MEDISON

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אפריל 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

הריני להודיעכם כי העלון לרופא של התכשיר עודכן:

Upstaza **אפסטזה**

Solution for infusion

eladocagene exuparvovec : **מרכיב פעיל**

התוויה מאושרת :

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.

להלן העדכונים בעלון לרופא המהווים החמרות (הוספה בכחול ומחיקה באדום):

4.4 Special warnings and precautions for use

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~~, increase in dyskinesia have been reported in 24/28 patients~~ (see section 4.8). The occurrence ~~increase~~ of dyskinesia is due to ~~this~~ 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, ~~The use of dopamine antagonists (~~risperidone) ~~may be considered to control dyskinesia symptoms~~ (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

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.~~Vaccination schedule should proceed as normal.~~

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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 ~~28~~ 30 AADC-deficient patients aged 19 months to 8.5 years at the time of dosing. Patients were followed for a median duration of ~~52~~59.3 months (minimum of ~~3.1~~11.8 months to a maximum of ~~9.63~~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 ~~24~~ 26 (~~85~~86.7%) patients and was prevalent during the first 2 months post-treatment.

[...]

Table 1 Adverse reactions occurring in ≥ 2 patients in 3 open-label clinical studies (n = ~~28~~30)

System organ class	Very common	Common
Metabolism and nutrition disorders		Feeding disorders
Psychiatric disorders	Initial insomnia~~, irritability~~	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=~~28~~30)

[...]

Table 3 Anaesthesia and postoperative related adverse reactions in ≥ 2 patients within ≤ 2 weeks after administration, in 3 open label clinical studies (n=~~28~~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	~~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 ~~24~~ 26 (~~85~~86.7%) subjects (see section 4.4).
Of the ~~35~~ 37 events of dyskinesia, ~~33~~ 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~~.8~~ days after receiving gene therapy. Events of dyskinesia were managed with routine medical care, such as anti-dopaminergic treatment.

Immunogenicity

Patients with titres ~~Titres~~ of anti-AAV2 antibodies <1:1200 were allowed to participate ~~measured pre- and post-gene therapy~~ in the clinical studies. However, all ~~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.

4.9 Overdose

The risk of overdose is unlikely due to controlled and neurosurgical administration.

5.1 Pharmacodynamic properties

Table 4 **Percent change from baseline in ~~PET specific~~ uptake of ^{18}F-DOPA after ~~eladocagene~~ Eladocagene ~~exuparvovec~~ Exuparvovec treatment (Studies AADC-010 and~~,~~ AADC-011)**

Timepoint	~~Change from baseline~~	~~Change from baseline~~	~~Change from baseline~~

	Month 12 (n=~~17~~19)	Month 24 (n=~~15~~17)	Month 60 (n=~~4~~11)
PET specific uptake **% Change from baseline**	220.3~~0.32~~	261.39~~0.36~~	287.88~~0.39~~

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 ~~20~~ 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 = ~~7~~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 ~~60~~ 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 ~~, and~~ 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).~~) walking assisted.~~

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.~~Table 5 summarises patient motor milestone achievement at specific timepoints during the first 60 months following treatment administration and cumulatively throughout the entire clinical programme. The primary~~

~~efficacy endpoint was assessed at 24 months after gene therapy. Not all subjects reached the timepoints specified in the Table 5 at the time of data cut.~~

Treatment with eladocagene exuparvovec demonstrated acquisition of motor milestones observed as early as ~~12~~ 3 months post-surgery. Key motor milestone acquisition was continued or maintained beyond 24 months and up to ~~60~~ 96 months, corresponding to 8 years follow-up (Figure 2).

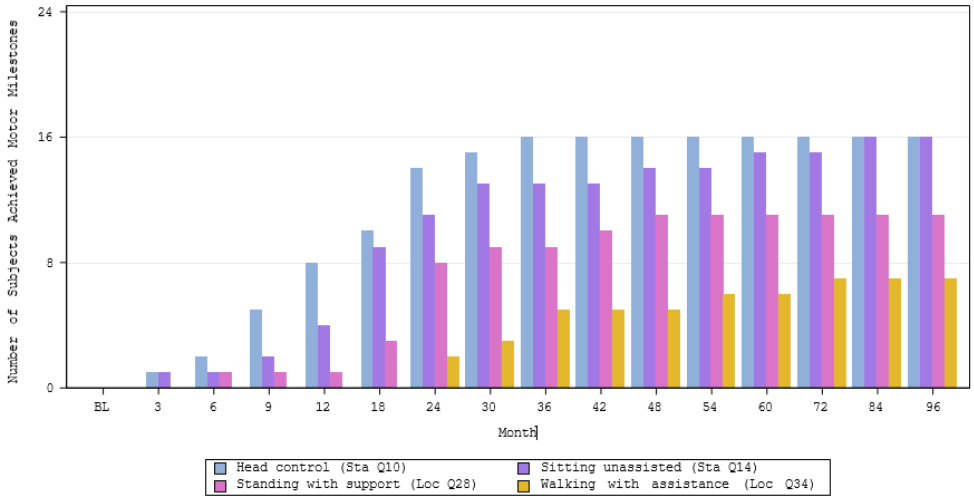
Table 5 **Cumulative number ~~Number~~ of ~~patients~~ subjects achieving new PDMS-2 motor milestones (~~mastery of the skill – score 2) after eladocagene exuparvovec treatment~~Mastery) at month 24, month 60, and month 96) ~~(mastery of the skill – score 2) after eladocagene exuparvovec treatment~~ (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)

