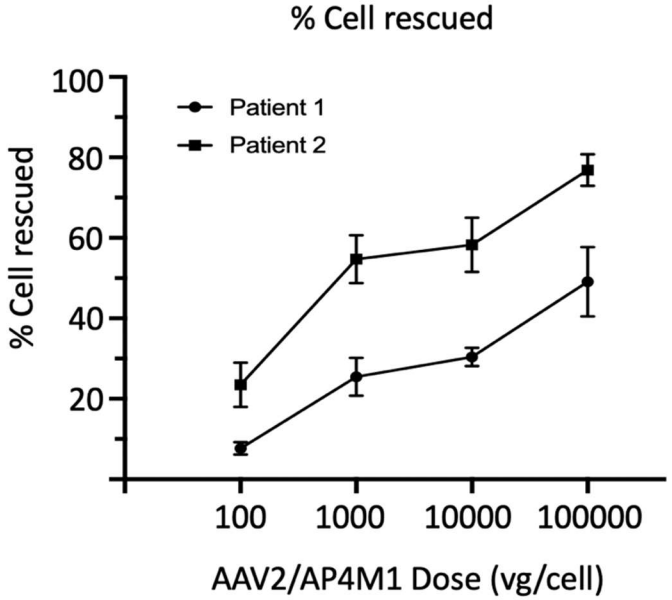
4.3.1. Study 1: in vitro efficacy study using patient-derived fibroblasts in Dr. Juan Bonifacino Lab at NIH (unpublished)

This in vitro study was conducted with an AAV2 capsid instead of AAV9 in fibroblasts derived from SPG50 patients. The objective of this study was to determine whether adeno-associated virus (AAV) -mediated expression of wild-type (WT) *AP4M1* could restore AP-4 level and correct ATG9A localization in SPG50 patient-derived fibroblast cultures expressing mutant *AP4M1*.

In two repeat *in vitro* efficacy experiments, fibroblast cell lines from two patients (#1 and #2) carrying *AP4M1* mutations were infected with the scAV2/*AP4M1* vector (similar to MELPIDA being progressed to the clinic, except for the use of an AAV2 serotype) for 72 hours (at multiplicity of infection [MOI] of 1E2, 1E3, 1E4 and 1E5 vg/cell). Twenty thousand (20,000) cells were plated in each well of a 24-well plate. The cells were then fixed and stained with 4′,6-diamidino-2-phenylindole (DAPI) and with antibodies against ATG9A, AP4E1, and TGN46. The total number of cells, and the number of cells exhibiting normal AP-4 and ATG9A staining (*i.e.*, “rescued” cells) were counted, and the percent rescue was calculated.

At the highest virus dose of 1E5 vg/cell, the rescue of AP-4 and ATG9A phenotypes was 49% and 77% of the cells for patients #1 and #2, respectively (Figure 4).

Figure 4 Dose-dependent Rescue of AP-4 and ATG9A Normal Localization by Expression of AAV2/AP4M1 in SPG50 Patient Cells



Total and rescued cells from two experiments were counted, and the percent rescue was calculated. Values are the mean ± SD from the two experiments

In summary, the vector scAAV2/*AP4M1* partially restored AP-4 levels and corrected ATG9A localization in fibroblasts from patients with SPG50.

4.3.2. Study 2020-06: An 8-month Interim Non-GLP Study to Determine the Efficacy of MELPIDA in a Mouse Knock-out (KO) Model of SPG50

The ability of MELPIDA to transduce multiple types of cells including neurons and glia in the CNS, which is the primary mechanism of action, was demonstrated in the Ap4m1 mouse through measurement of hAP4M1opt mRNA (Study 2020-06).

The design of this study is provided in Table 5. The in-life phase of this study is ongoing at University of Texas Southwestern (UTSW) Medical Center, Dallas, TX and assessments were as follows:

- Cage side observation to assess acute tolerability of MELPIDA following intrathecal administration.
- Monitoring for body weight, clinical signs including behavioral changes and alterations in neurological status, adverse events, and mortality.
- Three weeks post injection, 6 mice from each group were euthanized. Mouse brains were used for AP4M1 mRNA expression by RNAscope and mouse serum was used to check

serum toxicity with a panel or markers including Aspartate transaminase (AST), Total bilirubin (TBIL), Albumin (ALB), Creatine Kinase (CK), and Blood Urea Nitrogen (BUN). Splenocytes from mouse spleen and lymph nodes were used in ELISpot assays to detect any immune responses to either AAV9 or transgene.

