Physician Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Upstaza

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Eladocagene exuparvovec is a gene therapy medicinal product that expresses the human aromatic L-amino acid decarboxylase enzyme (hAADC). It is a non-replicating recombinant adeno-associated virus serotype 2 (AAV2) based vector containing the cDNA of the human dopa decarboxylase (DDC) gene under the control of the cytomegalovirus immediate-early promoter.

Eladocagene exuparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each single-dose vial contains 2.8×10^{11} vector genomes (vg) of eladocagene exuparvovec in 0.5 extractable mL of solution. Each mL of solution contains 5.6×10^{11} vg of eladocagene exuparvovec.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Following thaw from frozen, the solution for infusion is a clear to slightly opaque, colourless to faint-white liquid.

Patient Alert card
The marketing of UPSTAZA is subject to a Risk management plan (RMP) including a 'patient Alert card'. The 'patient Alert card', emphasizes important safety information that the patient should be aware of before and during the treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Upstaza is indicated for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency with a severe phenotype (see section 5.1).

4.2 Posology and method of administration

Treatment should be administered in a centre which is specialised in stereotactic neurosurgery, by a qualified neurosurgeon under controlled aseptic conditions.

Posology

Patients will receive a total dose of 1.8×10^{11} vg delivered as four 0.08 mL (0.45×10^{11} vg) infusions (two per putamen).

The posology is the same for the entire population covered by the indication.

Special populations

Paediatric population
The safety and efficacy of eladocagene exuparvovec in children aged below 18 months have not yet been established. No data are available.
There is limited experience in patients aged 12 years and older. The safety and efficacy of eladocagene exuparvovec in these patients have not been established. Currently available data are described in section 5.1. No dose adjustment should be considered.

Hepatic and renal impairment
The safety and efficacy of eladocagene exuparvovec in patients with hepatic and renal impairment have not been evaluated.

Immunogenicity
There is no safety or efficacy data for patients whose pre-treatment neutralising antibody levels to AAV2 was > 1:20 (see section 4.4).

Method of administration

Intraputaminal use.

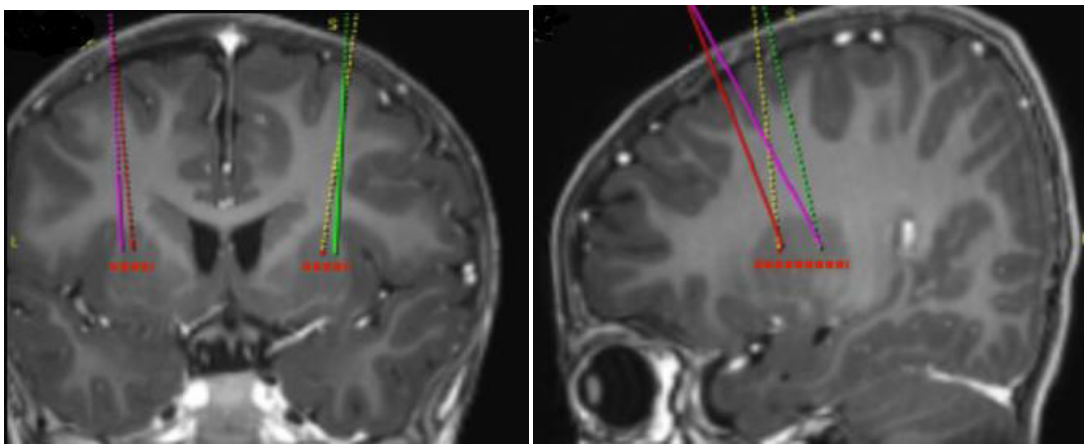
Preparation
Upstaza is a sterile solution for infusion that requires thawing and preparation by the hospital pharmacy prior to administration.

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Upstaza, see section 6.6.

Neurosurgical administration
Upstaza is a single use vial administered by bilateral intraputaminal infusion in one surgical session at two sites per putamen. Four separate infusions of equal volumes are performed to the right anterior putamen, right posterior putamen, left anterior putamen, and left posterior putamen.
For instructions on preparation of the surgical suite infusion of Upstaza, see section 6.6.

