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Division / Office	DCEGM/OCE/OTP
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Applicant	PTC Therapeutics
Established Name	eladocagene exuparvovec
(Proposed) Trade Name	KEBILIDI
Pharmacologic Class	Adeno-associated virus vector-based gene therapy
Formulation(s), including Adjuvants, etc	A sterile, parenteral formulation containing the active biological substance, a recombinant adeno-associated virus, serotype 2 (rAAV2) vector containing the human DDC gene that encodes the human AADC, and (b) (4) excipients
Dosage Form(s) and Route(s) of Administration	A total dose of 1.8×10^{11} vg (0.32 mL total volume) delivered as four 0.08 mL (0.45×10^{11} vg) infusions (two sites per putamen-anterior and posterior) at a rate of 0.003 mL/minute (0.18 mL/hour) for a total of 27 minutes per site using a cannula that is cleared by FDA for intraparenchymal infusion
Dosing Regimen	One-time dose
Indication(s) and Intended Population(s)	Treatment of aromatic L-amino acid decarboxylase (AADC) deficiency

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GLOSSARY

¹⁸ F-DOPA	L-6-[¹⁸ F] fluoro-3,4-dihydroxyphenylalanine
AADC	aromatic L-amino acid decarboxylase
AAV2	AAV2 adeno-associated virus, serotype 2
AE(s)	adverse event(s)
AIMS	AIMS Alberta Infant Motor Scale
Bayley-III	Bayley-III Bayley Scales of Infant and Toddler Development – third edition
BLA	biologic license application
CBER	Center for Biologics Evaluation and Research
cDNA	complementary DNA
COVID-19	coronavirus disease of 2019
CSF	cerebrospinal fluid
CSR	clinical study report
DDC	DDC DOPA decarboxylase
DOPA	dihydroxyphenylalanine
DP	drug product
DSMB	Data Safety Monitoring Board
EMA	EMA European Medicine’s Agency
H ₀	null hypothesis
hAADC	human aromatic L-ascorbic acid decarboxylase
HVA	homovanillic acid
IND	Investigational New Drug Application
ISE	Integrated Summary of Efficacy
ITT	intent-to-treat
L-DOPA	L-3,4-dihydroxyphenylalanine
M	month
MAO	monoamine oxidase
max	maximum
MHRA	United Kingdom’s Medicinal Health Products Regulatory Agency
min	minimum
MR	magnetic resonance
MRI	magnetic resonance imaging
NHDB	natural history database
PDMS-2	Peabody Developmental Motor Scale, second edition
PD	pharmacodynamics
PMR	postmarketing requirement
rAAV2	recombinant adeno-associated vector, serotype 2
SAE(s)	serious adverse event(s)
SD	standard deviation
SoC	standard of care
TEAE	treatment-emergent adverse event

1. Executive Summary

The applicant (PTC Therapeutics) submitted the original Biologics License Application (BLA) for the accelerated approval of KEBILIDI (gene therapy eladocogene exuparvec), for the treatment of aromatic L-amino acid decarboxylase (AADC) deficiency.

The primary evidence to support the efficacy and safety of KEBILIDI comes from data in the pivotal study PTC-AADC-GT-002 (referred to as AADC-002 hereafter). Data in an external untreated natural history cohort (referred to as “Natural History Database” [NHDB]) were also used as reference in the efficacy evaluation. Study AADC-002 is an ongoing open-label, multicenter, single arm study aiming to evaluate the efficacy and safety of KEBILIDI in pediatric patients with genetically confirmed AADC deficiency (severe phenotype) who had achieved full skull maturity. Thirteen pediatric patients aged 1.3 to 10.8 years (median: 2.8 years) were administered a total dose of 1.8×10^{11} vg KEBILIDI in a single neurosurgical procedure.

The applicant proposed to use a biomarker of cerebrospinal fluid (CSF) homovanillic acid (HVA), as a surrogate endpoint to support an application for accelerated approval. CSF HVA change from baseline to Week 8 was designated as the primary efficacy endpoint in Study AADC-002 for the purpose of this application. Please refer to the reviews by the clinical pharmacology and clinical reviewers regarding the evaluation of this biomarker as a surrogate endpoint to reasonably likely predict the clinical benefit of KEBILIDI. The review team concluded that the submitted evidence was inadequate to support the surrogacy of this biomarker endpoint.

