DE NOVO CLASSIFICATION REQUEST FOR SMARTFLOW NEURO CANNULA

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Brain intraparenchymal infusion cannula.** A brain intraparenchymal infusion cannula is a non-powered, hollow tube-like device with a rigid component for stereotaxic aided temporary placement in brain parenchyma tissue to deliver a therapy.

NEW REGULATION NUMBER: 21 CFR 882.4110

CLASSIFICATION: Class II

PRODUCT CODE: SDG

BACKGROUND

DEVICE NAME: SmartFlow Neuro Cannula

SUBMISSION NUMBER: DEN240023

DATE DE NOVO RECEIVED: May 22, 2024

CONTACT: ClearPoint Neuro, Inc.

120 S. Sierra Avenue, Suite 100
Solana Beach, California 92075

INDICATIONS FOR USE

The SmartFlow Neuro Cannula, when used with compatible stereotaxic and therapeutic delivery devices, is indicated for intraputaminal administration of eladocagene exuparvovec-tneq for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.

LIMITATIONS

For prescription use only.

Do not use in individuals with genetically confirmed AADC deficiency in whom the cranium is not sufficiently developed to allow stable placement of the stereotactic head frame for surgery.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The SmartFlow Neuro Cannula has a stepped distal tip with a rigid ceramic cannula body protecting the fluid lumen. Soft tubing protects the lumen in the center portion and at the proximal end where it terminates at a female luer fitting. The SmartFlow Neuro Cannula must be used with a supporting structure (e.g., stereotactic guide tube and frame) to provide support and control during insertion. A guide tube is provided with the device for this purpose. The fluid carrying central lumen is manufactured from non-reactive silica.

The SmartFlow Neuro Cannula is provided sterile in a plastic sealed tray in a secondary pouch which enables dual aseptic transfer. The device is available in two sizes: 4- or 10-feet length (NGS-NC-01-EE or NGS-NC-02-EE).