The target infusion sites are defined per standard stereotactic neurosurgical practice. Upstaza is administered as a bilateral infusion (2 infusions per putamen) with an intracranial cannula. The final 4 targets for each trajectory should be defined as 2 mm dorsal to (above) the anterior and posterior target points in the mid-horizonal plane (Figure 1).

Figure 1 Four target points for infusion sites



- After stereotactic registration is complete, the entry point on the skull should be marked. Surgical access through the skull bone and dura should be performed.

- The infusion cannula is placed at the designation point in the putamen using stereotactic tools based on the trajectories planned. Of note, the infusion cannula is placed and infusion performed separately for each putamen.

- Upstaza is infused at a rate of 0.003 mL/min at each of the 2 target points in each putamen; 0.08 mL of Upstaza is infused per putaminal site resulting in 4 infusions with a total volume of 0.320 mL (or 1.8×10^{11} vg).

- Starting with the first target site, the cannula is inserted through a burr hole into the putamen and then slowly withdrawn, distributing the 0.08 mL of Upstaza across the planned trajectory to optimise distribution across the putamen.

- After the first infusion, the cannula is withdrawn and then re-inserted at the next target point, repeating the same procedure for the other 3 target points (anterior and posterior of each putamen).

- After standard neurosurgical closure procedures, the patient then undergoes a postoperative computerised tomography imaging examination to ensure there are no complications (ie, bleeding).

- The patient must reside within the vicinity of the hospital where the procedure was performed for a minimum of 48 hours following the procedure. The patient may return home, post-procedure, based on treating physician's advice. The post-treatment care should be managed by neurosurgeon and the referring neurologist. The patient should have a follow-up 7 days after surgery to ensure that no complications have developed. A second follow-up visit should take place 2 weeks later (ie, 3 weeks after the surgery) to monitor post-surgical recovery and occurrence of adverse events.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Proper aseptic techniques should always be used for the preparation and infusion of Upstaza.

<u>Monitoring</u>

Patients undergoing gene therapy should be closely monitored for procedure-related complications, complications related to their underlying disease, and risks associated with general anaesthesia during the peri-operative period. Patients may experience exacerbations of symptoms of their underlying AADC deficiency as a result of surgery and anaesthesia (see section 4.8).

Autonomic and serotonergic symptoms of AADC may persist after treatment with eladocagene exuparvovec.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Immunogenicity

Experience with eladocagene exuparvovec in patients with anti-AAV2 antibody levels > 1:20 prior to treatment is not available.

Cerebrospinal fluid leaks

Cerebrospinal fluid (CSF) leaks occur when there is a tear or hole in the meninges surrounding the brain or spinal cord, allowing the CSF to escape. Upstaza is administered by bilateral intraputaminal infusion using burr holes, therefore, CSF leak may occur postoperatively. Patients undergoing eladocagene exuparvovec treatment should be carefully monitored after administration for CSF leaks, particularly in relation to the risk of meningitis and encephalitis.

Dyskinesia

AADC-deficient patients may have increased sensitivity to dopamine due to their chronic dopamine deficiency. Dyskinesia has been reported in 26/30 patients after treatment with eladocagene exuparvovec (see section 4.8). The occurrence of dyskinesia is due to dopamine sensitivity and generally starts 1 month after the administration of gene therapy and gradually decreases over several months. Events of dyskinesia were managed with routine medical care, such as antidopaminergic treatment (eg, risperidone) (see section 5.1).

Risk of viral shedding

The risk of shedding is considered to be low due to very limited systemic distribution of eladocagene exuparvovec (see section 5.2). As a precautionary measure, patients/caregivers should be advised to handle waste material generated from dressings and/or any secretions (tears, blood, nasal secretions, and CSF) appropriately, which may include storage of waste material in sealed bags prior to disposal and patients/caregivers wearing gloves for dressing changes and waste disposal. These handling precautions should be followed for 14 days after administration of eladocagene exuparvovec. It is recommended that patients/caregivers wear gloves for dressing changes and waste disposal, especially in case of pregnancy, breast-feeding, or immunodeficiency of caregivers.