The secondary efficacy endpoints related to clinical outcomes in Study AADC-002 included long-term motor milestone achievement, Peabody Developmental Motor Scale, Second Edition (PDMS-2) score, and Bayley-III scores through 60 months post treatment. The efficacy endpoint of motor milestone achievement was planned to be compared to the untreated pediatric patients with severe AADC deficiency and at least one motor milestone assessment after 2 years of age in the NHDB. However, up to the 01 March 2024 data cut, the median duration of follow-up among the treated patients was 82 weeks (range 23 to 109 weeks). All patients (except for one subject who withdrew at 23 weeks) reached 48 weeks of follow-up. Consequently, the assessments on motor milestone achievement at Week 48 in these patients are used instead as an intermediate clinical efficacy endpoint to support accelerated approval in FDA’s review of the application.

Among 12 treated patients with the severe phenotype, defined as no motor milestone achievement and no clinical response to standard of care therapy at baseline, 8 (67%) achieved a new gross motor milestone at Week 48: 8 (67%) achieved full head control, 5 (42%) achieved sitting with assistance, 4 (33%) achieved sitting without assistance, and 2 (17%) achieved walking backwards. In contrast, among 43 untreated subjects for whom the assessments were performed at the median age of 7.2 years (range 2 to 19 years), none of the 43 untreated pediatric patients with the severe phenotype had documented motor milestone achievement.

The comparison of above motor milestone achievement results between the treated and untreated patients was performed in a descriptive manner. As a post hoc exploratory analysis and under a strong assumption that the two groups were comparable, the difference in the proportion of patients achieving full head control between the KELBILIDI treated patients (8/12 [67%]) and untreated patients (0/43 [0%]) would reach statistical significance at a one-sided 2.5% level. However, because of the limited availability of the data among the NHDB patients with highly variable time spans between the first and last reported motor milestone assessments (e.g., some did not have data at earlier age), it is difficult to match patients on an individual level and properly compare the motor milestone achievement at comparable time points. Specifically, KEBILIDI-treated patients were assessed at 48 weeks post-treatment while the NHDB patients were often assessed only across longer time spans.

Without long-term data, there is limited statistical evidence for the conclusion that the observed motor milestone achievements at Week 48 in the treated patients is reasonably likely to predict clinical benefit KEBILIDI in a longer term. However, based on the clinical context and submitted clinical data, this conclusion is supportable due to the following considerations:

- The enrolled population had severe disease – all were at least two years old at baseline with no or poor head control and no clinical response to standard of care therapies. Their prognosis for achieving major motor milestones was poor.
- Some treated patients achieved motor milestones by Week 48 that are beyond what would be expected based on the natural course of the disease.
- The observed effect size for proportion of treated patients achieving minimum motor milestone (i.e., full head control) was high (8/12 [67%] for treated patients at Week 48 compared to 0/43 [0%] among untreated patients over a longer time span). Such a large effect size may be robust to uncertainty or possible sources of bias in the comparison and may be more likely to ensure preservation of a meaningful positive effect at later timepoints.

Regarding safety, in Study AADC-002, the most common TEAEs were pyrexia (in 11 patients, 4 related to surgery) and dyskinesia (in 10 patients, 10 related to treatment). The majority of TEAEs were of mild or moderate intensity and resolved. No subject discontinued due to TEAEs. No deaths occurred during the study.

In conclusion, based on the findings stated above and in consideration of the rarity of the disease and clear unmet need for the indicated AADC deficiency population, I recommend granting accelerated approval of KEBILIDI for treatment of AADC deficiency.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

AADC deficiency is an ultra-rare highly morbid and fatal disease due solely to the presence of pathological variants in the dihydroxyphenylalanine (DOPA) decarboxylase (DDC) gene that encodes for the AADC enzyme. AADC is required for the production of dopamine. Loss of AADC enzyme activity in the brain from birth results in marked or complete loss of dopamine production, causing most patients not to develop any motor function over their lifespan. Disease symptoms do not spontaneously improve, and death often occurs in the first decade of life. The disease significantly impacts the quality of life of patients and their caregivers.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are no approved treatments for this disease in the United States (US). The current standard of care (SoC) is intended to treat the symptoms of the disease and does not treat the underlying cause of the disease.