	~~Baseline~~	~~Time interval post-treatment (months)~~						~~Overall (cumulative) post-treatment~~
~~Motor milestone~~	~~Pre-treatment N = 20~~	~~0 to 3 N = 20~~	~~3 to 12 N = 17~~	~~12 to 24 N = 17~~	~~24 to 36 N = 13~~	~~36 to 48 N = 8~~	~~48 to 60 N = 6~~	~~60 months N = 20~~
~~Head control~~	~~0~~	~~1~~	~~5~~	~~6~~	~~2~~	~~0~~	~~0~~	~~14 (70%)~~
~~Sitting unassisted~~	~~0~~	~~1~~	~~2~~	~~6~~	~~2~~	~~1~~	~~1~~	~~13 (65%)~~
~~Standing with support~~	~~0~~	~~0~~	~~0~~	~~4~~	~~1~~	~~1~~	~~0~~	~~6 (30%)~~
~~Walking with support~~	~~0~~	~~0~~	~~0~~	~~0~~	~~2~~	~~0~~	~~0~~	~~2 (10%)~~

Figure 1 Cumulative number of subjects demonstrating motor milestone (mastery skill) up to Month 96 (Studies AADC-010, AADC-011, and AADC-1602)~~Mean PDMS-2 total scores by visit – through month 60 (Studies AADC-010, AADC-011)~~

~~Note: Cumulative column includes all subjects who achieved that particular milestone at any point during the clinical study up to 60 months; Patients needed to reach the score of 2 (indicative of mastery of the skill) on a milestone item to be rated as having achieved that milestone.~~



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 ~~2~~3). At the 24-month timepoint, the least squares (LS) mean of change from baseline in PDMS-2 total score was ~~104.4~~111.2 points. Improvement from baseline in PDMS-2 total score was as early as 12 months after treatment (~~76.1~~77.6 points) and was maintained to 60 months (~~108~~139.~~2~~ 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)

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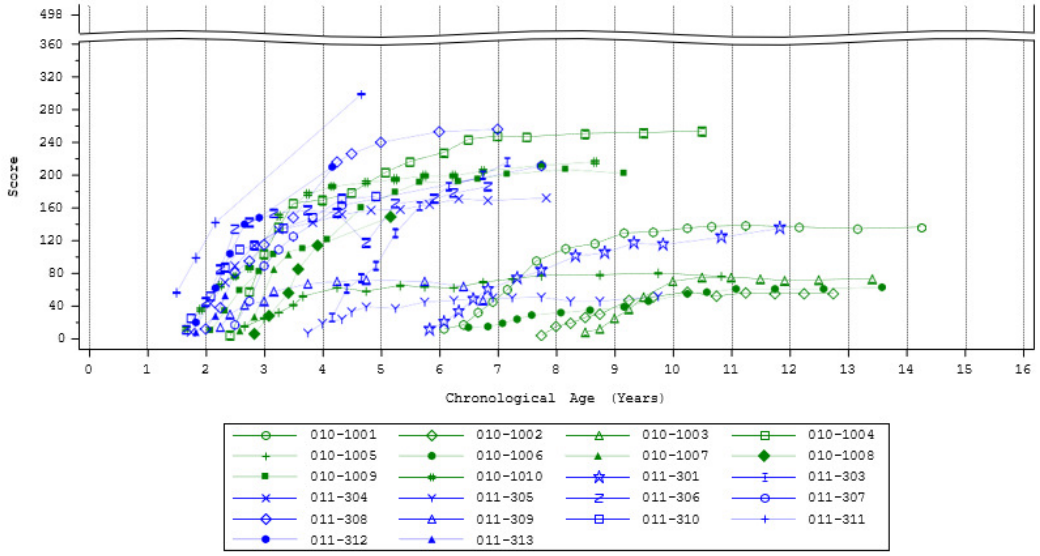

Cognitive and communication skills

~~The total language score, subscales of~~ Bayley-III, a standard assessment of cognition, language, and motor development for, infants and toddlers (1-42 months of age), was utilized~~assessed~~ 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 ~~subscales~~scores. ~~The total score of the language subscale is 97.~~ The mean raw total score for cognitive subscale at baseline was ~~17.70~~12.41 (N=~~20~~22). The LS mean change from baseline in cognitive ~~for total language~~ score showed an increase of 12.3 ~~was 7.35~~ at Month 12, 16.4 ~~(N = 17), 9.87~~ at Month 24, and 23.6 ~~(N = 15), and 12.60~~ 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~~36 (N = 10)~~.

Body weight

Eighteen ~~Sixteen~~ out of ~~17~~ 19 subjects (~~94~~95%) maintained (47%, ~~8~~ 9 subjects) or increased (47%, ~~8~~ 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 ~~77~~55.~~8~~0% at baseline (N=~~20~~22) to ~~46.7~~23.5% at Month 12 (N = 17). No subject experienced limb dystonia ~~and stimulus-provoked dystonia~~ 12 months post-treatment, compared with ~~66.7~~40.0% ~~and 11.1%~~ subjects at baseline (N = ~~20~~22)~~, respectively~~.

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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 ~~12.30~~11.90 hours/week at baseline (N=21). This time was reduced following treatment by 1.~~85~~ 39 hours per week by Month 3 (N=~~16~~19) and by ~~3.66~~4.82 hours per week by Month 12 (N=6).

5.2 Pharmacokinetic properties

[..]

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 ~~Subjects~~ treated with eladocagene exuparvovec, very low levels, far below treatment concentrations, have been detected ~~Upstaza showed no evidence of detectable viral vector~~ in ~~blood or~~ urine at ~~baseline or through 12~~ M~~m~~onth 6~~s after treatment~~.

6.6 Special precautions for disposal and other handling

[…]

Preparation prior to administration

[…]

- 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.

[…]

- 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.

[…]

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.

העלון לרופא נמצא בקישור, וכן מפורסם במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

בברכה,

מדיסון פארמה בע"מ

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