National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Eladocagene exuparvovec for treating aromatic L-amino acid decarboxylase deficiency [ID3791]

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	PTC Therapeutics (PTC)	AADC-d is an ultra-rare genetic disorder with very few patients in the UK. It is estimated that just [redacted] patients in England will be eligible for eladocagene exuparvovec single-use gene replacement therapy at the time of its marketing authorisation, with [redacted] newly diagnosed patients presenting in each subsequent year. Given the low patient numbers, PTC does not agree with the proposal that this topic is appraised as an STA. Eladocagene exuparvovec should be referred for a NICE's Highly Specialised Technology (HST) appraisal as it meets the HST appraisal criteria, and there is precedence for gene therapies for ultra-orphan conditions to be appraised via HST. Further information is provided below to confirm that eladocagene exuparvovec meets all seven of the HST eligibility criteria.	Comment noted. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.
	Metabolic Support UK	It is timely and appropriate for this topic to be referred to NICE given that there are no specific current licensed treatments currently available in the UK to treat patients living with AADC.	Thank you for your comment. No action necessary.

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	The AADC Research Trust	It is appropriate and timely for this topic to be referred to NICE as there are no current licensed treatments available in the UK to treat AADC deficiency patients.	Thank you for your comment. No action necessary.
Wording	PTC Therapeutics (PTC)	PTC requests that the remit is amended to align with the proposed wording in the Summary of Product Characteristics (SmPC) for eladocagene exuparvovec, which specifies its use [redacted]. PTC therefore request the following wording to be used in the 'Population' scope: [redacted]	Thank you for your comment. Until the marketing authorisation is finalised the preference is to keep the remit for the scope broad. However, if this topic is referred, it will be appraised in line with its marketing authorisation only. No action necessary.
	Metabolic Support UK	The wording is appropriate.	Thank you for your comment. No action necessary.
	The AADC Research Trust	The wording is appropriate	Thank you for your comment. No action necessary.
Timing Issues	PTC Therapeutics (PTC)	AADC-d is a fatal, ultra-rare genetic disorder that causes severe disability and suffering from the first months of life and affects every aspect of life – physical, mental and behavioural.[1–4] There are currently no licensed disease-modifying treatments for AADC-d in the UK, highlighting the high unmet need. Eladocagene exuparvovec was granted Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency	Thank you for your comment. No action necessary.

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		(MHRA) in June 2020, further highlighting the unmet need and urgency in treating these fatally ill infants and children. While there is an urgent need for eladocagene exuparvovec, [redacted]	
Additional comments on the draft remit	PTC Therapeutics (PTC)	As stated above, PTC has considerable concerns regarding the proposed referral of eladocagene exuparvovec to the STA programme and urge NICE to reconsider this recommendation. Eladocagene exuparvovec is an innovative gene therapy that replaces the faulty *DDC* gene, thus restoring AADC enzyme functioning and in turn the production of dopamine and serotonin, essential neurotransmitters with critical roles in the brain and body. Given that AADC-d is a fatal, ultra-rare condition affecting children, administration of eladocagene exuparvovec requires a highly specialised multidisciplinary team including qualified neurosurgeons. In line with this, patients with AADC-d in England are currently routinely managed via existing specialised services at a small number of centres with the relevant expertise and facilities. PTC believes eladocagene exuparvovec meets all seven of the required HST criteria. Please see below for more information on how eladocagene exuparvovec in AADC-d meets the seven criteria for HST. PTC would be very happy to respond to further queries from NICE in relation to these points: 1. The target patient group for the technology in its licensed indication is so small that treatment will be concentrated in very few centres in the NHS	Comment noted. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.

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		• As highlighted in the scoping document, there are currently no licensed disease-modifying treatments that directly target the underlying genetic cause of AADC-d, meaning that there is a clear unmet need for eladocagene exuparvovec. • The number of patients living with AADC-deficiency is estimated to be 853 in EU, indicating a prevalence of 1:118,000;[1,3] however, as of 2021 only around [redacted] have been described in the literature and confirmed as unique cases of AADC deficiency (based on data on file from a comprehensive natural history database developed by PTC). • PTC estimates the number of [redacted] patients eligible for eladocagene exuparvovec to be [redacted] patients in England currently, with a yearly incidence of a further [redacted] patients. • Use of eladocagene exuparvovec in England is expected to be concentrated to a very small number [redacted] of [redacted] centres that currently manage patients with AADC-d, including providing the pre- and post-operative specialist management and support required in collaboration with their local clinician. [redacted] 2. The target patient group is distinct for clinical reasons • AADC-d is a fatal, ultra-rare genetic disorder that causes severe disability and suffering from the first months of life.[1–4] • Clinically distinct characteristics of patients with AADC-d include: early onset hypotonia, oculogyric crises, ptosis, dystonia, hypokinesia, impaired development and autonomic dysfunction.[1,5]	