- Performance in a battery of behavioral tests is being assessed at 3, 5, 8, 12 and 18 months of age compared to homozygous (KO) control littermates.
- Blood and tissue samples are collected from mice that are euthanized for humane reasons. Where possible, a detailed necropsy is also performed to investigate or identify the reason for the ailment by a trained technician or veterinary staff.
- Terminal serum and tissue samples at 18 months (or 21 months) old will be collected for serum toxicity panel and histopathological assessment, respectively.

Two reports will be issued for this study, an interim from in-life for the initial 8 months which was submitted to the original IND (SN0000, dated 12 July 2022), and a final report with in-life and histopathology assessments after the 21 month assessments.

Table 5 21-month Efficacy Study in AP4M1 KO Mouse (ongoing)

***Ap4m1* Allele**	**AAV9/*AP4M1* Dose**	**Dose Group (Name)**	**Number of Animals (Male/Female)**	**Time of Dosing**
Ap4m1 (+/+)	na	A (WT)	12 (7/5)	na
Ap4m1 (+/-)	na	B (Het)	45 (23/22)	na
Ap4m1 (-/-)	Vehicle*	C	41 (19/22)	PND 7-10 or 90
Ap4m1 (-/-)	1.25E11 vg/animal*	D	16 (7/9)	PND 7-10
Ap4m1 (-/-)	5E11 vg/animal*	E	21 (8/13)	PND 7-10
Ap4m1 (-/-)	1.25E11 vg/animal*	F	17 (10/7)	PND 90
Ap4m1 (-/-)	2.5E11 vg/animal*	G	22 (9/13)	PND 90
Ap4m1 (-/-)	5E11 vg/animal*	H	19 (8/11)	PND 90

*Animals dosed via lumbar IT injection. WT, Wild type. Het, Heterozygous. KO, Knockout. PND, post-natal day.

Interim results for the initial 8 months demonstrated that MELPIDA dose dependently increases AP4M1 mRNA expression (Figure 5), induces minimal immune responses, causes minimal toxicity, generates minimal effects on body weight, creates minimal effects on survival, and improves abnormal behaviors (Figure 6).

Figure 5 MELPIDA Increased hAP4M1opt mRNA in All Brain Regions 3 Weeks Post Injection of PND 90 Mice

