Pharmacy Manual

A Phase 1/2 Open-label Intrathecal Administration of MELPIDA to Determine the Safety and Efficacy for Patients with Spastic Paraplegia Type 50 (SPG50) caused by a Mutation in the AP4M1 gene.

Sponsor:	**CureSPG50**
Principal Investigator:	**Dr. Susan Iannaccone**
Indication:	**SPG50 / AP4M1**

Version Date: November 17, 2021

CONFIDENTIALITY STATEMENT

This document contains confidential information, which should not be copied, referred to, released or published without written approval from University of Texas Southwestern Medical Centre & CureSPG50. Investigators are cautioned that the information given in this brochure might be subject to change and revision. Any conclusion regarding efficacy and safety must be considered provisional.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AAV9	Adeno-Associated Virus
AP4M1	Adaptor Related Protein Complex 4 Subunit Mu 1
BSC	Biohazard safety cabinet
CoA	certificate of analysis
CTA	Clinical Trials Application
DOA	Delegation of Authority
DSMB	Data Safety Monitoring Board
EU	endotoxin limit
GMP	Good Manufacturing Practice
HEK	Human embryonic kidney
IND	Investigational New Drug
IT	Intrathecal
IV	Intravenous Therapy
PBS	Phosphate Buffered Saline
PICU	Pediatric Intensive Care Unit
PP	polypropylene
SPG50	Spastic Paraplegia Type 50
TGN	trans-Golgi network
vg	Vector genomes
VVC	Viralgen Vector Core, San Sebastian, Spain

1. INTRODUCTION

1.1. Purpose of Investigation

To assess the safety and efficacy of the gene transfer vector MELPIDA (scAAV9/AP4M1) through intrathecal delivery to patients with Spastic Paraplegia Type 50 (SPG50).

1.2. Sponsor and IND

CureSPG50 is the sponsor of this investigation. Dr Susan Iannaccone is the Principal Investigator. The Investigation New Drug Application (IND) number is 028202.

2. CONTACT INFORMATION

2.1. Principle Investigator and Institute

Susan T. Iannaccone, MD, FAAN

Warren A. Weinberg Chair in Pediatric Neurology and Learning
Associate Director of the UT Southwestern Wellstone Muscular Dystrophy Center
CoPI UTSW NeuroNEXT Program
CoDirector, Pediatric MDA Care Center
CoDirector, PPMD Center of Excellence
Professor of Pediatrics and Neurology
UT Southwestern Medical Center
5323 Harry Hines Blvd
Dallas TX
75390-9063
214-456-5220

2.2. Drug Administration/Performance Site

Children's Health Dallas
1935 Medical District Drive
Dallas TX 75235

3. INFORMATION ON AGENT

3.1. Vial/Package Labeling

The investigational agent is labeled as MELPIDA.

3.2. Other Names, Manufacturer

Lot T-Geminis-029 was provided by Viralgen Vector Core (VVC), San Sebastian, Spain, a contracted Good Manufacturing Practice (GMP) manufacturing facility with experience of AAV vector production for use in human clinical trials. Other names for the drug are: scAAV9/AP4M1, AAV9/USP-AP4M1, scAAV9/USP-hAP4M1opt-BGHpA or MELPIDA.

3.3. Description and Use

MELPIDA, a biological gene transfer reagent, is an adeno-associated virus (AAV) containing a self-complementary DNA payload of a codon-optimized human AP4M1 cDNA. The vector was produced by triple transfection of 3 plasmids into a suspension cell line of HEK293 cells. The vector is produced in the HEK293 cells, then purified and finally prepared in the formulation buffer.

MELPIDA will be administered via intrathecal delivery to the nervous system of patients with SPG50, a chronic neurodegenerative autosomal recessive disease. The disease pathology is due to loss of function mutations in the AP4M1 gene, which encodes the protein AP4M1, one of the 4 proteins forming the AP-4 complex. The AP-4 complex consists of four subunits (β4, ε, μ4 and σ4) and has been implicated in trafficking of transmembrane proteins from the trans-Golgi network (TGN) to endosomes.

3.4. MELPIDA (lot # T-GEMINIS-029, Date of Manufacture (DOM): 06JUL2021)

MELPIDA is supplied as a 2 mL polypropylene cryovial containing 1.15 mL of a sterile clear solution. Each mL contains 1E14 vector genome-containing particles (vg) of MELPIDA in phosphate buffered saline (PBS) containing 5% sorbitol and 0.001% Poloxamer 188.