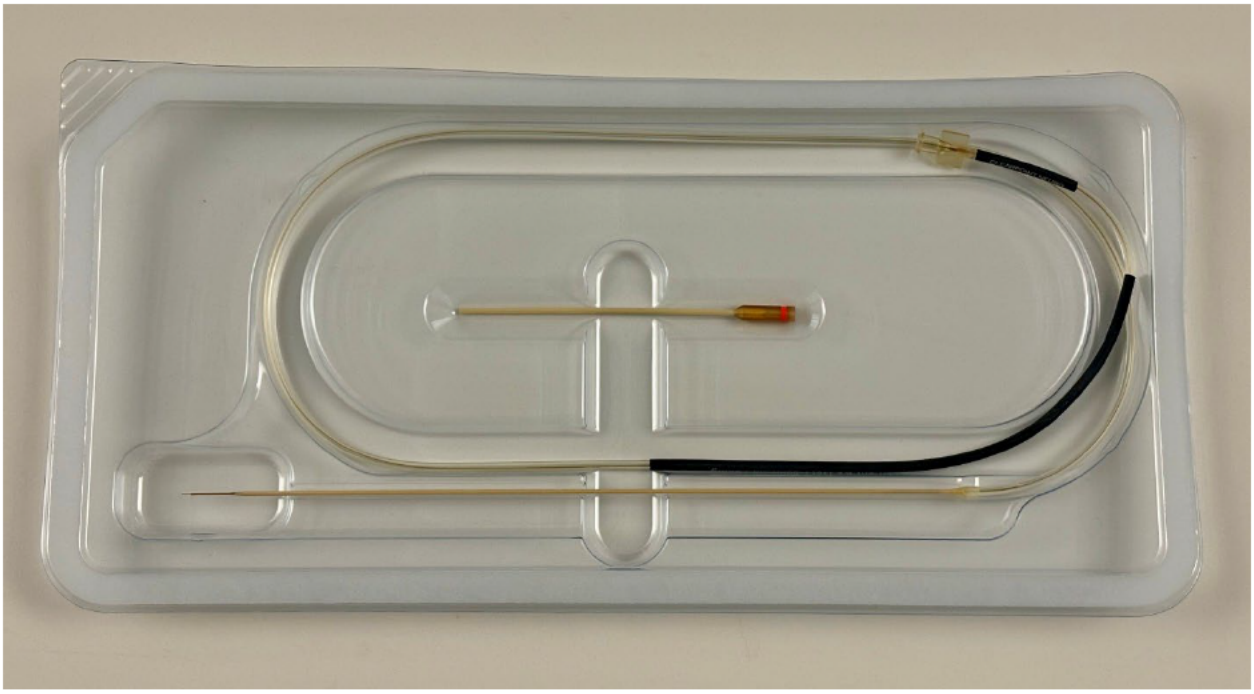

Figure 1: SmartFlow Neuro Cannula

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY

The SmartFlow Neuro Cannula is considered to be an external communicating device in limited (≤ 24 hours) contact with tissue and/or bone, cerebrospinal fluid (CSF), and blood (indirect blood contact through CSF as CSF is reabsorbed into the venous system). As such, its biocompatibility evaluation was conducted in accordance with ISO 10993-1:2018, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process," the FDA guidance, "Use of International Standard ISO-

10993, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process'," and ASTM F2901-19, "Standard Guide for Selecting Tests to Evaluate Potential Neurotoxicity of Medical Devices." For a limited duration contact external communicating device, the SmartFlow Neuro Cannula was evaluated for the following biocompatibility tests: cytotoxicity, sensitization, irritation/intracutaneous reactivity, acute systemic toxicity, material mediated pyrogenicity, genotoxicity, hemocompatibility (indirect hemolysis test), and neurotoxicity. The cytotoxicity, sensitization, irritation/intracutaneous reactivity, acute systemic toxicity, and material mediated pyrogenicity endpoints were assessed from testing submitted in K102101 for the cleared SmartFlow Neuro Cannula (previously cleared under the name SurgiVision Ventricular Cannula) for a different intended use.

Table 1: Biocompatibility Evaluations for the SmartFlow Neuro Cannula

Test	Test Method	Results
Cytotoxicity	ISO 10993-5:2009, ISO Elution Method	Non-cytotoxic
Sensitization	ISO 10993-10:2002, Maximization Test in Guinea Pigs	Non-sensitizing
Intracutaneous Reactivity	ISO 10993-10:2002, Intracutaneous Reactivity in Rabbits	Non-irritant
Acute Systemic Toxicity	ISO 10993-11:2006, Acute Systemic Toxicity in Mice	Non-toxic
Pyrogenicity	ISO 10993-11:2006 and USP 34 <151>, USP Rabbit Pyrogen Study, Material Mediated	Non-pyrogenic
Hemolysis (Indirect Contact)	ISO 10993-4:2017 and ASTM F756 – 17	Non-hemolytic
Genotoxicity	ISO 10993-3:2014, Bacterial Reverse Mutation Test (Ames Assay)	Non-genotoxic
	ISO 10993-3:2014, Mouse Lymphoma Assay	
Neurotoxicity	Risk Assessment & Animal Studies	Non-neurotoxic

SHELF LIFE/STERILITY

The SmartFlow Neuro Cannula and its packaging has been validated for a shelf life of 4 years. The test units for shelf life testing were each packaged in a polyethylene terephthalate glycol (PETG) tray with a PETG tray insert to protect the components during transit, sealed with a high-density polyethylene (HDPE) (Tyvek) lid to maintain a primary sterile barrier, and sealed in a secondary pouch made from polyethylene terephthalate (PET) / low-density polyethylene (LDPE) with HDPE fiber. The pouched product is packaged in a white solid bleached sulphate (SBS) chipboard box. The packaged test units underwent two gamma sterilization cycles, preconditioning, and packaging distribution testing followed by real-time shelf life testing to support the integrity of the sterile barrier and functional performance of the device for a shelf life of 4 years.

The SmartFlow Neuro Cannula is provided sterile and is intended for single use only. The final finished product is sterilized to a sterility assurance level (SAL) of 10^{-6} using gamma radiation. Gamma sterilization achieves a minimum internal dose of 25 kGy using the VD_{max25} method for the SmartFlow Neuro Cannula. To continue to substantiate the minimum dose of 25 kGy, dose audits are performed quarterly during production.