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		• AADC-d significantly impacts cognitive development and functioning, motor skills, growth, language skills and behaviour.[1] Most children will never be able to hold their head up, sit by themselves, stand or speak and require 24/7 care throughout their lives.[2] • There are no licensed disease-modifying treatments for AADC-d that target the underlying genetic cause of the disease, and the lives of affected children are highly disrupted, sometimes involving many different medications to try and manage each symptom modality, and ongoing physical, occupational and speech therapy. Invasive procedures, including surgery, attempt to manage the consequences of potentially life-threatening complications (infections, severe feeding/breathing problems, and scoliosis).[1,6,7] • Eladocagene exuparvovec is an innovative gene therapy requiring highly specialised surgical administration into the putamen region of the brain.[4] This gene therapy was awarded PIM designation, highlighting that it treats a seriously disabling, life-threatening disease with a high unmet need, and that the benefits outweigh the risks.[8] • Given that AADC-d is an ultra-rare, life-shortening and life-threatening paediatric condition, eladocagene exuparvovec is indicated for a patient group that is distinct for clinical reasons. 3. The condition is chronic and severely disabling • AADC-d is a severe disease, regardless of phenotype; all patients with AADC-d are severely affected in terms of restrictions on living and loss of independence. All patients can therefore benefit from eladocagene exuparvovec gene therapy irrespective of their severity.	

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		• AADC-d is a fatal, ultra-rare genetic disorder that causes severe disability and suffering from the first months of life, affecting every aspect of life – physical, mental and behavioural.[1–4] • AADC-d significantly impacts development, motor skills, growth, function, cognitive and language skills, and behaviour.[1] Most children will never be able to hold their head up, sit by themselves, stand or speak.[2] Unable to move or communicate, they may never play with toys, go to school, or be able to feed themselves, with many reliant on feeding tubes or breathing support to survive.[2,9–11] • Patient suffering is exacerbated by episodes of distressing seizure-like oculogyric crises, which can happen daily and last for hours, causing the eyes to roll up in the head, frequent vomiting, behavioural problems, difficulty sleeping, and life-threatening complications such as respiratory infections and gastrointestinal problems.[1,3,12,13] • A mean life expectancy of 4.6 years was calculated in a natural history of disease study (range 1-7 years, based on the 10 deaths that occurred among 16 untreated patients),[14] suggesting that most patients die within the first decade of life.[14] Patients' shortened life is one of severe disability and frequent hospitalisations, including periods in intensive care as a result of breathing, feeding and swallowing problems.[1,6,9,10] • Caregivers provide round-the-clock care, spending an average of 13 hours (8-20 hours) per day on practical and emotional care for their child with AADC-d.[10] Furthermore, caregivers spend a mean of 15 hours (7-33 hours) per week on administrative tasks such as planning activities or travelling to/attending appointments related to their child's disease.[10] • Caregiving impacts quality of life, with EQ-5D data showing that carers experience slight to severe anxiety and depression and slight	

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		to moderate pain and discomfort, emphasising both the emotional and physical burden of caring for a child with AADC-d.[15] • Caregiving also impacts work productivity, with 75% of caregivers reporting that they stopped working or reduced their working hours in order to care for their child with AADC-d.[10] 4. The technology is expected to be used exclusively in the context of a highly specialised service • Eladocagene exuparvovec is expected to be administered at [redacted] centres within the context of a highly specialised service. • It is injected into the bilateral putamina of the brain by stereotactic surgery and involves a multidisciplinary team, including neurosurgeons and operating theatre staff with experience of the procedure, paediatric anaesthetists, paediatric neurologists and pharmacists.[4] 5. The technology is likely to have a high acquisition cost • Eladocagene exuparvovec is administered as a one-off surgical injection into the bilateral putamina in paediatric patients and requires a multidisciplinary team including neurosurgeons and operating theatre staff with experience of the procedure, paediatric anaesthetists, paediatric neurologists and pharmacists.[4] Patients are expected to be in intensive care for 48 hours following surgery and in hospital for days after therapy. • As a gene replacement therapy, it provides potentially life-long benefits to patients and is continuing to show benefits after more than five years of follow-up.[16] • Eladocagene exuparvovec is expected to have a [redacted], given that there are [redacted] patient	

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		numbers within England, eladocagene exuparvovec is expected to have a [redacted] net budget impact to the NHS. 6. The technology has potential for life-long use • AADC-d is an ultra-rare, fatal, genetic disorder with severely debilitating and life-long symptoms.[1–4] • While eladocagene exuparvovec is a one-off administration, as it treats the underlying cause of AADC-d, it is expected to provide life-long effects and this has been demonstrated in over five years of efficacy and safety follow-up data.[16] 7. The need for national commissioning of the technology is significant Due to the very selective and small number of centres expected to administer eladocagene exuparvovec, national commissioning and oversight is essential.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	PTC Therapeutics (PTC)	PTC agrees with the overall summary provided in the draft scope but would like to include the following information regarding mortality: AADC-d is a life-threatening and severely disabling condition, with a life expectancy reported to be under a decade.[1,14,17] A mean life expectancy of 4.6 years was calculated in a natural history of disease study (range 1-7 years, based on the 10 deaths that occurred among 16 untreated patients).[14] Patients often die before the age of 7 due to severe motor dysfunction, autonomic	Thank you for your comment. The background is only intended to be a broad summary of the disease area. No action necessary.