3.5. Dilution Buffer

MELPIDA dilution buffer is supplied as a 2 mL cryovial containing 1.15 mL of a sterile buffer solution comprised of 10mM phosphate, 137mM sodium chloride, 2.7mM potassium chloride, 5% sorbitol and 0.001% poloxamer 188, pH 7.4 buffer. *Note that while the dilution buffer is supplied, the concentration of this lot of MELPIDA (# T-GEMINIS-029) should not require dilution.*

3.6. Storage

MELPIDA must be stored in a secure location at ≤ -60°C. Sites are required to maintain 24-hour temperature monitoring and have logs available for review. MELPIDA may only be dispensed by a pharmacist with oversight from the Principal Investigator. Authorization for dispensing must be documented on the Delegation of Authority (DOA) log. Full dispensing information is provided below.

3.7. Shipping and Handling

MELPIDA will be shipped from VVC, to Childrens Health Investigational Pharmacy, Dallas in a Styrofoam box with at least the following internal dimensions of 320x320x320mm (32.7L volume) and the external dimensions of 465x458x478mm (17 volumetric wight), with at least 15 Kilograms of dry ice, which has been shown to provide temperatures ≤ -60°C to ≥ -90°C for holding times of up to 4 days. Shipment can be by air, train or road and should not exceed 2 days without replenishment of dry ice.

3.8. Temperature Excursion

A temperature monitor is included in each shipment. A reading is collected every 15 min and the results are assembled into a graph that can be downloaded from the device by USB. Alarm limits are set at -60°C.

If there is a storage temperature excursion (≥10 minutes), then follow the steps below:

- Do not dispense the affected MELPIDA
- Quarantine the affected drug to prevent inadvertent dispensing (in the freezer)
- Complete and submit the Temperature Excursion Report according to the procedures outlined in the Temperature Excursion Report.
- Once a determination regarding the stability of the affected MELPIDA has been made, you will be notified regarding disposition of the drug.

3.9. Stability

Stability is ongoing and the expiration date will be defined and based on the data generated. The 6m timepoint is January 2022 with the final 2y stability timepoint being 06JUL2023. The dose, prepared in a syringe, is stable for up to 4 hours when stored at 4°C (i.e. on iced water/cold packs) starting from when the dose preparation is complete.

3.10. Administration

Administration will be via intrathecal (IT) delivery.

3.11. Compatibility

MELPIDA is compatible with the supplied dilution buffer and is compatible with

- BD Blunt Fill Needle (BD Item # 305180)
- BD 20 mL Syringe Luer-Lok Tip (Item # 302830)
- Baxter Micro-Volume Extension Set (Baxter Item # 2N3380)
- Stopcock (B. Braun Medical Inc., Item # 456020)
- Pajunk Atraumatic Sprottle Needle (Item # 321151-31A).

4. DOSE CALCULATION AND DISPENSING

MELPIDA should be handled and labeled as a hazardous drug.

Biosafety level 2 practices are recommended. Safety glass or goggles are recommended when handling MELPIDA. All dose preparations using MELPIDA will be performed in the negative pressure room in the central pharmacy cleanroom suite.

4.1. Materials Needed for Preparing MELPIDA for Administration

The components needed for the preparation of MELIDA are listed in Table 1.

Table 1 Materials Needed for Infusion

Part Information	Manufacturer	Part Number
Infusion syringe pump control unit	CareFusion	Alaris 8110 model Alaris Medley 8015 control unit model
BD Blunt Fill Needle	Becker Dickinson	305180
20 mL BD luer lock syringe	Becker Dickinson	302830
Baxter Micro-Volume Extension Set	Baxter	2N3380
Stopcock	B. Braun Medical Inc.	456020
Pajunk Atraumatic Sprottle Needle	Pajunk	321151-31A

4.2. Dose and dose calculation

The patients will receive MELPIDA at a dose of up to 1E15 vg depending on age, which will be prepared as outlined in the table below:

Age (years)	Brain Volume (approx. cm3)	Infusion Volume (mL)	Total IT 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

Dose preparation will NOT begin until the pharmacy staff receives a call from the study staff.

The vector will be administered into the intrathecal space by a lumbar puncture at a rate of 1 mL per minute. The rate of administration will be maintained with the use of the Carefusion Alaris 8110 syringe pump with the Carefusion Alaris Medley 8015 control unit.

4.2.1. NOTE: Dosing of vg and Volume was Calculated by CSF Volume Calculating the Dose

MELPIDA is provided at a concentration of 1E14 vg/mL. Dosing is based on CSF volume, which remains relatively constant after age 3 years old. Thus, all patients 4 years old and older will receive 1E15 vg total in 10 mL.