Bacterial endotoxin testing using the limulus amebocyte lysate (LAL) kinetic chromogenic test method was evaluated for the SmartFlow Neuro Cannula to meet the endotoxin limit of ≤ 2.15 endotoxin units (EU)/device. Bacterial endotoxin testing will be performed on each lot of the SmartFlow Neuro Cannula as part of the manufacturing process.

MAGNETIC RESONANCE (MR) COMPATIBILITY

MR compatibility testing was not conducted for the SmartFlow Neuro Cannula or guide tube accessory because the materials of composition are known to be MR safe.

PERFORMANCE TESTING – DEVICE COMPATIBILITY WITH THE THERAPY

- Leachables Characterization of the Device: An assessment of the formulation of eladocagene exuparvovec-tneq to its potential effects on compatibility with the SmartFlow Neuro Cannula was performed. Based on the perceived extractable power of the drug formulation when compared to literature, leachables risks were determined to be appropriately addressed by the completed biocompatibility testing on the device.

- Particulate Testing of the Device: Particulate testing was conducted to evaluate the particle numbers of clinically relevant particle sizes that could be shed from the SmartFlow Neuro Cannula during simulated use. Particulate testing was performed per ASTM F2743-11(2018), "Standard Guide for Coating Inspection and Acute Particulate Characterization of Coated Drug-Eluting Vascular Stent Systems." Twenty-two (22) samples of the longest cannula configuration, NGS-NC-02, were tested. Each sample was primed in the packaging tray with filtered distilled water until one (1) drop of water came from the sample's tip. The sample was then advanced in a clinically relevant glass vascular model, flushed, and then retracted while counting particles in bin sizes: ≥ 10 µm, ≥ 25 µm, ≥ 50 µm, and ≥ 70 µm. The numbers of particles counted in the bin sizes were comparable or less than those reported for other neurosurgical devices intended for use in the brain.

- Characterization of Therapy Adsorption by the Device: Adsorption of eladocagene exuparvovec-tneq following simulated administration using the SmartFlow Neuro Cannula (NGS-NC-02) and other administration devices (i.e., syringe, filter needle) was assessed by vector titer assay using quantitative polymerase chain reaction (qPCR). There was no substantial loss of vector genome titer compared to the lot release and stability data, demonstrating there is no notable adsorption of the vector to the therapy administration devices

including the SmartFlow Neuro Cannula.

- Characterization of Therapy Aggregation by the Device: Aggregation of eladocagene exuparvovec-tneq following simulated administration using the SmartFlow Neuro Cannula (NGS-NC-02) and other administration devices (i.e., syringe, filter needle) was assessed by analysis of the percent monomer in test samples using dynamic light scattering (DLS). No aggregation of vector was detected in the test samples collected from the distal end of the SmartFlow Neuro Cannula after the biologic product had passed through the entire fluid path of the administration devices.

- Therapy Potency Testing Following Simulated Administration: Potency testing of eladocagene exuparvovec-tneq following simulated administration using the SmartFlow Neuro Cannula (NGS-NC-02) and other administration devices (i.e., syringe, filter needle) was assessed using the relative potency assay. The reported potency value was the average of results from three (3) independent plates. The relative potency data indicate that there was no detectable reduction of biologic product potency following simulated administration of the product with worst-case hold times.

- Therapy Quality Testing Following Simulated Administration: The risk of microbial contamination during biologic product preparation and administration was assessed using the SmartFlow Neuro Cannula (NGS-NC-01) and other administration devices (i.e., syringe and filter needle). The biologic product was passed through the delivery devices, including the SmartFlow Neuro Cannula, and then the biologic product was tested for bioburden in three independent runs. The test results were all below 1 colony-forming unit (CFU)/0.5 mL. The level of cumulative endotoxin from the delivery devices and the biologic product was below the acceptable endotoxin limit for the biologic product specified in USP <85> and the acceptable limit for devices specified in USP <161>.

- Functional Compatibility with Other Devices Intended to be Used During the Procedure: Compatibility of the SmartFlow Neuro Cannula with stereotaxic and therapy administration devices was described in two (2) literature articles identified in the "Performance Testing – Animal" discussion below and demonstrated in the clinical study PTC-AADC-GT-002 summarized in the "Summary of Clinical Information" section below.

