

HEALTH TECHNOLOGY BRIEFING

MARCH 2020

Eladocagene exuparvovec for aromatic L-amino acid decarboxylase deficiency

NIHRIO ID	13410	NICE ID	10313
Developer/Company	PTC Therapeutics International Ltd	UKPS ID	652289

Licensing and market availability plans	Currently in phase I/II clinical trials.
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SUMMARY

Eladocagene exuparvovec is in clinical development for the treatment of patients with deficiency of a protein called aromatic L-amino acid decarboxylase (AADC). AADC-deficiency is a very rare inherited disease which affects the way signals are passed between certain cells in the nervous system. AADC-deficiency is caused by changes or mutations in the dopa decarboxylase (DDC) gene, which provides instructions to make the AADC-enzyme. In patients with AADC-deficiency, the production of the AADC-enzyme is reduced, leading to lower levels of dopamine and serotonin (chemicals that send information between cells in the nervous system). The condition appears in the first year of life and prevents sufferers from ever talking, walking and sitting up.

Eladocagene exuparvovec is a type of gene replacement therapy which involves the transfer of the gene encoding the production of the enzyme needed by the brain for the formation of dopamine and serotonin. The gene therapy is injected via a surgical procedure into an area of the brain called the putamen. By increasing production of the AADC-enzyme, this therapy increases dopamine production in the target area of the brain and improves motor and cognitive symptoms in patients. If licensed, eladocagene exuparvovec will provide the first medicinal treatment option for adult and child patients with AADC-deficiency, a disease of very high unmet clinical need.

PROPOSED INDICATION

Eladocagene exuparvovec is indicated for the treatment of adult and paediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.^{1,2}

TECHNOLOGY

DESCRIPTION

Eladocagene exuparvovec (PTC-AADC, Upstaza™) is an gene replacement therapy for patients with AADC-deficiency.³ The disease is caused by mutations in the gene that produces the AADC-enzyme. AADC is involved in the decarboxylation of aromatic amino acids; if the enzyme is defective, formation of the neurotransmitters dopamine and serotonin is impaired and the passage and signalling within the brain is disrupted.⁴

The medicine consists of a virus that contains a functional version of the AADC-gene, which when given to the patient it is expected that the virus will carry the AADC-gene to the nerve cells, enabling them to produce the missing enzyme.⁵ The goal is to increase the production of the AADC-enzyme, thereby improving symptoms caused by this deficiency. The treatment is injected via a surgical procedure into the putamen. This region is fundamental for the production of neurotransmitters (chemicals that relay messages from neurons) such as dopamine and serotonin, which fail to be produced in patients because their neurons lack a functional AADC-enzyme.³

Eladocagene exuparvovec is in phase I/II clinical development (NCT02926066, NCT01395641) for the treatment of AADC-deficiency,^{1,2} and has also been given to patients for compassionate use (AADC-CU/1601). Eladocagene exuparvovec dosing is 1.8×10^{11} vector genomes (vg) delivered as four 0.080 mL (0.45×10^{11} vg) infusions (two per putamen).³

INNOVATION AND/OR ADVANTAGES

Currently, no approved therapeutics exist for the curative treatment of AADC-deficiency.⁶ Eladocagene exuparvovec utilises gene therapy which involves a recombinant adeno-associated viral (AAV) vector carrying the gene for the human aromatic L-amino acid decarboxylase protein.⁷ Clinical trial evidence suggests that a single dose of eladocagene exuparvovec delivered into the brain achieved clinically meaningful, sustained improvements in motor, cognitive, and language milestones for up to 5 years, with no new safety signals identified at data cut-off date of 27th March 2019.^{7,8}

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Eladocagene exuparvovec does not currently have a Marketing Authorisation in the EU/UK for any indication.

Eladocagene exuparvovec has an Orphan Drug Designation in the EU awarded in 2016 for AADC-deficiency.⁵

^a Information provided by PTC Therapeutics International Ltd on the UK PharmaScan.