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		abnormalities, and secondary complications such as hypoxia, aspiration, and pneumonia.[1] Please also see below some additional information regarding the burden of AADC-d, which NICE may find supportive: • AADC-d is a fatal, ultra-rare genetic disorder that causes severe disability and suffering from the first months of life as affects every aspect of life – physical, mental and behavioural.[1–4] • The mean age of onset of signs and symptoms of AADC-d in 68 cases was 2.7 months.[1] • The burden on infants and children with AADC-d is extremely significant impacting on development, motor skills, growth, function, cognitive and language skills as well as behaviour.[1] • The physical burden is extreme as most children will never be able to hold their head up, sit by themselves, stand, or speak. Many children are reliant on feeding tubes or breathing support to survive.[2,9–11] • The social burden and subsequent mental and behavioural detrimental effects stem from children with AADC-d being unable to move and communicate, therefore these children will never be able to play with toys or go to school and interact with classmates.[2,9–11] • There is also a significant burden for carers of patients with AADC-d compared to healthy peers; caring for a child with AADC-d impacts the whole family physically, emotionally, and financially. It requires constant one-to-one support with all aspects of carrying out daily living tasks, such as getting dressed, bathing, eating, toileting and simply being able to move.[9,10] There are currently no licensed disease-modifying therapeutic options for patients with AADC-d; current treatment options focus on managing symptoms only.[1,6,7]	

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		• Treatments tend to only be effective when the specific symptoms they treat are mild. • Current management options offer little improvements for most patients with AADC-d and are often accompanied by unpleasant side effects and drug-drug interactions; 97% of patients with AADC-d receiving current treatment options fail to achieve any motor milestones.[1,2] If eladocagene exuparvovec is approved, it will be the first and only licensed treatment to directly correct the genetic cause of AADC-d and will become the standard of care for patients with AADC-d.	
	Metabolic Support UK	The symptoms included in the background are not comprehensive of all the symptoms, signs and the resulting complications of AADC. People living with AADC also suffer oculogyric crises, lasting several hours and recurring every 2 to 5 days. The background information references movement disorder however it important that more detail is included regarding the impact of this particular symptom. Other movement disorders such as decreased movement can be prevalent in patients living with AADC. Patients with ADDC can also suffer from. - Sustained muscle contraction - Abnormal posture - Tremors - Droopy eyelids - Temperature instability - Low blood pressure and low sugar levels - Seizures - Insomnia - Gastrointestinal problems	Thank you for your comment. Background and outcomes have been updated to include oculogyric crisis.

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		In addition to the physical symptoms listed, we would like to see the inclusion of the psychosocial impact AADC has on patients and their caregivers. Symptoms such as those listed impact the employability, ability to work and attend school and participate in social activities, leading to isolation. Employability is severely affected by the debilitating nature of this rare disorder. The mental health of parents and caregivers should also be taken into consideration during this consultation.	
	The AADC Research Trust	The accuracy of symptoms is correct but does not cover the most common symptom share by 99% of the global AADCd affected population; the Oculogyric Crisis (OGC). The symptoms of AADCd are complex and multi-faceted and best described in the publication 'Consensus guidelines for diagnosis and treatment of AADC deficiency'. Although AADCd is not described as degenerative, certain mutations can prompt premature death before age of 7 and medical complications of AADCd can result in premature death in any of our patient population. In addition to undiagnosed populations there will also be those mis-diagnosed too. East Asian communities see a higher prevalence because of an ancestral mutation prevalent in the population. More than 84 AADC mutations have now been discovered in the wider global population.	Thank you for your comment. Background and outcomes have been updated to include oculogyric crisis.