- Cross-Labeled Products Quality Technical Agreement: A quality technical agreement documents activities associated with the cross-labeled device and biologic product production, analysis, release, and distribution.

PERFORMANCE TESTING – BENCH

- Dimensional Evaluation: Dimensional evaluation was conducted to assess the SmartFlow Neuro Cannula physical dimensions including confirming priming

volume of each SmartFlow Neuro Cannula model.

- Dose Accuracy: The accuracy of injection volume was assessed using water, two different syringe pumps, and 5 mL or 10 mL syringes. Two setups were able to accurately deliver 80 µL volume.

- Tensile Strength Testing: Tensile strength of the SmartFlow Neuro Cannula and guide tube accessory were assessed from separation force testing submitted in K102101 for the cleared SmartFlow Neuro Cannula (previously cleared under the name SurgiVision Ventricular Cannula) and determined to be adequate to withstand typical forces encountered during the intended clinical use without breaking.

- Compressive Strength Testing: Compressive strength of the SmartFlow Neuro Cannula was assessed from distal tip compression testing submitted in K102101 for the cleared SmartFlow Neuro Cannula (previously cleared under the name SurgiVision Ventricular Cannula) and determined to be adequate to withstand typical forces encountered during the intended clinical use without breaking.

- Bending Strength Testing: Bending strength of the SmartFlow Neuro Cannula was assessed from lateral tip testing and proximal tubing radius testing submitted in K102101 for the cleared SmartFlow Neuro Cannula (previously cleared under the name SurgiVision Ventricular Cannula) and determined to be adequate to withstand typical forces encountered during the intended clinical use without breaking.

- Leakage: Leakage resistance of the SmartFlow Neuro Cannula was assessed from pressure and vacuum testing submitted in K102101 for the cleared SmartFlow Neuro Cannula (previously cleared under the name SurgiVision Ventricular Cannula) and determined to be adequate to exhibit no leakage under typical forces encountered during the intended clinical use.

- Maximum Infusion Pressure (Burst): Resistance of the SmartFlow Neuro Cannula to overpressure burst failure was validated in high pressure (70 psi) testing submitted in K102101 for the cleared SmartFlow Neuro Cannula (previously cleared under the name SurgiVision Ventricular Cannula). Additionally, three (3) cannula representatives of the SmartFlow Neuro Cannula for brain intraparenchymal infusion were tested at 250 psi and 300 psi without failure.

- Flow Rate: Compatibility of the SmartFlow Neuro Cannula with syringe pump systems for brain intraparenchymal infusion was demonstrated in the animal studies described in the "Performance Testing – Animal" section and in the clinical study PTC-AADC-GT-002 summarized in the "Summary of Clinical Information" section.

- Human Factors/Usability: Usability of the SmartFlow Neuro Cannula in a clinically relevant workflow was described in the literature articles discussed in the "Performance Testing – Animal" section and evaluated in the clinical study PTC-AADC-GT-002 summarized in the "Summary of Clinical Information" section.

PERFORMANCE TESTING – ANIMAL

Multiple animal studies were performed to evaluate the in vivo performance, safety, and biocompatibility of the SmartFlow Neuro Cannula that are described below.

A non-Good Laboratory Practices (non-GLP) safety and biodistribution study of recombinant adeno-associated vector, serotype 2 (rAAV2)-enhanced green fluorescent protein (eGFP) following intraputaminal infusion in the non-human primate (NHP): The purpose of the study was to assess the safety and biodistribution of the test article (rAAV2-eGFP), in formulations with and without 0.001% poloxamer, following a single, bilateral intra-putamen injection in cynomolgus monkeys using the SmartFlow Neuro Cannula. The monkey was selected specifically for use in this study because the neuroanatomy in a non-human primate resembles humans most closely, and therefore, most appropriately predicts the outcome in humans. There were four groups tested: poloxamer only, low dose rAAV2-eGFP without poloxamer, low dose rAAV2-eGFP with poloxamer, and high dose rAAV2-eGFP with poloxamer. Each group was further subdivided into an 8-day survival cohort and a 28- to 29-day survival cohort, each with 3 animals representing both sexes, with the exception of the low-dose rAAV2-GFP with no poloxamer group, which had only 1 male and 1 female.