PATIENT GROUP

DISEASE BACKGROUND

AADC-deficiency is an ultra-rare autosomal recessive disease caused by a non-functional AADC-enzyme, which normally synthesizes serotonin and dopamine, among other important compounds. As a result, patients with AADC-deficiency lack crucial neurotransmitters, including serotonin, dopamine, norepinephrine, epinephrine, and melatonin, and have severe developmental and motor deficiencies.⁹ AADC-deficiency is more prevalent in certain Asian (especially Taiwanese and Japanese) populations, probably due to a founder effect.¹⁰ In patients identified with AADC deficiency where gender was reported, the distribution was essentially equivalent; approximately 57% were male and 43% were female.¹⁰

Symptom onset typically occurs during the first months of life.¹¹ The majority of patients present a severe phenotype with early onset hypotonia, oculogyric crises, ptosis, dystonia, hypokinesia, impaired development and autonomic dysfunction, a few patients with a milder disease course are known.¹⁰ Patients with AADC-deficiency also present with autonomic dysfunction that is characterized by impairment of the sympathetic regulation of heart rate and blood pressure, paroxysmal sweating, emotional instability, and sleep disturbance.¹²

The life expectancy of patients with severe AADC-deficiency has been reported to be less than a decade. Patients with AADC-deficiency achieve few or no motor development milestones over their lifetime, such as head control, sitting, or standing, and consequently are fully dependent.⁹

CLINICAL NEED AND BURDEN OF DISEASE

The exact global incidence of AADC-deficiency is unknown,¹⁰ and the number of patients in the UK is also not reported. One new-born screening study carried out in Taiwan, suggested an incidence of 1:32,000 live births.¹³ The predicted birth rate of individuals with AADC deficiency is estimated to be 1:90,000 in the US, approximately 1:118,000 in the EU, and 1:182,000 in Japan.¹⁴ These birth rates translate into a current estimate of about 840 living patients with AADC deficiency in the US, 853 in the EU, and 125 in Japan.¹⁴

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

When a child first presents with a neurological disorder and a dopamine related disease is suspected then it is expected that the treating physician/consultant will arrange the correct and necessary tests.⁴

Such tests typically involve a blood test taken to measure levels of the AADC-enzyme and a spinal tap or lumbar puncture to collect cerebrospinal fluid (CSF). Levels of dopamine and serotonin in the CSF can help to diagnose AADC-deficiency. Finally, genetic testing can also be performed to detect mutations in the DDC-gene and confirm the diagnosis.¹⁵

According to the consensus guidelines for AADC-deficiency, the average age of symptom onset for these patients is 2.7 months; however, the average age of diagnosis is 3.5 years, indicating that misdiagnosis or delayed diagnosis is likely frequent in this disorder.¹⁰

CURRENT TREATMENT OPTIONS

Limited treatment options are available for individuals diagnosed with AADC-deficiency and none are curative.⁶ Only patients with relatively mild forms of the disease respond to drugs, and patients obtain relief from only a limited subset of symptoms. Drug therapy provides little or no benefit for many patients who often die during childhood.^{11,16}

The symptomatic treatment options for AADC-deficiency include dopamine agonists, monoamine oxidase (MAO) inhibitors, pyridoxal phosphate, pyridoxine, anticholinergic agents, folinic acid, L-Dopa with carbidopa, L-Dopa without carbidopa, 5-hydroxytryptophan, benzodiazepines, melatonin, and selective serotonin reuptake inhibitors (SSRIs).¹⁰

Systematic review evidence highlighted core recommendations for medical treatment of AADC-deficiency:¹⁰

1. First line symptomatic treatment agents are selective dopamine agonists, monoamine oxidase (MAO) inhibitors, and pyridoxine
2. Additional symptomatic treatment agents are anticholinergic agents, melatonin, benzodiazepines, and alpha-adrenoreceptor blockers.
3. In general, therapy with multiple drugs will be needed and doses should be titrated individually and sequentially.
4. General treatment principles to adhere to are a stepwise approach: start low, and go slow when increasing the doses, and discontinue/wean off medication that is not helpful.