Blood, organ, tissue, and cell donation

Patients treated with Upstaza must not donate blood, organs, tissues, and cells for transplantation.

Sodium and potassium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
This medicinal product contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No interaction is expected due to very limited systemic distribution of eladocagene exuparvovec.

Vaccinations

There has been no reported interaction between general vaccinations and gene therapy administration. The health care provider should determine if adjustments to the patient's vaccination schedule are necessary.

4.6 Fertility, pregnancy and lactation

Based on the lack of systemic exposure and negligible biodistribution to the gonads, the risk for germline transmission is low.

Pregnancy

There are no data from the use of eladocagene exuparvovec in pregnant women. Animal reproductive studies have not been conducted with eladocagene exuparvovec (see section 5.3).

Breast-feeding

It is unknown whether eladocagene exuparvovec is excreted in human milk.
Eladocagene exuparvovec is not absorbed systemically following intraputaminal administration, and no effect on the breastfed newborns/infants are anticipated.

Fertility

There are no clinical or nonclinical data available regarding the effect of eladocagene exuparvovec on fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The safety information was observed in 3 open-label clinical studies in which eladocagene exuparvovec was administered to 30 AADC-deficient patients aged 19 months to 8.5 years at the time of dosing. Patients were followed for a median duration of 59.3 months (minimum of 11.8 months to a maximum of 5.7 years). Twenty-six patients treated in the clinical studies enrolled in a long-term follow-up study. The duration of follow-up from the time of gene therapy ranged from 27.2 to 126.5 months (approximately 2 to 10.5 years).
The most common adverse reaction was dyskinesia; it was reported in 26 (86.7%) patients and was prevalent during the first 2 months post-treatment.

Tabulated list of adverse reactions

The adverse reactions are reported in Table 1. The adverse reactions are listed by system organ class and frequency using the following convention: very common (≥ 1/10), common ≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1 Adverse reactions occurring in ≥ 2 patients in 3 open-label clinical studies (n = 30)

System organ class	Very common	Common
Metabolism and nutrition disorders		Feeding disorders
Psychiatric disorders	Initial insomnia	Irritability
Nervous system disorders	Dyskinesia	
Gastrointestinal disorders		Salivary hypersecretion

Table 2 Neurosurgery-related adverse reactions occurring in ≥ 2 patients in 3 open-label clinical studies (n=30)

Adverse reaction category	Very common
Blood and lymphatic system disorders	Anaemia
Nervous system disorders	Cerebrospinal fluid leakage[a]

[a] May include pseudomeningocele

Table 3 Anaesthesia and postoperative related adverse reactions in ≥ 2 patients within ≤ 2 weeks after administration, in 3 open label clinical studies (n=30)

Adverse reaction category	Very common	Common
Infections and infestations	Pneumonia	Gastroenteritis
Metabolism and nutrition disorders	Hypokalaemia	
Psychiatric disorders	Irritability	
Nervous system disorders		Dyskinesia
Cardiac disorders		Cyanosis
Vascular disorders	Hypotension	Hypovolemic shock
Respiratory, thoracic and mediastinal disorders		Respiratory failure
Gastrointestinal disorders	Upper gastrointestinal haemorrhage, Diarrhoea	Mouth ulceration
Skin and subcutaneous tissue disorders	Decubitus ulcer	Dermatitis diaper, Rash
General disorders and administration site conditions	Pyrexia Breath sounds abnormal	Hypothermia
Surgical and medical procedure		Tooth extraction

Description of selected adverse reactions

Dyskinesia
Events of dyskinesia were reported in 26 (86.7%) subjects (see section 4.4).
Of the 37 events of dyskinesia, 35 events were mild to moderate and 2 were severe. The majority of events resolved in approximately 2 months, and all resolved within 7 months from symptom onset. The mean time to onset of events of dyskinesia was 25 days after receiving gene therapy. Events of dyskinesia were managed with routine medical care, such as anti-dopaminergic treatment.