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		It is incorrect to explain that only mild sufferers respond to medication. Historically children have not been accurately diagnosed as mild, moderate, or severe sufferers. The array of symptoms is widespread, and some children may have a better response to medications than others and genetics may play a much bigger role in understanding phenotypes and how we describe these patients. E.G. Mild, Moderate and Severe phenotype Vs Mild, Moderate and Severe Genotype. Genetically Vs Clinically is not yet well enough understood to determine a blanket mild, moderate and a severe sufferer of AADC deficiency. Homozygous and Hemizygous affected populations may be easier to predict phenotype as mutation dominance is understood. Currently Heterozygous is more difficult to predict disease outcome. Often AADC deficiency will be accompanied by psychosocial issues, and these should be considered with regards to schooling, employment, and integration into normal life. Often higher functioning patients suffer with additional symptoms such as autism, ocd, adhd and other mental health issues that need careful consideration. Particularly into adulthood. Parents and care providers must make major adjustments to their lives to manage the care of a person suffering this chronic disease; AADCd.	
The technology/ intervention	PTC Therapeutics (PTC)	PTC request that the remit is updated as follows to reflect that the indication [redacted]	Thank you for your comment. Until the marketing authorisation is finalised the preference is to keep the remit for the scope

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		PTC also requests that NICE consider the following information regarding the technology: • Eladocagene exuparvovec is intended to be the only licensed treatment to directly correct the genetic cause of AADC-d disease and will become the standard of care treatment for patients with AADC-d. • Eladocagene exuparvovec is a gene transfer vector that employs an adeno-associated virus serotype 2 (AAV2), containing the human cDNA encoding the AADC enzyme (hAADC) capsid, as a delivery vehicle for the human transgene encoding the hAADC.[4] • It is infused bilaterally into the putamen of the brain by stereotactic surgery and involves a multidisciplinary team including neurosurgeons and operating theatre staff with experience of the procedure, paediatric anaesthetists, paediatric neurologists and pharmacists.[4] • Eladocagene exuparvovec was granted PIM designation in AADC-d by the MHRA in June 2020, highlighting that it is an innovative technology. Furthermore, PTC requests that NICE consider the following information regarding the clinical studies: • Eladocagene exuparvovec has been studied in three clinical trials (AADC-1601, AADC-010, and AADC-011).[18–20] Together, these three studies include 28 patients with severe AADC-d. • At baseline, patients did not display any motor milestone developments which included head control and the ability to sit, stand or walk. After the one-time treatment with eladocagene exuparvovec, patients demonstrated meaningful clinical benefit with sustained improvements in motor function, cognitive and communication skills (as measured via the PDMS-2, AIMS, and Bayley-III scores and scales), decrease of respiratory infections, body weight gain, and decrease in floppiness, limb dystonia, stimulus-provoked dystonia, and oculogyric crisis (OGC) episodes.[18–20]	broad. However, if this topic is referred, it will be appraised in line with its marketing authorisation only. No action necessary.

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		• The safety of eladocagene exuparvovec has been demonstrated in 26 patients with severe AADC-d (aged 21 months to 8.5 years) across three separate clinical trials, with the first patient dosed over 10 years ago (2010).[21]	
	Metabolic Support UK	This section is accurate to the best of our knowledge.	Thank you for your comment. No action necessary.
	The AADC Research Trust	This section is accurate but special attention should be given to which surgical delivery method is being adopted for this treatment. We should ensure it is the most technologically advanced with regards to safety and precision of this invasive neurosurgical procedure in children.	Thank you for your comment. No action necessary.
Population	PTC Therapeutics (PTC)	PTC proposes updating the Population to reflect that eladocagene exuparvovec is expected to be licensed [redacted] Regarding subgroups, while studies indicate that there can be mild phenotypes of AADC-d, the vast majority of patients have a severe phenotype and AADC-d is a severely disabling condition.[1] In the context of the very high unmet need and the [redacted] number of patients expected to be eligible for eladocagene exuparvovec in the UK, PTC considers there to be no specific subgroups of patients for consideration in this appraisal.	Thank you for your comment. Until the marketing authorisation is finalised the preference is to keep the remit for the scope broad. However, if this topic is referred, it will be appraised in line with its marketing authorisation only. No action necessary.
	Metabolic Support UK	The population defined is accurate.	Thank you for your comment. No action necessary.

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	The AADC Research Trust	accurate	Thank you for your comment. No action necessary.
Comparators	PTC Therapeutics (PTC)	PTC agrees with the proposed comparator of 'established clinical management without eladocagene exuparvovec' as there are currently no licensed disease-modifying therapies approved for AADC-d. There is therefore a very high unmet need for eladocagene exuparvovec Current clinical management for patients with AADC-d involves symptomatic treatment only and the choice of therapy varies based on clinician preference. It is therefore difficult to describe one treatment as "best alternative care". According to 2017 guidelines,[1] therapies used in AADC-d include: • First line: Monoamine oxidase (MAO) inhibitors, dopamine antagonists, and vitamin B6. • Other therapies used for symptomatic treatment: anticholinergic agents, benzodiazepines.[1]	Thank you for your comment. No action necessary.
	Metabolic Support UK	Treatment for patients with AADC is symptomatic and patients will usually see healthcare professionals from a range of disciplines such as physical therapist, occupational therapist, speech therapist and development and behavioural specialists. Patients are also prescribed the following medicines to manage and treat the disease. Dopamine receptor agonists, Monoamine oxidase (MAO) inhibitor Pyridoxine (Vitamin B6), Anticholinergic agents to treat movement disorders, Seizure medication, Gastrointestinal medications, Melatonin to treat sleep disturbances.	Thank you for your comment. No action necessary.