The systematic review also recommended a number of medical treatments that should be avoided in AADC, especially centrally acting dopamine antagonists because they have the potential to worsen symptoms of dopamine deficiency.¹⁰

PLACE OF TECHNOLOGY

If licensed, eladocogene exuparvec will provide the first curative treatment option for patients with AADC-deficiency who do not currently have any approved treatment.⁶

CLINICAL TRIAL INFORMATION

Trial	NCT01395641 ; A Phase I/II Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC-) Deficiency Using AAV2-hAADC (NTUH-AADC-010) Phase I/II Location(s): Taiwan	NCT02926066 ; A Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC-) Deficiency Using AAV2-hAADC - An Expansion (NTUH-AADC-011) Phase II Location(s): Taiwan
Trial design	Single group assignment (open label)	Single group assignment (open label)
Population	n=10; children aged 24 mths and older with a confirmed diagnosis of AADC and displaying classical clinical characteristics of AADC-deficiency (such as oculogyric crises, hypotonia and developmental retardation); or a head circumference big enough for surgery.	n=10 (planned); patients up to 6 yrs with a confirmed diagnosis of AADC and displaying classical clinical characteristics of AADC-deficiency (such as oculogyric crises, hypotonia and developmental retardation); patient has to be over 2 yrs old or a thickness of skull enough for surgery.
Intervention(s)	Intracerebral infusion of a single dose of aqueous AAV2-hAADC (1.81×10^{11} vg)	Intracerebral infusion of a single dose of aqueous AAV2-hAADC: <ul style="list-style-type: none"> • Dose: 2.37×10^{11} vg/case (for children younger than 3 yrs of age) • Dose: 1.81×10^{11} vg/case
Comparator(s)	No comparator	No comparator
Outcome(s)	Primary outcome (time frame: 12 mths):	Primary outcome:

	<ul style="list-style-type: none"> At one year post-surgery, neurotransmitter metabolites (HVA or HIAA) is detectable in CSF (higher than that at pre-surgery). At one year post-surgery, PDMS-II score is higher than that at pre-surgery, with an improvement over 10 points. 	<p>Evaluation of therapeutic effect (time frame: 13 months):</p> <ul style="list-style-type: none"> At one year post-surgery, neurotransmitter metabolites (HVA or HIAA) increased in the CSF (compared to the pre-surgery (Baseline) level). At one year post-surgery, PDMS-II score is higher than that at pre-surgery (Baseline), with an improvement over 10 points. <p>See trial record for full list of other outcomes.</p>
Results (efficacy)^b	<p>All patients met the primary efficacy endpoint: 12 months after gene therapy, PDMS-2 scores were increased by a median of 62 points (IQR 39-93; $p=0.005$) and homovanillic acid (HVA) concentrations by a median of 25 nmol/L (IQR 11-48; $p=0.012$); however, there was no significant change in 5-hydroxyindoleacetic acid (5-HIAA) concentrations (median difference 0, IQR 0-5; $p=0.20$).</p>	<ol style="list-style-type: none"> All patients achieved meaningful gains in motor function: <ol style="list-style-type: none"> Four patients treated with eladocagene exuparvovec achieved the motor milestone of head control at mth 12. One patient was also able to sit unassisted. All patients demonstrated improvement in PDMS-2 and AIMS total and subscale scores. Bayley-III total and subscale scores also increased from baseline, providing further support for the mastery of skill items observed on the PDMS-2 and AIMS. An improvement in movement disorders (floppiness, OGC episodes and limb dystonia) was observed 1 year after treatment. Anti-AAV2 antibody titres had little impact on efficacy as measured by change from baseline in PDMS-2 total score for patients in the 1.8×10^{11}vg dose group. Increased dopamine metabolites in the CSF of treated patients demonstrates that the noted clinical effects are due to eladocagene exuparvovec gene therapy.
Results (safety)^b	<p>In total, 101 adverse events were reported, with the most common being pyrexia (16 [16%] of 101 events) and orofacial dyskinesia (ten [10%]). 12 serious adverse events occurred in six patients, including one death (treatment-unrelated encephalitis due to influenza B infection), one life-threatening pyrexia, and ten events that led to hospital admission. Transient post-gene therapy dyskinesia occurred in all patients but was resolved with risperidone. Of 31 treatment related adverse events, only one (patient 1) was severe in intensity, and none led to hospital admission or death.</p>	<p>A total of 130 AEs were reported during the 12 month study as follows:</p> <ul style="list-style-type: none"> 43 AEs in 3 patients (37.5%) in the 1.8×10^{11} vg dose group and 87 AEs in 5 patients (62.5%) in the 2.4×10^{11} vg dose group. All 3 patients in the 1.8×10^{11} vg dose group reported AEs of pyrexia, dehydration, and dyskinesia and 2 of the 3 patients in this group reported AEs of upper gastrointestinal haemorrhage, gastroenteritis, pneumonia, upper respiratory tract infection, and breath sounds abnormal. The most common AEs experienced by the 2.4×10^{11} vg dose group were pyrexia and breath sounds abnormal (5 of 5 patients), upper respiratory tract infection and anaemia (4 of 5 patients) and dyskinesia, gastroenteritis, hypotension, and irritability (3 of 5 patients).