Eladocagene exuparvovec was approved as UPSTAZA by the European Medicines Agency (EMA) on 18 July 2022, by the United Kingdom's Medicinal Health Products Regulatory Agency (MHRA) in November 2022, and by Israel Ministry of Health in February 2023 for pediatric patients 18 months and older with the severe phenotype of AADC deficiency.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Orphan drug designation was granted for AADC deficiency in 2016 (#16-5269). Rare pediatric disease designation was granted in 2016 (#RPD-2016-63). The Investigational New Drug (IND) Application 19653 was opened in 2020. Two Type C meetings were held on November 14, 2019 and October 06, 2022, respectively to obtain the feedbacks on natural history database and discuss the use of a biomarker as a surrogate endpoint. A pre-BLA meeting was replaced with written preliminary responses on December 12, 2023, to discuss the BLA submission contents and strategies.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from Study AADC-002, which is the focus of this review memo. In addition, the data for untreated pediatric patients in an external natural history data base (NHDB) were used for efficacy comparisons. The review of the pre-specified primary endpoint of AADC-002, CSF HVA, was performed by the clinical pharmacological and clinical reviewers and is not included in this memo. Selected secondary efficacy endpoints related to clinical outcomes are reviewed in this memo. Study AADC-002 used the final manufacturing process (Process C) as in the commercial products. Because the products used in Studies AADC-1601, AADC-010, AADC-011, and AADC-1602 were based on different manufacturing processes (Process A or Process B), the clinical data from these studies are considered not applicable and therefore not reviewed in this memo. Please refer to Table 1 in Section 5.3 for summaries of these studies.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

- STN 125722/0 Module 1.14. Labeling
- STN 125722/0.21 Module 1.11.4 Multiple Information Amendments
 - Response to FDA Information Request (IR) received May 20, 2024
 - Response to FDA IR #12 received July 01, 2024
 - Response to FDA IR #17 received July 26, 2024
 - Response to FDA IR #23 received September 09, 2024
 - Response to FDA IR #28 received September 16, 2024
 - Response to FDA IR #30 received September 18, 2024
 - Response to FDA IR #35 received October 04, 2024
- STN 125722/0 Module 2.5. Clinical Overview
- STN 125722/0 Module 2.7. 3. Summary of Clinical Efficacy
- STN 125722/0 Module 2.7. 4. Summary of Clinical Safety
- STN 125722/0 Module 5.3.5 Clinical Study Reports (CSRs), supporting documents, datasets, and programs
- IND 19653/53 Module 1.14.4 Investigator's Brochure Version 6.0

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the clinical studies in the KEBILIDI development program. In addition, five patients have been treated under the French Compassionate Use Early Access Program and are under ongoing long-term follow-up. Nine additional patients have been treated in the compassionate use or commercial setting. In total, 27 patients have been treated with the product using materials under Process C.