The procedure was performed by taking a baseline magnetic resonance imaging (MRI) of the animal to establish targets. In the surgical suite, the animals were prepared by being shaved and having a hole drilled through the skull over the target location. The SmartFlow Neuro Cannula was primed, flow was initiated at 1 µL/min, and the SmartFlow Neuro Cannula was lowered using a stereotaxic frame to the target location (approximately 1 minute to depth). The test article or vehicle was infused initially at a rate of 2.0 µL/min for 5 minutes, increased to 3.0 µL/min for 1 minute, increased to 4.0 µL/min for 1 minute, and then 5.0 µL/min for 26 minutes, 24 seconds or 26 minute, 36 seconds. The cannula remained in place for 5-10 minutes following completion of the infusion and then retracted. The animals were evaluated for abnormalities before and after dosing and were maintained for 28-29 days for evaluation.

The following parameters and endpoints were evaluated in this study: mortality, detailed clinical signs, body weights, clinical pathology parameters (hematology and clinical chemistry), bioanalysis (anti-drug antibody [ADA] and CSF), gross necropsy findings, histopathologic examinations, and tissue biodistribution.

All animals tolerated the procedure well. There were no device-related adverse events observed. The results of this study demonstrated that intraputaminal administration of the infusates with the SmartFlow Neuro Cannula were not associated with any unexpected

mortality, clinical findings, changes in body weights, or macroscopic observations. Upon evaluation of clinical pathology endpoints, there were no test article-related changes.

The histologic findings noted in the brain are consistent with bilateral passage of the needle through the craniodorsal parenchyma of the brain (including the gray and white matter of the dorsal and/or middle frontal gyri) and into the underlying putamen. Parenchymal necrosis and associated gliosis were present in one to multiple brain slab sections in all animals examined, including in the control groups, for animals terminated on both day 8 and day 28 from all 4 test groups. Across all animals, the lesions generally conformed to the pattern of focal to bilateral, linear necrosis in the superior and middle frontal gyri (gray and white matter), representing the path taken by the needle as it approached the injection site, and more focally extensive necrosis and gliosis within and around the targeted injection site in the putamen. The main difference in tissues from animals terminated on days 28 to 29 was the presence of gitter cells within necrotic foci, considered to be a normal component of maturing necrotic lesions in the central nervous system (CNS). Green fluorescent protein (GFP) immunohistochemistry was positive in select group 2, 3, and 4 animals at both day 8 and day 28-29, generally highlighting a small number of scattered cells within and around the injection site in the putamen. The findings histologically were an expected minimal amount of tissue reaction along the cannula track, which is consistent with penetration into the brain parenchyma with any linear catheter, probe, or cannula for neurosurgical procedures.

4-week biodistribution study of rAAV2-human aromatic L-amino acid decarboxylase (hAADC) by multiple routes of administration in cynomolgus monkeys: The objective of this study was to compare gene transfer and distribution in the CNS of monkeys following delivery of rAAV2-hAADC, at a single dose, through intra-putamen, ventricular, or intrathecal routes of administration. Each of the three cohorts had 4 animals with equal numbers of males and females. In this study, the intra-putamen injections involved 150 µL of the test article into 4 animals. The following parameters and endpoints were evaluated in this study: mortality, detailed clinical observations, body weights, body weight gains, clinical pathology parameters (hematology, coagulation, and clinical chemistry), bioanalysis (ADA), biodistribution (blood and tissue via qPCR), nerve tissue gene expression via reverse transcription polymerase chain reaction (RT-PCR), and gross necropsy findings. This study provided in-life evidence for safety of accessing different areas of the brain, as well as the injection volume, but was limited in the ability to fully provide for safety by the lack of histologic evaluation of the tissues.

Results demonstrated intra-putamen, ventricular, or intrathecal administration were not associated with any mortality, clinical findings, changes in body weights, or macroscopic observations, and there were no test article-related changes in clinical pathology parameters. There were no adverse effects noted clinically.