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	The AADC Research Trust	Treatment for patients with AADC is symptomatic and established according to the Consensus Guidelines for the Diagnosis and Treatment of AADC Deficiency. Patients will additionally see healthcare professionals from a range of disciplines such as physical therapist, occupational therapist, speech therapist and development and behavioural specialists. Patients are usually treated according to the presenting symptoms and although similar medications are traditionally used the situation remains fluid as aging, puberty and adolescents all affect medication efficacy. A patient is usually treated symptomatically on a case-by-case basis.	Thank you for your comment. No action necessary.
Outcomes	PTC Therapeutics (PTC)	PTC appreciates that the outcomes proposed in the draft scope largely capture the key health-related benefits for patients with AADC-d but would like to request that additional outcomes are considered. The regulatory submission to the EMA for eladocagene exuparvovec in patients with AADC-d is based on results observed in the three clinical trials: AADC-1601, AADC-010 and AADC-011. The key primary and secondary outcomes measures in these trials were the Peabody Developmental Motor Scales (PDMS-2), the Alberta Infant Motor Scale (AIMS) and Bayley-III scales. PTC requests that these outcomes measures are clearly specified in the revised scope. Similarly, PTC request that the following outcomes are added to the scope to further align with the outcomes reported in the clinical trials: • Change in levels of neurotransmitter metabolites (HVA and/or 5-HIAA) in the CSF • Change in putaminal signal in 6-[^{18}F]fluorodopa-PET study post-surgery.	Thank you for your comment. The outcomes have been updated to include 'changes in levels of neurotransmitter metabolites in the cerebral spinal fluid'

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		PTC therefore proposes the following alternative text for the "Outcomes" section of the Scope: "The outcome measures to be considered include: • Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking) including assessments through PDMS-2, AIMS, and Bayley-III totals and subscales • Autonomic nervous system functioning • Speech and language development • Change in levels of neurotransmitter metabolites (HVA and/or 5-HIAA) in the CSF • Cognitive development • Change in putaminal signal in 6-[^{18}F]fluorodopa-PET study post- surgery. • Body weight • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)"	
	Metabolic Support UK	These outcome measures are appropriate, however, the psycho-social aspects within the health-related quality of life (for patients and carers) should be explicitly reviewed. Consideration should also be given to the disruptions and burden caused by current treatment options.	Thank you for your comment. If this topic is referred, the inclusion of carer quality of life will be considered by the committee. No action necessary.
	The AADC Research Trust	Oculogyric Crisis is one of the most important outcomes to be measured as it frequently impacts the sufferer and the caregiver. The outcome measures are otherwise appropriate, however, the psycho-social aspects within the health-related quality of life (for patients and carers)	Thank you for your comment. The background and outcomes have been

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		should be explicitly reviewed. Consideration should also be given to the disruptions and burden caused by current treatment options.	updated to include oculogyric crisis.
Economic analysis	PTC Therapeutics (PTC)	In line with HST criteria, AADC-d is an ultra-rare condition, meaning that the evidence base (disease background, burden, clinical, quality of life, economic) supporting eladocagene exuparvovec is associated with the typical limitations observed with ultra-orphan therapies ([redacted]). In addition, as an advanced, one-off gene therapy with potentially life-long benefits, eladocagene exuparvovec comes with a [redacted]. PTC therefore considers the traditional STA appraisal route as inappropriate for the appraisal for eladocagene exuparvovec. In addition, caregiver outcomes (i.e., carer burden and disutility) are relevant aspects to consider in the model. Caregivers provide round-the-clock care, spending an average of 13 hours (8-20 hours) per day on practical and emotional care for their child with AADC-d.[10] Furthermore, caregivers spend a mean of 15 hours (7-33 hours) per week on administrative tasks such as planning activities or travelling to/attending appointments related to their child's disease.[10] There are wider societal costs associated with AADC-d and these are relevant to capture as a scenario analysis in the economic analysis. The societal costs that should be considered include caregiver and patient productivity loss, and formal and informal care costs.	Comment noted. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.
Equality and Diversity	PTC Therapeutics (PTC)	PTC does not consider the proposed scope to exclude any people on equality or unlawful discrimination grounds. PTC would like to reiterate that eladocagene exuparvovec should be made available to all eligible patients in the UK, regardless of the apparent disease severity. AADC-d is a severe, life-threatening disorder that impacts patients	Thank you for your comment. No action necessary.