Table 1 Synopses of Individual Studies

Study Identifier	Objective(s) of the Study	Study Design; Type of Control	Dosage Regimen (Manufacturing Process)	Number Of Patients	Study Status; Type of Report
AADC-CU/1601	First-in-human, retrospective and prospective evaluation of safety and efficacy data, and further to observe the safety and efficacy for a period of up to 5 years after gene delivery	Single arm, Phase 1 interventional and observational study with a historical control	1.8x10 ¹¹ vg (Process A)	8	Completed; Full
AADC-010	Evaluate the safety and efficacy for up to 5 years after gene delivery	Phase 1/2, single arm, prospective study with a historical control	1.8x10 ¹¹ vg (Process B)	10	Completed; Full
AADC-011	Evaluate the safety and efficacy for up to 12 months after gene delivery in patients who were not enrolled in the AADC-010 trial; evaluate higher dose (2.4x10 ¹¹ vg)	Phase 2b, single arm, nonrandomized, prospective study	1.8x10 ¹¹ vg or 2.4x10 ¹¹ vg (Process B)	12 total Lower dose: 3 patients >3 years Higher dose: 9 patients <3 years of age	Completed, Full
AADC-1602	Long-term systemic follow-up of patients with AADC deficiency for 10 years post eladocogene exuparvovec therapy	Single arm, observational study, to evaluate long-term safety and efficacy in patients who were administered eladocogene exuparvovec in Studies AADC/CU-1601, AADC-010, and AADC-011	N/A	24	Ongoing, Interim CSR
AADC - 002	To assess the safety of the SmartFlow MR compatible ventricular cannula for administering eladocogene exuparvovec to pediatric patients and to assess pharmacodynamics of eladocogene exuparvovec treatment by evaluating HVA levels.	Single arm, Phase 2, open label study	1.8x10 ¹¹ vg (Process C)	13	Ongoing, Interim CSR

Source: Adapted from BLA125722/0; Module 2.7.6 Synopses of Individual Studies.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study AADC-002 and Natural History Data Base (NHDB)

In this section, I include the pre-specified study objectives, design, and analyses for Study AADC-002. Information for the NHDB is also included in relevant sections.

6.1.1 Objectives

6.1.1.1 Primary Objectives

The primary objectives for Study AADC-002 are:

- To assess the PD of KEBILIDI treatment by evaluation of HVA levels at 8 weeks after administration.
- To assess the safety of the SmartFlow MR-compatible ventricular cannula for administering KEBILIDI to pediatric patients

6.1.1.2 Secondary Objectives

The secondary objectives of Study AADC-002 are:

- To assess the PD of KEBILIDI by evaluation of the following:
 - HVA at Week 48
 - 18F-DOPA uptake evaluated by PET Weeks 8 and 48
 - 5-HIAA at Weeks 8 and 48
 - 3-OMD at Weeks 8 and 48
- To evaluate the long-term efficacy of KEBILIDI through Month 60 as assessed by the following:
 - Motor milestone attainment
 - PDMS-2 score
 - Bayley-III
 - EQ-5D-Y
 - Body weight
 - AADC-specific symptoms
- To evaluate the safety of KEBILIDI treatment as assessed by TEAEs, neurological examinations, MRI, and clinical laboratory tests

6.1.2 Design Overview

Study AADC-002

Study AADC-002 is an open-label single-arm study in patients with AADC deficiency. Patients underwent screening and a baseline visit before receiving KEBILIDI by intraputaminial infusion. Eligible pediatric patients were enrolled and received KEBILIDI at 1.8×10^{11} vg via SmartFlow MR-compatible ventricular cannula in a single operative session. Patients also received SoC for their AADC deficiency during the study and return for regular visits during the course of the study. The length of the study, including the screening window, is approximately 63 months (approximately 5 years). The study has three phases: Trial Phase, Extension Phase, and Long-Term Extension Phase. The Trial Phase includes 8 weeks after gene therapy and its objective is to assess the PD and

safety of KEBILIDI. The Extension Phase consists of the 9 to 48 weeks after gene therapy and its objective is to capture additional clinical information through study evaluations, changes in motor development, AADC-specific symptoms, and other PD measures. The Long-Term Extension Phase is designed to capture long-term safety and efficacy data from 49 weeks to 60 months after gene therapy.