Immunogenicity
Patients with titres of anti-AAV2 antibodies <1:1200 were allowed to participate in the clinical studies. However, all patients that received eladocagene exuparvovec had anti-AAV2 titres at or below 1:20 before treatment. Following treatment, most subjects (n = 18) were positive for anti-AAV2 antibodies at least once within the first 12 months. In general, antibody levels stabilised or declined with time. There was no specific follow up program to capture potential immunogenicity reactions in any of the clinical studies, but presence of anti-AAV2 antibodies in the clinical studies was not reported to be associated with increase in severity, number of adverse reactions, or with decreased efficacy.
Experience with eladocagene exuparvovec in patients with anti-AAV2 antibody levels > 1:20 prior to treatment is not available.
The immune response to the transgene and the cellular immune response were not measured.

Cerebrospinal fluid leaks
Three patients who received eladocagene exuparvovec in clinical studies experienced CSF leaks. One patient reported two separate events as serious adverse events potentially related to the surgical procedure whereas all other events were nonserious.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il .

4.9 Overdose

The risk of overdose is unlikely due to controlled and neurosurgical administration. There is no clinical experience with overdose of eladocagene exuparvovec. Symptomatic and supportive treatment, as deemed necessary by the treating physician, is advised in case of overdose. Close clinical observation and monitoring of laboratory parameters (including complete blood count with differential, and comprehensive metabolic panel) for systemic immune response are recommended. For instructions in case of accidental exposure, see section 6.6.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Enzymes; ATC code: A16AB26

Mechanism of action

AADC deficiency is an inborn error of neurotransmitter biosynthesis with an autosomal recessive inheritance in the dopa decarboxylase (*DDC*) gene. The *DDC* gene encodes the AADC enzyme, which converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine. Mutations in the *DDC* gene result in reduction or absence of AADC enzyme activity, causing a reduction in the levels of dopamine and the failure of most patients with AADC deficiency to achieve developmental milestones.

Eladocagene exuparvovec is a gene therapy based on recombinant AAV2 vector containing the human cDNA for the *DDC* gene. After infusion into the putamen, the product results in the expression of the AADC enzyme and subsequent production of dopamine, and consequently, development of motor function in treated AADC-deficient patients.

Pharmacodynamic effects

L-6-[^{18}F] fluoro-3, 4-dihydroxyphenylalanine (^{18}F-DOPA) uptake in central nervous system (CNS)
Measurement of ^{18}F-DOPA uptake in the putamen via positron emission tomography (PET) imaging following treatment is an objective measurement of de novo dopamine production in the brain and assesses the success and stability of the *DDC* gene transduction over time. Most patients demonstrated small, sustained increases in PET-specific uptake. An increase was evident as early as 6 months, was further increased by 12 months after treatment, and sustained at least for 5 years.

Table 4 Percent change from baseline in uptake of ^{18}F-DOPA after Eladocagene Exuparvovec treatment (Studies AADC-010 and AADC-011)

Timepoint	Month 12 (n=19)	Month 24 (n=17)	Month 60 (n=11)
PET specific uptake **% Change from baseline**	220.3	261.39	287.88

Clinical efficacy and safety

The efficacy of Upstaza gene therapy was assessed in 2 clinical studies (AADC-010, AADC-011). Together, these 2 studies included 22 patients with severe AADC deficiency, diagnosed by decreased homovanillic acid and 5-hydroxyindoleacetic acid and elevated L-DOPA CSF levels, the presence of *DDC* gene mutation in both alleles, and the presence of clinical symptoms of AADC deficiency (including developmental delay, hypotonia, dystonia, and oculogyric crisis [OGC]). These patients had not achieved motor development milestones at baseline including the ability to sit, stand, or walk, compatible with the severe phenotype. Patients were treated with a total dose of 1.8×10^{11} vg (N = 13) or 2.4×10^{11} vg (N = 9) during a single operative session. The results for efficacy and safety parameters were similar between the 2 doses.
Data beyond the Month 60 and Month 12 timepoints in Study AADC-010 and Study AADC-011, respectively, were collected in the long-term follow-up Study AADC-1602 as indicated below, with a data cutoff date of 16 June 2023.
Study AADC-CU/1601 was conducted with treatment from an older manufacturing process. This study enrolled 8 subjects and demonstrated similar results with benefits maintained up to 126.5 months.