4.2.2. Endotoxin Levels

After calculating the dose and prior to preparation of MELPIDA for administration, the pharmacist will ensure that the endotoxin (EU) levels being administered to a given subject are

below 0.2 EU/kg/h. MELPIDA lot # T-Geminis-029 has <0.05 EU/mL, or <0.5 EU per 10 mL. Thus, as long as the subject is larger than 2.5 kg then they can receive up to a 10 mL dose and remain below the approved 0.2 EU/kg/hr endotoxin limit for an intrathecal drug.

The endotoxin level will be provided in the certificate of analysis (CoA) from the manufacturer and a copy of that CoA will be provided with the shipment of MELPIDA to the Pharmacy.

Multiply the EU value from the CoA by the volume needed for the subject to confirm the EU burden to the subject and to ensure it is below 0.2 EU/Kg.

4.2.3. Preparation (1E15 vg in 10 mL)

1. Ten (10) vials of MELPIDA (1.15 mL each) will be thawed at room temperature and then placed on cold packs. Allow 30 minutes for thawing of the vials.
2. Follow institutional standard operating procedures to clean biological safety cabinet, class 2, used to prepare dose.
3. Connect a BD Blunt Fill Needle (Item # 305180) to a 20 mL BD luer-lock syringe (Item # 302830). NOTE: To use the spinal needle, aseptically remove and put aside for later disposal, the (inner) stylet. Only the "outer" needle will be used to withdraw drug from the vector vial.
4. Using the 20 mL syringe with the attached needle, withdraw the entire contents of vector solution from the thawed vials.

   NOTE: Depending on the amount of overfill volume withdrawn from the drug vials, the syringe may contain up to 11.5 mL. The syringe will contain excess vector solution (overfill volume) needed to prime the extension set used for infusion. The correct 10 mL dose will be administered using the setting on the pump. Any material left after the infusion is complete should be pushed into a polypropylene (PP) conical tube and frozen at < -60° C for possible later analysis. This excess can be preserved and stored at the UTSW Translational Gene Therapy Core.
5. Invert the syringe 10 times to ensure the contents are fully mixed.
6. Carefully remove the needle and connect a Baxter Micro-Volume Extension Set (Baxter Item # 2N3380) for additional length between the infusion pump and the needle.
7. Prime the tubing with vector solution and cap the tubing closed.
8. Wipe outside of syringe with alcohol swab before removing from BSC.
9. **The product will be given a 4-hour expiration (at 4°C) from the time it was prepared (after final preparation of the patient's dose, the product will be given a 4-hour expiration). The dosing syringe label will contain the statement: "Caution: NOT for IV USE". Ancillary labels will be placed indicating "HAZARDOUS drug" and "For Intrathecal Use Only".**
10. Place the syringe and tubing in a plastic zipper locked hazardous drug bag to dispense. The bag should be placed on cold packs for transport.
11. Place the empty vials in a separate zipper-locked hazardous drug bag to be picked up along with the excess prepared vector in the syringe.
12. Decontaminate the BSC per institutional standard operating procedures.

5. GENERAL INFORMATION

- Just prior to injection, warm the syringe by hand (for approximately 5 minutes) by rolling it between both palms and ensuring the end of the extension tube remains sterile (ie, not touched during this process).
- Load the syringe into the Carefusion Alaris 8110 syringe pump with the Carefusion Alaris Medley 8015 control unit and confirm that it is set correctly to deliver 1 mL per minute.
- The Baxter Micro-Volume Extension Set tubing will be connected to the stopcock (B. Braunm Medical Inc., Item # 456020) that is attached to the Pajunk Sprotte needle (already in use on the patient, Item # 321151-31A) and the stopcock will be placed in an open position to allow for flow between the tubing and the needle.
- The patient will then be placed in a Trendelenburg position, with the head of the bed tilted down at a 15-degree angle. Fluoroscopy may be used to verify placement of the needle before starting the infusion.
- The Carefusion Alaris 8110 syringe pump with the Carefusion Alaris Medley 8015 control unit will be started at a rate of 1 mL per minute to allow for delivery of the vector over 10 minutes (10 mL total infusion volume).

Following completion of IT administration of MELPIDA and removal of the needle, the patient will resume the Trendelenburg position, with the head of the bed tilted down at a 15 degree angle for a period of 60 minutes. Every 15 minutes during that 60 minute period, the patient will be moved onto their opposite side (left side to right side, or *vice versa*).

The patient will remain on continuous vital sign monitoring after being transferred to the Pediatric Intensive care Unit (PICU) for at least 24 hours. For full safety monitoring and reporting plan refer to the study protocol.