Natural History Database (NHDB)

The NHDB were sourced from a comprehensive review of published AADC deficiency literature through July 2022 which identified 156 publications that met the NHDB inclusion criteria. Across the different reports, a total of 396 patients were identified as unique. Of these, 288 had available high-quality data that identified them as unique patients with high certainty. These data included subject demographics, author institution, and genotype. Disease phenotype (severity) was classified based on the achievement of motor milestones at the age of 24 months. The definitions of the phenotypes utilized in the analyses of the NHDB are as follows:

- Severe: Subjects with no or poor head control at 24 months
- Mild: Subjects who walk with assistance before 24 months
- Moderate: All other subjects with ‘valid’ motor milestone assessments
- Unknown: Subjects with too little information about motor milestone achievements

Note, when adjudicating verbatim descriptions of motor developments into motor milestones some descriptions were potentially applicable to more than one motor milestone category. In these cases, a range of possible motor milestones was entered into the NHDB. For the definition of phenotype, a conservative approach using the highest possible motor milestone category was utilized. The disease phenotypes of the patients in the NHDB were adjudicated to identify those that had similar disease characteristics (severe phenotype) as those included in KEBILIDI clinical trials and hence could be used as a historical control.

After adjudication, a group of 51 unique patients who had not participated in KEBILIDI clinical studies and had similar disease phenotypes to the study patients (described as having no or little motor milestone achievement at 24 months) in the gene therapy clinical studies. These patients were used as a control group to compare acquisition of motor milestones with KEBILIDI-treated patients in Study AADC-002.

Reviewer’s comment: Among the 51 pediatric patients with the severe phenotype who were included in the NHDB as the external control group by the applicant, 8 pediatric patients were further excluded from the NHDB set based on FDA clinical review team’s suggestion. Among these eight pediatric patients, three likely did not have the severe phenotype given improvements standard care as discussed in the sponsor responses to IR#17, and five did not have any motor assessment after 24 months of age. As a result, 43 patients in the NHDB will be used in the analyses.

6.1.3 Population

Pediatric patients with genetically confirmed AADC deficiency between the age of 1 year to <18 years with a cranium sufficiently developed to allow placement of the stereotactic head frame for surgery were included in the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

KEBILIDI was administered during a single operative session as a one-time dose with four 0.08 mL infusions at a dose of 0.45×10^{11} vg and a volume of 80 μ L per site to 4 sites (2 per putamen), for the total dose of 1.8×10^{11} vg and a total volume of 320 μ L per subject.

6.1.6 Sites and Centers

Study AADC-002 is being conducted at four study sites in the US, one study site in Israel, and one study site in Taiwan.

6.1.7 Surveillance/Monitoring

In Study AADC-002, a Data Safety Monitoring Board (DSMB) conducted reviews of safety data as outlined in the DSMB charter. Review by DSMB is not required in order to enroll successive patients. The DSMB monitors ongoing study results to ensure subject well-being, safety, and study integrity. Please refer to the clinical review regarding details of study monitoring.

6.1.8 Endpoints and Criteria for Study Success

The primary and secondary efficacy endpoints in Study AADC-002 are:

- Primary efficacy endpoint: Change from baseline in HVA (a metabolite of dopamine) levels at the end of the Trial Phase (8 weeks after administration)
- Secondary efficacy endpoints:
 - Change from baseline in putaminal-specific F-DOPA uptake evaluated by PET at the end of the Trial Phase (8 weeks after administration) and the Extension Phase (48 weeks after administration)
 - Change from baseline in neurotransmitter CSF metabolites HVA (at 48 weeks after administration), 5-HIAA, and 3-OMD (at Weeks 8 and 48)
 - Attainment of motor milestones:
 - Motor skills and development milestones will be assessed using PDMS-2. Motor milestones are achieved in sequential order. Each skill item is assessed as a simple, 3-level scoring as a consistent way of describing the child's achievement of a particular motor skill, as listed below:
 - 0 = the skill is not met
 - 1 = the skill is emerging and shows a clear resemblance to mastery of the skill item
 - 2 = the child is mastering the motor skill
 - In assessing motor milestones achievement, if the PDMS-2 score for the question used to define a milestone achievement is 1, the milestone is considered "Emerging"; if the score for that question is 2, the milestone achievement is considered "Mastery".
 - Motor development as assessed by the PDMS-2
 - Cognitive, language, and motor development as assessed by Bayley-III
 - Change in EQ-5D-Y
 - Change in body weight
 - Assessment of AADC-specific symptoms

6.1.9 Statistical Considerations & Statistical Analysis Plan

Three analysis populations are defined in Study AADC-002:

- Definitions of analysis populations
 - Pharmacodynamics Population: all patients enrolled in the study who have received any amount of the study drug and have both baseline and at least one post-baseline value of at least one PD variable.
 - Safety Population: all enrolled patients who received any amount of study drug.
 - Efficacy Population: all patients enrolled in the study who have received any amount of study drug and have both baseline and at least one post-baseline evaluation of at least one efficacy variable.