Motor function
Motor milestone achievement was derived from the Peabody Developmental Motor Scale, version 2 (PDMS-2). The PDMS-2 is an assessment of a child's motor development up to the developmental age of 5, and assesses both gross and fine motor skills, and with items that specifically capture motor milestone achievement. The PDMS-2 motor skill items were chosen to determine the number of patients who achieved at least the following motor milestones (Mastery of the skill – score of 2): 1) full head control (sitting supported at his/her hips and holding his/her head aligned while rotating his/her head to follow a toy for 8 seconds), 2) sitting unassisted (sit without support and maintain balance while in a sitting position for 60 seconds), 3) standing with support (take at least 4 alternating steps, either in place or in forward motion, with the evaluator's hands around the child's trunk), and 4) walking assisted (walk at least 8 feet with alternating steps, with the evaluator beside the patient and holding only one of the child's hands).

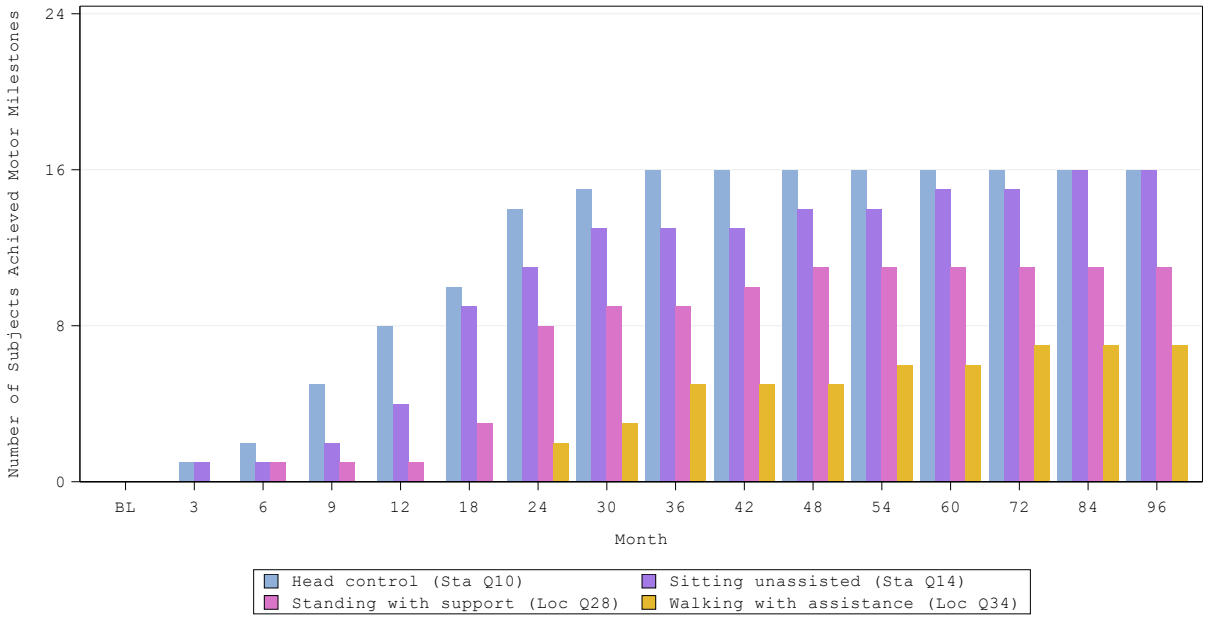
Table 5 summarizes the primary analysis, which evaluated the number of patients who demonstrated acquisition of the key motor milestones (Mastery), at 24 months, 60 months and 96 months after gene therapy.