Trial	<p>AADC-CU/1601^{b,17}; A retrospective observational study of treatment with AAV2-hAADC viral vector in aromatic L-amino acid decarboxylase (AADC-)deficiency patients</p> <p>Compassionate use</p> <p>Location(s): Taiwan</p>
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^b Information provided by PTC Therapeutics International Ltd.

Trial design	Single-centre, retrospective observational study
Population	n=8 (treated); receiving humanitarian assistance treatment following AAV2-hAADC administration via intra-putaminal infusion. Parent(s) or legal guardian(s) must have provided written informed consent prior to data abstraction.
Intervention(s)	Treated with dose 1.8×10^{11} vg
Comparator(s)	No comparator
Outcome(s)	Clinical outcomes: <ul style="list-style-type: none"> • Acquisition of PDMS-2 motor milestones compared to historical controls • Secondary functional test: AIMS measures • Cognitive development test: CDIIT measures • Individual patient narratives • Imaging data
Results (efficacy)	All of the patients showed improvement in motor function, with increases in total PDMS-2 scores. Half of the patients, (4/8) achieved full head control at 12 months post treatment and developed the ability to sit unassisted at 24 months post treatment, and 2 patients achieved the ability to stand at 60 months post treatment, indicating progressive acquisition of clinically meaningful milestones post gene therapy.
Results (safety)	The major adverse event observed in this study was transient dyskinesia.

ESTIMATED COST

The cost of eladocogene exuparvovec is currently not known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Children). E06/S/b.

OTHER GUIDANCE

Wassenberg, T., Molero-Luis M., Jeltsch K., Hoffmann G. F., Assmann B., Blau N., et al. Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC-) deficiency. Orphanet Journal of Rare Diseases. 2017;12(1):12.¹⁰

Himmelreich, N., Montioli R., Bertoldi M., Carducci C., Leuzzi V., Gemperle C., et al. Aromatic amino acid decarboxylase deficiency: Molecular and metabolic basis and therapeutic outlook. Molecular genetics and metabolism. 2019;127(1):12-22.¹⁴