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		from the first year of life. While there is evidence of milder forms of AADC-d, these cases are very rare and disease severity in AADC-d is not well defined or consistently reported in guidelines.[1,3] PTC would also like to note the need to treat AADC-d patients at as young an age as possible. Given that patients with AADC-d fail to hit any motor or developmental milestones as they age, the gap between the development of a child with AADC-d and an age-matched healthy peer progressively widens with increasing age. It is therefore essential to treat patients with eladocagene exuparvovec as early as possible. Evidence from trials for eladocagene exuparvovec shows that, while the treatment provides substantial and sustained benefit in patients of all ages, patients treated at a young age reach a higher score in motor and developmental measures than those treated at an older age.[18,19] This underlines the importance of treating as early as possible.	
Other considerations		No comments	
Innovation	PTC Therapeutics (PTC)	PTC considers eladocagene exuparvovec to be innovative and is a 'step-change' in the management of AADC-d with the potential to have a significant impact on health-related benefits and improve the way that the current unmet need is met. This is highlighted by the following: • Eladocagene exuparvovec was awarded PIM designation by the UK MHRA. • Eladocagene exuparvovec is the first disease-modifying treatment to be considered for approval by the EMA in AADC-d. • There are currently no licensed disease-modifying treatments for patients with AADC-d.[1]	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence presented to it, if the topic is referred for appraisal. No action necessary.

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		PTC also believes that the use of the technology will result in significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation. Most notably, eladocagene exuparvovec will provide huge value to caregivers and wider society given that caring for patients requires round-the-clock support. PTC therefore requests that caregiver utilities are considered in the economic analysis, and wider societal benefits (e.g. productivity, presenteeism, absenteeism) are included as a scenario. The caregiver burden of AADC-d includes: • Currently, caregivers have reported spending an average of 13 hours (8-20 hours) per day on practical and emotional care for their child with AADC-d. In addition, some caregivers spent a mean of 15 hours (7-33 hours) per week on administrative tasks such as planning activities or travelling to/attending appointments related to their child's disease.[10] • 75% of caregivers report that they stop working or have reduced their working hours due to their duties of looking after their child with AADC-d[10] 55% of caregivers received paid and/or unpaid help with care. Unpaid support was provided mainly by the partner with a mean of 37 hours per week. Paid support was provided by a registered nurse or training assistant with a mean of 27 hours per week. [10]	
	Metabolic Support UK	A single use gene replacement therapy can be considered a 'step-change' in treatment options for people living with AADC. MSUK and the AADC Research Trust will be running a consultation during this review to understand the current landscape for patients and caregivers living with AADC and their thoughts and opinions regarding this potential treatment. Based on the information available it can be suggested the treatment is innovative, however we would like to see the results from the clinical trial data and patient testimonials on the impact of the treatment to date, both short and longitudinal data if available.	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence presented to it, if the topic is referred for

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			appraisal. No action necessary.
	The AADC Research Trust	A single use gene replacement therapy can be considered a 'step-change' in treatment options for people living with AADC. MSUK and the AADC Research Trust will be running a consultation during this review to understand the current landscape for patients and caregivers living with AADC and their thoughts and opinions regarding this potential treatment. Based on the information available it can be suggested the treatment is innovative, however we would like to see the results from the clinical trial data and patient testimonials on the impact of the treatment to date. Longitudinal studies are not available yet for this treatment, and gene therapy trials have limited numbers of AADC participants due to how rare the disease is. We would like to see a summary of compassionate use data (since 2009) in basic terms, such as no of children still surviving, whether OGC's changed and whether conventional medications have been re-introduced. This data is only available from Taiwan where the majority of trial applicants also reside.	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence presented to it, if the topic is referred for appraisal. No action necessary.
Questions for consultation	PTC Therapeutics (PTC)	**What is the approximate number of people with AADC deficiency in the UK?** There are estimated to be [redacted] patients with AADC-d living in the UK currently, based on clinical expert insights. At the time of UK launch, it is expected that [redacted] patients with AADC-d in England will be eligible for eladocagene exuparvovec therapy, with a further [redacted] eligible patients per year thereafter.	Comment noted. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.

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		Are the clinical trial results generalisable to the population who would be treated in the UK? The baseline characteristics (e.g., age, phenotype and disease characteristics) of patients recruited in the clinical trials of eladocagene exuparvovec are similar to the anticipated eligible population in the UK. From PTC's conversations with UK clinical experts, no issues have been raised regarding the demographic differences between the clinical trial populations and those suitable for treatment in the UK. It is therefore anticipated that the clinical trial results are generalisable to the population in the UK. It should be noted, however, that due to the extremely rare nature of AADC-d, the clinical studies for eladocagene exuparvovec did not include any centres or patients from the UK. Patients for the clinical trials were recruited in Asia, where AADC-d prevalence is highest. Supplementary real-world data are available from patients in Europe, including France. **How would you define a mild, moderate or severe disease phenotype?** As an ultra-rare condition, there is no standard clinical practice regarding diagnosing AADC-d based on disease severity.	