Novel platform for MRI-guided convection enhanced delivery of therapeutics, preclinical

validation in nonhuman primate (NHP) brain[1]: The SmartFlow Neuro Cannula was used as part of a NHP study to demonstrate the safety and efficacy of convection enhanced delivery (CED) of therapeutics into the brain. This study's objective was to validate the targeting accuracy of the delivery system and the performance of the infusion cannula in an NHP model. Two adult rhesus monkeys were included in the study. Each animal received 2 or 3 infusions of 1 mM gadoteridol (Gd) in one hemisphere during a first MRI session, and 2 or 3 infusions in the contralateral hemisphere during a second MRI session. The animals recovered for a 2–3-week period between infusion sessions. The infusions of gadoteridol were delivered to multiple brain targets and the targeting error was determined for each cannula placement. Using a stereotaxic guided trajectory, the SmartFlow Neuro Cannula performance was assessed by analyzing gadoteridol distributions and by histological analysis of tissue damage.

Satisfactory cannula placement was achieved on the first attempt (without the need for repositioning) in all cases. The targeting error was 0.8 mm (95% confidence interval (CI) = 0.14 mm). No technical limitations were encountered in redirecting the cannula for infusing multiple targets in the same hemisphere. No infusions in any target produced occlusion, cannula reflux or leakage from adjacent tracts, and no signs of unexpected tissue damage were observed. Histologic evaluation of the tissues was performed 7 days after the last infusion procedure, using hematoxylin and eosin (H&E), glial fibrillary acidic protein (GFAP), and ionized calcium-binding adaptor molecule 1 (Iba1) staining techniques. In each animal, there was moderate Iba1 and GFAP expression along the cannula tracts, as is expected for any device that traverses the brain parenchyma, but no overt pathology was noted. These results demonstrate that the delivery platform, including the cannula, allows real-time CED to be performed with a high level of precision, predictability, and safety.

Interventional MRI-guided putaminal delivery of AAV2-GDNF for a planned clinical trial in Parkinson's disease[2]: The SmartFlow Neuro Cannula was used to administer adeno-associated virus serotype 2 (AAV2)-glial-derived neurotrophic factor (GDNF) into the putamen of 3 NHPs, as well as the thalamus of 3 additional NHPs. This animal study was performed as a model for a planned clinical trial in patients with Parkinson's disease (PD). Three NHPs underwent sequential, bilateral delivery of 50–60 µL Gd/AAV2-GDNF to two intraputaminal locations on each side of the brain hemisphere, and three NHPs underwent sequential, bilateral delivery of 150, 200, or 300 µL Gd/AAV2-GDNF into the thalami, which allowed the larger volumes expected for the human putamen injections. Accurate cannula placement was achieved on the first attempt, without the need for repositioning, in all cases. No technical limitations were encountered in redirecting the cannula for infusing two putaminal sites within the same hemisphere. The infusion rate was slowly increased to reach a maximal rate of 5 µL/min. No adverse events resulted from the surgical procedure or from the subsequent gene expression.

[1] Richardson MR, Kells AP, Martin AJ, Larson PS, et al. "Novel platform for MRI-guided convection-enhanced delivery of therapeutics: preclinical validation in nonhuman primate brain." Stereotactic and Functional Neurosurgery. 2011;89(3):141–151.
[2] Richardson MR, Kells AP, Rosenbluth KH, Salegio EA, et al. "Interventional MRI-guided putaminal delivery of AAV2-GDNF for a planned clinical trial in Parkinson's disease." Molecular Therapy. 2011;19(6):1048–1057.

Upon postmortem examination, H&E-stained brain sections revealed no evidence of hemorrhage or significant neuropathology at the infusion sites, other than expected minor glial scarring along the cannula tract. These results demonstrate that a SmartFlow Neuro Cannula can safely and effectively administer cell therapies into the putamen in an NHP model.