Treatment with eladocagene exuparvovec demonstrated acquisition of motor milestones observed as early as 3 months post-surgery. Key motor milestone acquisition was continued or maintained beyond 24 months and up to 96 months, corresponding to 8 years follow-up (Figure 2).

Table 5 Cumulative number of subjects achieving new PDMS-2 motor milestones (Mastery) at month 24, month 60, and month 96) (Studies AADC-010, AADC-011, and AADC-1602; N=22)

Motor Milestone/ Month	Number of Subjects (%)		
	Month 24	Month 60	Month 96
Full head control	14 (64)	16 (73)	16 (73)
Sitting unassisted	11 (50)	15 (68)	16 (73)
Standing with support	8 (36)	11 (50)	11 (50)
Walking with assistance	2 (9)	6 (27)	7 (32)

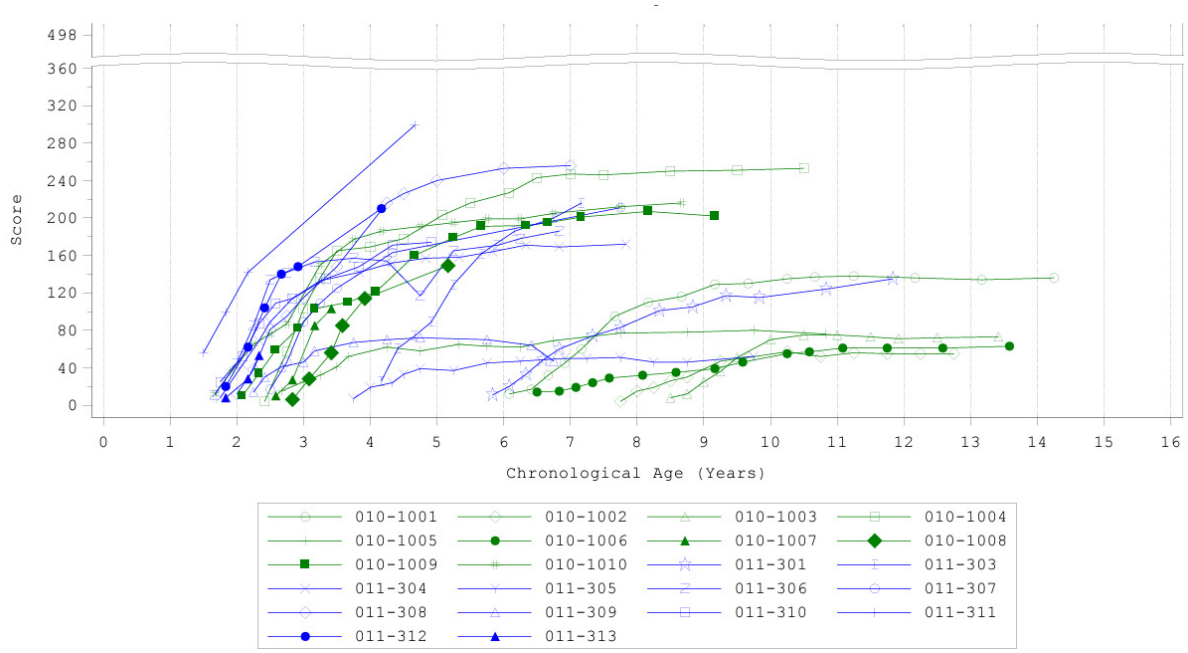
Figure 2 Cumulative number of subjects demonstrating motor milestone (mastery skill) up to Month 96 (Studies AADC-010, AADC-011, and AADC-1602)



PDMS-2 total score

PDMS-2 total score was measured as a secondary endpoint throughout the clinical studies. PDMS-2 maximal scores are 450-482, depending on age (<12 months or > 12 months). All subjects treated with eladocagene exuparvovec showed increases from baseline in mean PDMS-2 total scores over time, with some benefit observed as early as 3 months (Figure 3). At the 24-month timepoint, the least squares (LS) mean of change from baseline in PDMS-2 total score was 111.2 points. Improvement from baseline in PDMS-2 total score was as early as 12 months after treatment (77.6 points) and was maintained to 60 months (139.0 points) and 96 months (141.6 points). Patients who receive eladocagene exuparvovec at a younger age demonstrate a faster treatment response and appear to reach a higher final level.