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		A 2017 consensus guideline broadly classified the condition based on clinical descriptions from different studies, with a mild phenotype defined as a mild delay in developmental milestones, no requirement for ambulatory assistance, and mild intellectual disability, and severe phenotype defined as achieving no or very limited developmental milestones and being fully dependent.[1] Among 103 patients described in the guidelines, 82 (80%) were severe and 6 (6%) were mild, aligning with a natural history study describing 36 of 37 (97%) patients as severe.[12] Notably, the guidelines reported that there is no clear correlation between diagnostic markers and phenotype,[1] meaning that it is challenging to predict which patients will present with a mild versus a severe phenotype. PTC would therefore like to reiterate that even milder phenotypes face significant disabilities and it is difficult to predict the clinical course of young patients with seemingly mild initial symptoms. This is particularly relevant when considering the importance of treating at as young an age as possible, when severity of phenotype may not yet be known. AADC-d is severely debilitating and given that AADC-d patients fail to hit motor or developmental milestones as they age, the gap between the development of a child with AADC-d and an age-matched healthy peer progressively widens with increasing age.[1] Given that most patients have severe symptoms, there is a high unmet need, and a need to treat early, PTC would therefore like to reiterate that eladocagene exuparvovec is made available to all known patients with AADC-d in the UK (equating to an estimated [redacted] patients per year), regardless of phenotype.[1]	

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		What proportion of people with AADC deficiency in the UK have a severe disease phenotype? The most common occurring phenotype of AADC-d is the severe phenotype, where patients have no functional motor movement, fail to achieve motor milestones, and typically experience a shortened lifespan, often with an early death in the first decade of life.[1,14] All patients recruited into trials for eladocagene exuparvovec were deemed to have a severe disease phenotype due to the fact that they all had no or very little motor development. While the proportion of UK patients with a severe phenotype is not clear, a natural history study in Asia found that 36 of 37 patients (97%) had profound motor deficits (lack of full head control and unable to sit, stand, or speak) that did not improve during the course of the study, suggesting a severe phenotype.[2] Similarly, 2017 guidelines reported 80% of cases described in the literature as being severe. Importantly, clinical guidelines state that there is no link between genotype and phenotype,[1,3] meaning that prescribing therapeutics based on disease severity would not be able to occur based on a genetic confirmation alone. Eladocagene exuparvovec should therefore be made available for all patients with AADC-d in the UK (equating to an estimated [redacted] patients per year) **What is the life expectancy for people with a mild, moderate or severe disease phenotype?**	

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		There is limited published data on life expectancy for patients with AADC-d. However, three publications have consistently report life expectancy to be under a decade.[1,14,17] A mean life expectancy of 4.6 years was calculated in a natural history of disease study (range 1-7 years, based on the 10 deaths that occurred amongst 16 untreated patients studied).[14] Patients often die before the age of 7 due to the severe motor dysfunction, autonomic abnormalities, and secondary complications such as hypoxia, aspiration, and pneumonia.[1] ADDC-d is clearly associated with premature mortality. All AADC-d patients can face severely debilitating lives and given that AADC-d patients fail to hit motor or developmental milestones as they age, the gap between the development of a child with AADC-d and an age-matched healthy peer progressively widens with increasing age, increasingly highlighting the worse quality of life for these patients. **Would eladocagene exuparvovec be used to treat people with AADC deficiency with a mild or moderate disease phenotype?** Due to the ultra-rare and severely debilitating nature of the disease, PTC would expect eladocagene exuparvovec to be used to treat all patients with AADC-d regardless of genotype or phenotype. This is because all AADC-d patients have the same underlying cause of the disease (i.e., a mutation in the DDC gene that leads to AADC deficiency) and so should benefit from treatment with this therapy.	

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		Did the clinical trials include people who would be considered to have mild to severe AADC deficiency disease phenotype? The clinical trials only included patients with severe AADC-d disease phenotype. The severe phenotype was classed as no or very little motor development. As stated above, PTC proposes that eladocagene exuparvovec is made available to all eligible patients in the UK given the high unmet need, low estimated patient numbers, and severity of the disability in all patients, regardless of phenotype. **Have all relevant comparators for eladocagene exuparvovec been included in the scope?** Yes. Please refer to the “Comparator” section above. **Which treatments are considered to be established clinical practice in the NHS for AADC deficiency?** Currently, there are no other licensed disease-modifying treatments that aim to correct the underlying genetic cause of AADC-d. Current management options are symptomatic only and yield little improvement for most patients with AADC-d.[1]	