SUMMARY OF CLINICAL INFORMATION

The SmartFlow Neuro Cannula was studied, along with the biologic product eladocagene exuparvovec-tneq (KEBILIDI), for safety and efficacy in one open-label, single arm study (NCT04903288). The study enrolled pediatric patients with genetically confirmed, severe AADC deficiency who had achieved skull maturity assessed with neuroimaging. The main efficacy outcome measure was gross motor milestone achievement evaluated at week 48 and assessed using the Peabody Developmental Motor Scale, Second Edition (PDMS-2). Patients treated with KEBILIDI were compared to an external untreated natural history cohort of 43 pediatric patients with severe AADC deficiency who had at least one motor milestone assessment after 2 years of age.

A total of 13 patients received a single total dose of 1.8×10^{11} vg of KEBILIDI given as four intraputaminal infusions in a single stereotactic neurosurgical procedure. The demographic characteristics of the population were as follows: the median age was 2.8 years (1.3 to 10.8 years), 7 patients (54%) were female, 10 patients (77%) were Asian, 2 patients (15%) were White, and 1 patient was of "other" race. Twelve of the 13 patients had the severe phenotype of AADC deficiency, defined as having no motor milestone achievement at baseline and no clinical response to standard of care therapies. The one remaining patient had a "variant" of the severe disease phenotype, with the ability to sit with assistance but with lack of head control.

The primary safety outcome of the study was the assessment of adverse events (AEs) at the end of the trial phase (8 weeks after administration). None of the treatment-emergent adverse events (TEAEs) reported during the study were considered to be related to the SmartFlow Neuro Cannula. Twenty-one (21) AEs in 8 subjects were considered possibly or probably related to the neurosurgical procedure, the most common being pyrexia (see table 2). No events were serious; all were mild or moderate. All events resolved, with the exception of 2 events that were ongoing at the time of reporting (1 event of skin pressure mark, 1 event of anemia).

Table 2: Summary of Treatment-Emergent Adverse Events (TEAEs)

System Organ Class **Preferred Term**	**Number of Subjects (%)** **(N=13)**
Total number of TEAEs potentially related to the surgical procedure	21
Number of subjects with at least one TEAE potentially related to the surgical procedure	8 (61.5)
Blood and lymphatic system disorders	1 (7.7)
Anemia	1 (7.7)
Cardiac disorders	1 (7.7)
Tachycardia	1 (7.7)

Eye disorders	**2 (15.4)**
Oculogyric crisis	1 (7.7)
Periorbital oedema	1 (7.7)
Gastrointestinal disorders	**1 (7.7)**
Gastrointestinal hemorrhage	1 (7.7)
General disorders and administration site conditions	**4 (30.8)**
Face edema	1 (7.7)
Injury associated with device	1 (7.7)
Pyrexia	4 (30.8)
Injury, poisoning and procedural complications	**1 (7.7)**
Post procedural hypotension	1 (7.7)
Skin pressure mark	1 (7.7)
Investigations	**1 (7.7)**
Alanine aminotransferase increased	1 (7.7)
Aspartate aminotransferase increased	1 (7.7)
Metabolism and nutrition disorders	**1 (7.7)**
Hypophosphatemia	1 (7.7)
Psychiatric disorders	**1 (7.7)**
Insomnia	1 (7.7)
Vascular disorders	**3 (23.1)**
Hypotension	3 (23.1)

There were no AEs of dyskinesia, which was specified in the clinical protocol as an AE of interest to assess, related to the SmartFlow Neuro Cannula. There were also no AEs of CSF leaks reported, and no evidence found in brain imaging assessments post-operative. There was no intracerebral hemorrhage present or CSF leak in any subject during the surgical procedure as assessed by intraoperative MRI. A computed tomography (CT) scan immediately following surgery was normal for all but 1 subject, and no evidence of acute CSF leak or hemorrhage was seen. No deaths occurred during the study.

More detailed information on the complete clinical study outcomes for both the SmartFlow Neuro Cannula and the biologic product can be found in the KEBILIDI (eladocagene exuparvovec-tneq) Biologics License Application (BLA) #125722 public decision documents.

LABELING

The labeling includes instructions for use for the physician and satisfies the requirements of 21 CFR § 801.109 for prescription devices. The labeling also includes:

- Detailed instructions on proper device preparation and placement.
- Detailed description of the device technical parameters, including physical dimensions and priming volume.
- A shelf life.