Figure 3 PDMS-2 total scores by visit – through Month 96 (Studies AADC-010, AADC- 011, and AADC-1602; N=22)



The following data were collected as secondary endpoints in the clinical studies.

Cognitive and communication skills
Bayley-III, a standard assessment of cognition, language, and motor development for, infants and toddlers (1-42 months of age), was utilized in Studies AADC-010 and AADC-011 to assess cognitive and language development. The language subscale consists of receptive and expressive communications.

Over time, all subjects showed gradual and sustained increases in mean cognitive and total language scores, which is the combined score for receptive and expressive communication scores. The mean raw total score for cognitive subscale at baseline was 12.41 (N=22). The LS mean change from baseline in cognitive score showed an increase of 12.3 at Month 12, 16.4 at Month 24, and 23.6 at Month 60. The mean raw total score for language subscale at baseline was 18.09 (N=22). The LS mean change from baseline in total language score showed an increase of 7.6 at Month 12, 10.1 at Month 24, and 14.9 at Month 60.

Body weight
Eighteen out of 19 subjects (95%) maintained (47%, 9 subjects) or increased (47%, 9 subjects) their body weight over a 12-month period based on gender and age specific growth chart.

Floppiness (hypotonia) limb dystonia, stimulus-provoked dystonia
Following gene therapy, the percentage of subjects with symptoms of floppiness (hypotonia) decreased from 55.0% at baseline (N=22) to 23.5% at Month 12 (N = 17). No subject experienced limb dystonia 12 months post-treatment, compared with 40.0% subjects at baseline (N = 22).

OGC episodes
Following gene therapy, the duration of OGC episodes, was reduced and sustained over time and up to 12 months after treatment. The mean time in OGC was 11.90 hours/week at baseline (N=21). This time was reduced following treatment by 1.39 hours per week by Month 3 (N=19) and by 4.82 hours per week by Month 12 (N=6).

The magnitude of the effect of eladocagene exuparvovec on the autonomic symptoms of the AADC deficiency has not been systematically evaluated.

5.2 Pharmacokinetic properties

No pharmacokinetic studies with eladocagene exuparvovec have been conducted. Eladocagene exuparvovec is infused directly into the brain and has not been shown to distribute outside the CNS.

Distribution

The biodistribution of the AAV2-hAADC viral vector in blood and urine was measured in subjects using a validated real-time quantitative polymerase chain reaction assay. In one subject treated with eladocagene exuparvovec, very low levels, far below treatment concentrations, have been detected in urine at Month 6.

5.3 Preclinical safety data

No animal studies have been conducted to evaluate the effects of eladocagene exuparvovec on carcinogenesis, mutagenesis, or impairment of fertility. In animal studies, no toxicological effects on male or female reproductive organs were observed.

No toxicity was shown in rats up to 6 months following bilateral infusion into the putamen at doses 21 times higher than the human therapeutic dose on a vg per unit of brain weight (g) basis.

Studies in rats showed no viral shedding in blood or any systemic tissues outside of the CNS compartment except for CSF at day 7 where it was positive (copies/µg DNA) in the 6-month toxicology study. When tested at subsequent time points (day 30, day 90 and day 180) all samples were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium hydrogen phosphate
Potassium chloride
Potassium dihydrogen phosphate
Poloxamer 188
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened frozen vial

The expiry date of the product is indicated on the packaging materials.

After thawing and opening

Once thawed, the medicinal product should not be re-frozen.
The filled syringe prepared under aseptic conditions for delivery to the surgical site should be used immediately; if not used immediately, it can be stored at room temperature (below 25°C) and used within 6 hours of starting product thaw.