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		Clinical management, as mentioned in 2017 guidelines,[1] is a combination of symptomatic therapies. This may be a mixture of: • First line therapies: MAO inhibitors, dopamine antagonists, and vitamin B6. • Other symptomatic therapies: anticholinergic agents, benzodiazepines, melatonin, clonidine, and nasal decongestants. **Are the outcomes listed appropriate?** Please refer to the "Outcomes" section of the scoping response above. **Are there any subgroups of people in whom eladocagene exuparvovec is expected to provide greater clinical benefits or more value for money, or other groups that should be examined separately?** Given the high unmet need, [redacted] patient numbers, and devastating burden of AADC-d, PTC believes that eladocagene exuparvovec should be made available to all eligible patients, irrespective of severity. PTC would like to reiterate that classifications based on severity within AADC-d are not well defined and that there is no standard clinical practice regarding defining disease severity. The challenges of diagnosing and classifying the specific phenotypes are highlighted by studies highlighting a lack of correlation between genotype and phenotype.[1,3] As AADC-d impacts growth, development and achievement of motor milestones, patients need to	

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		be treated as young as possible, when the severity of the phenotype may not be known. While the clinical studies for eladocagene exuparvovec are in patients with a severe phenotype, eladocagene exuparvovec is expected to benefit all patients, independent of disease phenotype, due to all patients having the same underlying cause of the disease (a mutation in the DDC gene, resulting in deficiency of the AADC enzyme). Eladocagene exuparvovec replaces the faulty DDC gene with the aim of restoring AADC enzyme functioning. It is for these reasons that PTC believes that eladocagene exuparvovec will provide life-extending, life-changing treatment that has a long-lasting benefit in all patient types. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Eladocagene exuparvovec is a highly specialised and complex medical treatment for an ultra-rare and severely debilitating genetic disorder. Administration requires direct infusion into the putamen bilaterally using an established MRI-guided stereotactic system. Management of patients treated with eladocagene exuparvovec is therefore expected to take place in the [redacted] specialised centres in the UK with the necessary equipment and experience ([redacted]) and under the supervision of a small number of key opinion leaders with the necessary expertise.	

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		PTC appreciates that adoption of the technology into practice may present some initial challenges and will therefore collaborate closely with the [redacted] NHS centres in England to ensure a smooth process. It is worth noting that Great Ormond Street Hospital already has some experience with a similar procedure using gene therapy for Sanfilippo Syndrome.	
	The AADC Research Trust	• The UK AADDd patient population consists of 5 children, 3 adults and 2 deceased. • The clinical trial results cannot be generalised to the population who would be treated in the UK, because the data available doesn't cover enough mutation variables to quantify the outcome. • Historically children have not been accurately diagnosed as mild, moderate or severe suffers. The array of symptoms is widespread. Some children may have a better response to medications than others and genetics play a much bigger role in understanding phenotypes and how we describe these patients. E.g. Mild, Moderate and Severe phenotypes Vs Mild, Moderate and Severe Genotype. Genetically Vs Clinically it is not yet well enough understood to determine a blanket mild, moderate and a severe sufferer of AADC deficiency. Homozygous and Hemizygous affected populations may be easier to predict phenotype as mutation dominance is understood. Currently Heterozygous is more difficult to predict disease outcome. • The UK patient population have all presented as a severe phenotype at some point, either autonomically or physically. Phenotypically, a third of this population could be classified as mild to moderate, based on response to medication. The remainder will be classified as mild to severe with a varying medication response.	Thank you for your comment. The background and outcomes have been updated to include oculogyric crisis, and the background has been updated to better reflect population numbers.

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		• The life expectancy for all phenotypes is unknown, as there are many facets to the disease. • In terms of its use for mild or moderate disease phenotypes, we believe that every patient should be assessed on a case-by-case basis for suitability for Gene Therapy. • The majority of patients in this trial would have been considered to be severe phenotype as the common mutation found in the east Asian population is a severe genotype. • All relevant comparators have been included for the UK. However, there is an alternative Gene Therapy trial in the USA with published data that has also been used on a compassionate use basis in Europe, showing promise, and providing a child to adult age range with multiple mutation variables. • For established clinical practice in the NHS please refer to the published 'Consensus Guideline for the diagnosis and treatment of Aromatic L-amino Acid Decarboxylase (AADC) deficiency.' • The outcomes are appropriate, however oculogyric crisis is missing from the list. Oculogyric Crisis is one of the most important outcomes to be measured as it frequently impacts the sufferer and the caregiver. We also believe that long term efficacy data and psychosocial impacts must be included. • There are no subgroups that could be excluded as far as we are aware. • Barriers to adoption of this technology are: a) established contractures in AADCd patients such as scoliosis, poorly formed joints, including luxation and dislocation, b) multi-disciplinary therapeutic intervention post (Gene Therapy) op c) clinical management of post op side effects from Gene Therapy.	

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Additional comments on the draft scope	PTC Therapeutics (PTC)	As mentioned previously, PTC strongly believes that eladocagene exuparvovec meets all seven criteria for the NICE HST programme, making HST the appropriate appraisal route for eladocagene exuparvovec.	Comment noted. After discussion at the scoping workshop and topic selection oversight panel, the appraisal will be considered in NICE's Highly Specialised Technology program.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope