

**Office Director Memorandum**  
**Office of Clinical Evaluation**

**Summary of Regulatory Decision on Biologics License Application**

On March 15, 2024, PTC Therapeutics (the Applicant) submitted original Biologics License Application (BLA) 125722, seeking accelerated approval for KEBILIDI (eladocagene exuparvovec-tneq), for the following requested indication and dosage:

**Proposed Indication:** for treatment of aromatic L-amino acid decarboxylase deficiency.

**Proposed Dosage:**  $1.8 \times 10^{11}$  vg

KEBILIDI is an adeno-associated virus (AAV) vector-based gene therapy product that delivers a functional copy of the DDC gene into the putamen to increase levels of functional aromatic L-amino acid decarboxylase (AADC) in patients with AADC deficiency. AADC deficiency is a rare autosomal recessive disorder caused by biallelic mutations in the DDC gene that result in decreased synthesis of dopamine, serotonin, norepinephrine, and epinephrine. This neurodevelopmental disorder can be severe, life-threatening, and fatal; its most serious manifestations include severe hypotonia and autonomic dysfunction leading to complications such as feeding difficulties, failure to achieve developmental milestones, and death in childhood. The disease is heterogenous, with severe and less severe phenotypes. Treatment is typically with off-label use of dopamine agonists, monoamine oxidase inhibitors, and pyridoxine; however, these therapies provide limited effectiveness to treat the underlying cause of the disease.

The primary evidence supporting the Applicant's claims of safety and effectiveness is based on the results of Study AADC-002, a single-arm, multi-center study evaluating eladocagene exuparvovec in patients 1 to 18 years of age who have genetically confirmed, severe phenotype AADC deficiency; severe phenotype was defined as lacking achievement of gross motor milestones at baseline and having previously demonstrated lack of clinical response to standard of care medications. Patients with skull maturity (as assessed with imaging) received a single eladocagene exuparvovec dose of  $1.8 \times 10^{11}$  vg, administered via stereotactic neurosurgical procedure into the anterior and posterior putamen in a total of 4 infusions. Data from this single arm trial were compared to a historical cohort of untreated patients with severe phenotype AADC deficiency.

The main efficacy outcome measure in Study AADC-002 is increase in cerebrospinal fluid (CSF) homovanillic acid (HVA) levels of 20% or greater from baseline to Week 8 after treatment. HVA is a byproduct of dopamine breakdown. The Applicant proposed that a CSF HVA increase from baseline of  $\geq 20\%$  is a surrogate endpoint reasonably likely to predict clinical benefit. In Study AADC-002, additional outcome measures were collected, including motor milestone achievement assessed using the Peabody Developmental Motor Scale, Second Edition (PDMS-2); PDMS-2 assessments are conducted in Study AADC-002 at baseline, Week 24, Week 48, Week 72, Week 96, Week 156, Week 208, Week 260.

The data provided to support use of CSF HVA increase from baseline of  $\geq 20\%$  as a surrogate endpoint, were limited, as described in the clinical and clinical pharmacology review. Briefly, the limitations included:

- Absence of data or insufficiency of the data to characterize the potential for variability in the levels of CSF HVA due to factors unrelated to the gene therapy treatment (e.g., patient age, study and assay differences, concomitant treatment use, etc.);
- Unclear relationship between the proposed threshold of  $\geq 20\%$  and clinical outcomes- for example, the percent change noted in patients who were treated and considered responders, overlapped with the percent change in untreated patients;
- Insufficient data/information to justify the 8-week time point to assess increase in CSF HVA.

Due to these limitations, the FDA assessed eladocogene exuparvec's outcomes on motor milestone achievement as measured by PDMS-2. While not specified as a key efficacy endpoint in the study, the data collection plan was pre-specified in the protocol and data collection for this endpoint was deemed adequate to support its use.

The efficacy and safety analyses of Study AADC-002 were descriptive. Thirteen patients were enrolled with a median age of 2.8 years (1.3 to 10.8 years). Seven patients (54%) are female, 10 patients (77%) are Asian, two patients (15%) are White, and one patient reported "other" for race. Twelve of the 13 patients had the severe phenotype of AADC deficiency. All but one of the 13 patients enrolled in Study AADC-002 had data that permitted assessment of treatment effects on motor milestone achievement. In the 12 patients comprising the efficacy analysis population, eight patients (67%) achieved a new gross motor milestone at Week 48 (i.e., achieving a score of 2 on the PDMS-2 in at least "full head control"). In the eight patients with a clinical response, highest motor milestone achievement was as follows:

- "full head control" (N=3)
- "sitting with or without assistance" (N=3)
- "walking backwards" (N=2)

In comparison, none of the 44 patients the Applicant submitted as data from an external cohort of untreated patients with severe AADC deficiency, had documented motor milestone achievement. Patients in this historical cohort had severe gross motor developmental delay with no gross motor milestone achievement at a median age of 7.3 years (range 1.6 to 21 years).

With respect to pharmacodynamic data provided, all 13 patients in Study AADC-002 demonstrated consistent and sustained increases in HVA and L-DOPA, as assessed via quantitative assessment in CSF and by putamen specific 18F-DOPA PET uptake, respectively. These assessments are described in detail in the review documents.

Serious risks of treatment with KEBILIDI include dyskinesia and product administration-related risks. Common adverse events in Study AADC-002 occurring at an incidence of  $\geq 15\%$  include dyskinesia (77%), pyrexia (38%), hypotension (38%), anemia (31%), salivary hypersecretion

(23%), hypokalemia (23%), hypophosphatemia (23%), insomnia (23%), and hypomagnesemia (15%). The clinical review document provides a detailed review of safety data.

### **Regulatory Recommendation**

I reviewed the review team's assessment of the data submitted in the BLA, the team's interpretation of the results, and the recommendations of the primary clinical team (primary reviewers, branch chief, and division director); I have had the opportunity to discuss the team's perspective on the data and their subsequent recommendations, during the review of the BLA.

I agree with the primary clinical team's conclusions that AADC is a serious and life-threatening condition. I agree with the team's assessment of the data submitted in the BLA as constituting substantial evidence of eladocogene exuparvec's effectiveness. I agree with the team that there are therapies used off-label to treat patients with AADC deficiency. However, I differ in the perspective that these therapies are so effective as to mitigate the unmet medical need in patients with moderate or mild phenotypes of the disease; there is very limited information to characterize the effectiveness of what are essentially supportive therapies in this disease. Eladocogene exuparvec has demonstrated safety and effectiveness in patients with the most severe form of a disease that has an established single molecular pathway; the pharmacodynamic data (AADC disease-specific biomarkers) is supportive, and the results reflect a direct treatment effect of the product on this molecular pathway.

While there remains uncertainty regarding clinical benefit as is inherent with approvals based on an intermediate clinical endpoint reasonably likely to predict clinical benefit, it is reasonable, in the context of the benefits and risks of KEBILIDI in this rare disease, to extrapolate the observed effects in the 12 pediatric patients with severe phenotype evaluated in the pivotal study, to patients whose age and disease phenotype falls outside of that of the study population. The BLA did not include data to characterize the sustained effects on the gross motor function; this data will be necessary to verify KEBILIDI's clinical benefit, as a condition of accelerated approval.

I concur with the team's recommendation to grant accelerated approval to KEBILIDI based on effects on change from baseline in gross motor milestone achievement at 48 weeks post-treatment. I recommend approval for the treatment of adult and pediatric patients with aromatic L-amino acid decarboxylase (AADC) deficiency.

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Director, Office of Clinical Evaluation

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