6.4 Special precautions for storage

Store and transport frozen at ≤ -65° C.
Keep the vial in the outer carton.
For storage conditions after thawing and opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I borosilicate glass vial, with a siliconised chlorobutyl stopper with coating sealed with an aluminium/plastic cap.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

Each vial is for single use only. This medicinal product should only be infused with the SmartFlow ventricular cannula.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified virus. During preparation, administration, and disposal, personal protective equipment (including gown, safety glasses, mask, and gloves) should be worn when handling eladocagene exuparvovec and materials that have been in contact with the solution (solid and liquid waste).

Thawing in the hospital pharmacy

- Upstaza is delivered to the pharmacy frozen and must be maintained in the outer carton at ≤ -65 ºC until prepared for use.
- Upstaza should be handled aseptically under sterile conditions.
- Allow the frozen vial of Upstaza to thaw upright at room temperature until the content is completely thawed. Gently invert the vial approximately 3 times, do NOT shake.
- Inspect Upstaza after mixing. If particulates, cloudiness, or discolouration are visible, do not use the product.

Preparation prior to administration

- Transfer the vial, syringe, needle, syringe cap, sterile bags, or sterile wrappings compliant with hospital procedure for transfer and use of the filled syringe in the planned surgical suite, and label into the Biological Safety Cabinet (BSC). Wear sterile gloves and other personal protective equipment (including gown, safety glasses and mask) as per normal procedure for BSC work.
- Open the 1 mL or 5 mL syringe [1 mL or 5 mL, polypropylene syringes with latex-free elastomer plunger, lubricated with -medical grade- silicone oil] and label as the product-filled syringe per pharmacy procedure and local regulations.
- Attach the 18- or 19-gauge filter needle [18- or 19-gauge, 1.5-inch, stainless steel, 5-µm filter needles] to the syringe.
- Draw the full volume of the vial of Upstaza into the syringe. Invert the vial and syringe and partially withdraw or angle the needle as necessary to maximise recovery of product.
- Draw air in the syringe so that the needle is emptied of product. Carefully remove the needle from 1 mL or 5 mL syringe containing Upstaza. Purge the air from the syringe until there is no air bubble and then cap with a syringe cap.
- Wrap the syringe in one sterile plastic bag (or several bags based on standard hospital procedure) and place in an appropriate secondary container (eg, hard plastic cooler) for delivery

to the surgical suite at room temperature. Use of the syringe (ie, connecting the syringe to the syringe pump and starting priming of the cannula) should begin within 6 hours of starting product thaw.

Administration in the surgical suite

- Tightly connect the syringe containing Upstaza to the SmartFlow ventricular cannula.
- Install the Upstaza syringe into a syringe infusion pump compatible with the 1 mL or 5 mL syringe. Pump Upstaza with the infusion pump at 0.003 mL/min until the first drop of Upstaza can be seen from the tip of the needle. Stop and wait until ready for infusion.

Precautions to be taken for the disposal of the medicinal product and accidental exposure

- Accidental exposure to eladocagene exuparvovec, including contact with skin, eyes, and mucous membranes, is to be avoided.
- In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 5 minutes. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 5 minutes.
- In the event of needlestick injury, the affected area must be cleaned thoroughly with soap and water and/or a disinfectant.
- Any unused eladocagene exuparvovec or waste material should be disposed of in compliance with local guidance for pharmaceutical waste. Potential spills should be wiped with absorbent gauze and disinfected using a bleach solution followed by alcohol wipes.
- After administration, the risk of shedding is considered to be low. It is recommended that caregivers and patient families are advised on and follow proper handling precautions of patient bodily fluids and waste for 14 days after administration of eladocagene exuparvovec (see section 4.4).

7. MANUFACTURER

PTC Therapeutics International Limited
70 Sir John Rogerson's Quay,
Dublin 2,
Ireland

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach Street, P.O.B. 7090
Petach Tikva
Israel

9. REGISTRATION NUMBER:

175-66-37437-00
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