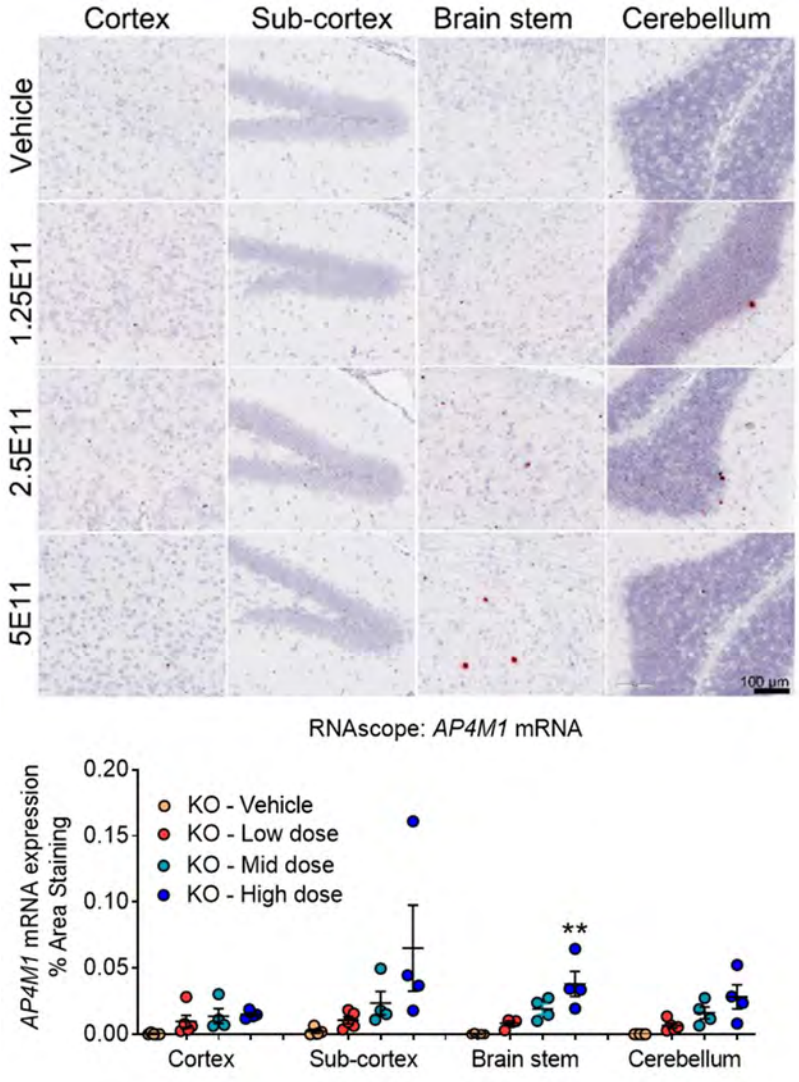
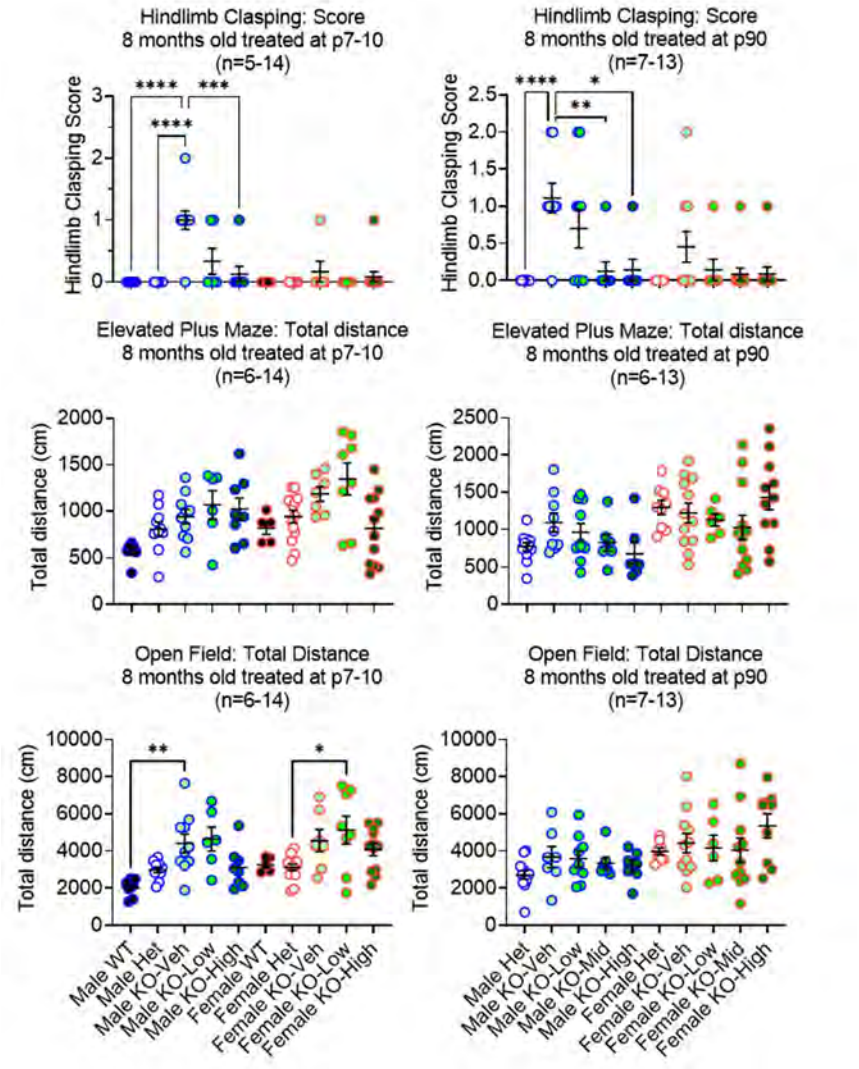


Figure 6 MELPIDA Improved Impaired Behaviors at 8 Months Post Dose



Hindlimb Clasping (upper panels), Elevated Plus Maze (middle panels), and Open Field (lower panels) performance of mice treated at p7-10 (left panels) and p90 (right panels). Each data point represents measurement from an individual animal, with lines representing the mean measurement ± SEM (n=5-14/group). *p<0.05, **p<0.001, ***p<0.001, and ****p<0.0001 compared to KO-Veh.

In summary, the high dose of 5E11 vg provided maximal pharmacological effects on Hindlimb Clasping whether administered early on PND7-10 or later on PND90 in male mice. For the Maze total distance, female mice had a less robust response when dosed at PND90 compared to PND7-10. The mid dose of 2.5E11 vg provided some pharmacological effects on Hindlimb Clasping when administered PND90 in male mice, suggesting MELPIDA may also generate benefits when dosed at the early-symptomatic stage.

5. PREVIOUSLY APPROVED DRUGS

There is no product currently approved for the treatment of SPG50. CureSPG50 is not seeking orphan-drug designation for a drug for which FDA has already granted orphan-drug designation for treatment of SGP50. This provision is, therefore, not applicable for purposes of the present request for orphan-drug designation.

6. TREATMENT OF A SUBSET OF PATIENTS

CureSPG50 is not requesting orphan-drug designation for an orphan subset. MELPIDA is intended to be used in the treatment of pediatric patients with SPG50.

7. REGULATORY STATUS AND MARKETING HISTORY

7.1. Regulatory Status

MELPIDA received Rare Pedicatric Disease Designation on 21 September 2020 (# RPD-2020-441), which was submitted with the original ODD request which was denied due to the lack of in vivo nonclinical data at that time.

Additionally, the sponsor submitted an IND to US FDA 12 July 2022 to treat 2 patients and this was cleared on 11 August 2022. Subjects are planned to be dosed 4Q2022. A CTA was also opened in Health Canada in January 2022, where a single male subject, aged 4y, was dosed in March of 2022; this subject continues to do well and shows some signs of stability from disease progression.

7.2. Marketing History

MELPIDA has not been marketed in any country. CureSPG50 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

SPG is an ultra-rare autosomal recessive disease with ~156 patients identified worldwide for all phenotypes and 59 identified with SPG50. There are ~9 patients with SPG50 in North America **Error! Reference source not found.**(AP4M1, OMIM #612936) (source: Ebrahimi-Fakhari et al, unpublished).

CureSPG50 is developing MELPIDA to treat SPG50. The therapeutic goal of MELPIDA is to reverse and/or prevent progressive symptoms of SPG50 in pediatric 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.

MELPIDA may be administered to patients only following diagnosis of SPG50, 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 (20 July 2020) without limit of publication date using the following search terms:

- "SPG50" (N=4),
- "AP-4 deficiency" (N=27),
- "hereditary spastic paraplegia", (N=1,382)
- "spastic paraplegia" (N=22,192)

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

No publications were identified that spoke specifically to the incidence of SPG50 in the US. Most of the limited information available was related to hereditary spastic paraplegias, without necessary information specific to SPG50.

The most robust data to support prevalence comes from the work by Ebrahimi-Fakhari et al, (under review) which describes 156 patients worldwide with AP-4 deficiency and 59 (38%) with SPG50 (Table 2). North America accounted for 15% of all patients. Estimation for the number in North America is derived by:

59 * 0.15 = 8.85 persons

Based on N=9 and a current US population size of 329,842,223 (source: U.S. Census Bureau and World Bank, June 25, 2020), prevalence for SPG50 is ([9/329,842,223]*100,000) 0.0027:100,000. These data support orphan designation for SPG50.

9. SUMMARY AND CONCLUSION

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

- Spastic Paraplegia Type 50 (SPG50) is one of a group of 4 genetic disorders (SPG47, SPG50, SPG51 and SPG52) involving a mutation that results in the production of an abnormal adaptor protein complex 4 (AP-4); all 4 subtypes present with the same clinical phenotype (Behne et al, 2020; Ebrahimi-Fakhari et al, 2018).

- SPG is an ultra-rare autosomal recessive disease with ~156 patients identified worldwide for all phenotypes and 59 identified with SPG50. There are ~9 patients with SPG50 in North America (AP4M1, OMIM #612936) (source: Ebrahimi-Fakhari et al, unpublished).

- Without new-born screening identification, patients are often 8 to 10 years of age before they are correctly diagnosed although symptoms start within infancy (Table 2). Patients are usually paralyzed by spasticity paraplegia within their first decade and tetraplegic and severely mentally delayed later on in life; epilepsy is also a key symptom (Ebrahimi-Fakhari, Behne et al, 2018). Only a few patients are identified over the age of 30 years (Figure 2) (Ebrahimi-Fakhari et al, under review);

- There are no approved treatments for SPG50, leaving an unmet medical need for this serious and quality of life limiting disease affecting pediatric patients.

- Melpida is a self-complimentary (sc) AAV9 gene therapy containing codon optimized human (h) AP4M1, which has been shown to rescue up to 77% of defective fibroblasts from two SPG 50 patients in vitro. In an in vivo model of heterozygous and homozygous Ap4m1 knock-out (KO) mice dosed intrathecally at post-natal day (PND) 7 to 10 or PND 90 with either no treatment, vehicle, low (1.25E11), mid (2.5E11) or high (5E11) doses of MELPIDA, improvements in Hindlimb clasping and total Maze distance were noted 8 months post dosing, suggesting MELPIDA generates benefits when dosed at the early-symptomatic stage in patients(Section 4.3).

- The therapeutic goal is to treat patients with a single one-time intrathecal administration of Melpida, which will provide the AP4M1 protein required to prevent further progression of the disease, improving functional outcomes and survival in these pediatric patients. The intrathecal route has been used with AAV9 as a way to deliver gene therapies to the central nervous system (CNS) (Bailey et al, 2018). As with similar pediatric diseases such as spinal muscular atrophy and aromatic l-amino acid decarboxylase, 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 Melpida.

10. REFERENCES

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