PEDIATRIC USE

The safety and effectiveness of the SmartFlow Neuro Cannula and KEBILIDI have been established in pediatric patients. The use of the SmartFlow Neuro Cannula and KEBILIDI was evaluated in a single-arm, open-label study that enrolled 13 pediatric patients aged 16 months to 10 years who had achieved skull maturity with AADC deficiency.

The safety and effectiveness of the SmartFlow Neuro Cannula and KEBILIDI have not been studied in pediatric patients younger than 16 months. No pediatric extrapolation has been performed.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a brain intraparenchymal infusion cannula and the measures necessary to mitigate these risks.

Risks to Health	**Mitigation Measures**
Product failure leading to: • Inability to deliver the therapy or incorrect location of the therapy administration • Inaccurate dosing of the therapy • Disease progression	In vivo performance testing Non-clinical performance testing Labeling
Adverse tissue reaction	In vivo performance testing Biocompatibility evaluation
Tissue injury resulting from • Device breakage • Use error	In vivo performance testing Non-clinical performance testing Human factors/usability testing Labeling
Infection	Sterilization validation Shelf life testing Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the brain intraparenchymal infusion cannula is subject to the following special controls:

(1) In vivo performance testing must demonstrate that the device performs as intended to deliver the intended dosage of the therapy and evaluate all adverse effects, including adverse tissue reaction and tissue injury.

(2) Non-clinical performance testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be evaluated:
   (i) A characterization of the therapy distribution profile in the intended brain parenchyma location, including infusate reflux and dose accuracy;

(ii) Device compatibility with the therapy or analog, including:
  (A) Leachables characterization of the device;
  (B) Particulate testing of the device;
  (C) Characterization of therapy or analog adsorption and aggregation by the device;
  (D) Therapy potency and quality testing; and
  (E) Functional compatibility with other devices intended to be used during the procedure;

(iii) A characterization of the brain intraparenchymal target placement accuracy in a clinically-relevant phantom compared to a pre-procedure plan; and

(iv) Mechanical testing:
  (A) Tensile strength;
  (B) Compressive strength;
  (C) Maximum infusion pressure (burst); and
  (D) Leakage.

(3) Human factors/usability testing must demonstrate that the intended user(s) in the intended use environment can correctly and safely use the device in a clinically-relevant workflow following the instructions for use.

(4) The patient-contacting components of the device must be demonstrated to be biocompatible.

(5) Performance data must demonstrate the sterility of all patient-contacting components of the device.

(6) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(7) Labeling must include:
  (i) Detailed description of the device technical parameters, including physical dimensions and priming volume; and
  (ii) A shelf life.

BENEFIT/RISK DETERMINATION

The risks of the device are based on data collected in a clinical study, animal studies, and nonclinical laboratories studies described above. The risks of the SmartFlow Neuro Cannula are inability to deliver the therapy or incorrect location of the therapy administration, inaccurate dosing of the therapy, and/or disease progression. These risks could occur from improper device use. Further, very little data are available for use of the SmartFlow NeuroCannula in very young pediatric patients. The clinical study enrolled a small number of patients (n=13) and the median age was 2.8 years (1.3 to 10.8 years), and so there is outstanding uncertainty related to the risks for very young pediatric patients. Labeling serves to mitigate this risk, with information not to use the SmartFlow NeuroCannula in individuals in whom the cranium is not sufficiently developed to allow stable placement of the stereotactic head frame for surgery.

The probable benefits of the device are also based on data collected in nonclinical laboratory, animal, and clinical studies as described above. The benefits of the device are to safely and effectively deliver the appropriate dose of the biologic product to the target location in the brain parenchymal tissue for patients with AADC deficiency.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The SmartFlow Neuro Cannula, when used with compatible stereotaxic and therapeutic delivery devices, is indicated for intraputaminal administration of eladocagene exuparvovec-tneq for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.

The probable benefits outweigh the probable risks for the SmartFlow Neuro Cannula. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the SmartFlow Neuro Cannula is granted and the device is classified under the following:

Product Code: SDG
Device Type: Brain intraparenchymal infusion cannula
Class: Class II
Regulation: 21 CFR 882.4110