ADDITIONAL INFORMATION

N/A

REFERENCES

- 1 ClinicalTrials.gov. *A Phase I/II Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC*. Trial ID. 2011. Status: Available from: <https://clinicaltrials.gov/ct2/show/NCT01395641> [Accessed 24th February 2020].
- 2 ClinicalTrials.gov. *A Clinical Trial for Treatment of Aromatic L-amino Acid Decarboxylase (AADC) Deficiency Using AAV2-hAADC - An Expansion (NTUH-AADC-011)*. Trial ID. 2016. Status: Available from: <https://clinicaltrials.gov/ct2/show/NCT02926066> [Accessed 24th February 2020].
- 3 Pena, I. *PTC Seeks Marketing Authorization for its AADC Gene Therapy in Europe*. 2020. Available from: <https://aadcnnews.com/2020/01/14/ptc-seeks-marketing-authorization-for-its-aadc-gene-therapy-in-europe/> [Accessed 20th February 2020].
- 4 AADC Trust. *About Aromatic Amino Acid Decarboxylase deficiency (AADCd)*. 2020. Available from: <https://www.aadcresearch.org/copy-of-board-of-directors-2> [Accessed 18th February 2020].
- 5 European Medicines Agency. *EU/3/16/1786* 2016. Available from: <https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3161786> [Accessed 19th February 2020].
- 6 Monteleone, B., Hyland K. *Case report: discovery of 2 gene variants for aromatic L-amino acid decarboxylase deficiency in 2 African American siblings*. BMC Neurology. 2020;20(1):12. Available from: <https://doi.org/10.1186/s12883-019-1596-8>
- 7 Silva, C. *#AANAM – AGIL-AADC Gene Therapy Improves Motor, Cognitive, and Speech Skills in AADC Children*. 2019. Available from: <https://aadcnnews.com/2019/05/09/aanam-agil-aadc-gene-therapy-improves-motor-cognitive-and-speech-skills-in-aadc-children/> [Accessed 24th February 2020].
- 8 Chien, Y.-H., Lee N.-C., Tseng S. H., Tai C.-H., Conway A., Pykett M., et al. *AGIL-AADC Gene Therapy Results in Sustained Improvements in Motor and Developmental Milestones Over 5 Years in Children With AADC Deficiency*. 2019. Available from: <https://www.childneurologysociety.org/docs/default-source/2019-CNS/2019-cns-program.pdf?sfvrsn=2> [Accessed 24th February 2020].
- 9 Das, S., Huang S., Lo A. W. *Acceleration of rare disease therapeutic development: a case study of AGIL-AADC*. Drug Discovery Today. 2019;24(3):678-84. Available from: <https://doi.org/10.1016/j.drudis.2018.12.006>
- 10 Wassenberg, T., Molero-Luis M., Jeltsch K., Hoffmann G. F., Assmann B., Blau N., et al. *Consensus guideline for the diagnosis and treatment of aromatic L-amino acid decarboxylase (AADC) deficiency*. Orphanet Journal of Rare Diseases. 2017;12(1):12. Available from: <https://doi.org/10.1186/s13023-016-0522-z>
- 11 Brun, L., Ngu L. H., Keng W. T., Ch, ng G. S., Choy Y. S., et al. *Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency*. Neurology. 2010;75(1):64. Available from: <http://doi.org/10.1212/WNL.0b013e3181e620ae>
- 12 Swoboda, K. J., Saul J. P., McKenna C. E., Speller N. B., Hyland K. *Aromatic L-amino acid decarboxylase deficiency: Overview of clinical features and outcomes*. Annals of Neurology. 2003;54(S6):S49-S55. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/ana.10631>
- 13 Chien, Y.-H., Chen P.-W., Lee N.-C., Hsieh W.-S., Chiu P.-C., Hwu W.-L., et al. *3-O-methyldopa levels in newborns: Result of newborn screening for aromatic L-amino-acid decarboxylase deficiency*. Molecular Genetics and Metabolism. 2016;118(4):259-63. Available from: <https://doi.org/10.1016/j.ymgme.2016.05.011>
- 14 Himmelreich, N., Montioli R., Bertoldi M., Carducci C., Leuzzi V., Gemperle C., et al. *Aromatic amino acid decarboxylase deficiency: Molecular and metabolic basis and therapeutic outlook*. Molecular Genetics and Metabolism. 2019;127(1):12-22. Available from: <https://doi.org/10.1016/j.ymgme.2019.03.009>
- 15 Iyer, V. *What Is AADC Deficiency?* 2019. Available from: <https://aadcnnews.com/what-is-aadc-deficiency/> [Accessed 19th February 2020].
- 16 Manegold, C., Hoffmann G. F., Degen I., Ikonomidou H., Knust A., Laaß M. W., et al. *Aromatic L-amino acid decarboxylase deficiency: clinical features, drug therapy and follow-up*. Journal of Inherited Metabolic Disease. 2009;32(3):371-80. Available from: <https://doi.org/10.1007/s10545-009-1076-1>

- 17 Hwu, W.-L., Muramatsu S.-i., Tseng S.-H., Tzen K.-Y., Lee N.-C., Chien Y.-H., et al. *Gene Therapy for Aromatic L-Amino Acid Decarboxylase Deficiency*. Science Translational Medicine. 2012;4(134):134ra61. Available from: <http://stm.sciencemag.org/content/4/134/134ra61.abstract>

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