- Sample size planning

No formal statistical hypothesis testing was planned in Study AADC-002. The sample size was not based on statistical power consideration, rather, it was based on feasibility.

- Statistical methods
 - Secondary endpoints were to be summarized using descriptive statistics for each timepoint. The number of patients achieving each motor milestone will be presented for each stage of achievement by timepoint after gene therapy. The number and percentage of patients achieved each motor milestone for each stage of achievement by time point will be presented. In addition, new milestones observed at a visit that had not been achieved in prior visits for a subject will also be summarized. Missing data due to missed visits or withdrawal or death will not be imputed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

There were 13 patients enrolled and treated in Study AADC-002.

6.1.10.1.1 Demographics

Table 2 shows the demographic information for patients in Study AADC-002 and the NHDB cohort. In Study AADC-002, the median age at time of treatment was 33 months (range: 16 to 129 months), there were 6 males and 7 females, 10 patients were Asian, 2 were White, and 1 was Other. Patients in Study AADC-002 were at a lower age at diagnosis than those in the NHDB cohort. The proportion of patients with heterozygous founder mutation in genotype is higher in study AADC-002 than the NHDB cohort. There are no notable differences in the remaining baseline variables.

Table 2 Demographics and Baseline Data Listing

Variable	Category	Study AADC-002 (N=13)	NHDB Cohort (N=43)
Age at symptom onset (months)	N	11 ^a	NA
	Mean (SD)	2.0 (1.84)	NA
	Median (min, max)	2.0 (0.0, 4.0)	NA
Age at diagnosis (months)	N	12 ^a	43
	Mean (SD)	13.3 (10.7)	33.4 (27.0)
	Median (min, max)	9.5 (1, 37)	27.5 (3, 108)
Age at Screening (months)	N	13	NA
	Mean (SD)	42.8 (29.9)	NA
	Median (min, max)	31 (13, 127)	NA
Age at gene therapy (months)	N	13	NA
	Mean (SD)	45.2 (29.5)	NA
	Median (min, max)	33.0 (16, 129)	NA
Sex (n [%])	Male	6 (46.2)	22 (51.1)
	Female	7 (53.8)	15 (34.9)
	Unknown	0 (0.0)	6 (14.0)
Ethnicity (n [%])	Hispanic or Latino	2 (15.4)	NA
	Not Hispanic or Latino	10 (76.9)	NA
	Unknown	1 (7.7)	NA
Race (n [%])	Asian - Chinese	10 (76.9)	20 (46.5)
	Asian - Other	0 (0.0)	8 (18.6)
	White	2 (15.4)	6 (14.0)
	Other*	1 (7.7)	0 (0.0)
	Unknown	0 (0.0)	9 (20.9)
Genotype (n [%])	Homozygous	2 (15.4)	15 (34.9)
	Heterozygous	11 (84.6)	18 (41.9)
	Not detected or unknown	0 (0)	10 (23.2)

a. When N < 13, data are missing for the variable.

Source: Adapted from BLA125722/0; Module 5.3.5.2 Interim Clinical Study Report of Study AADC-002 5.3.5.2, Table 6; Module 2.7.3 Summary of Clinical Efficacy, Table 7; Module 5.3.5.4 Natural History Database Summary Report, Table 6.

* Other: if not “White”, “Black or African American”, “Asian”, “American Indian or Alaska Native”, “Native Hawaiian or Other Pacific Islander” or “Multiple”.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In Study AADC-002, the types and frequencies of conditions/illness/surgical procedures present in the study population were consistent with those expected in patients with AADC deficiency. Twelve of the 13 patients had the severe phenotype of AADC

deficiency, defined as having no motor milestone achievement at baseline and no clinical response to standard of care therapies. One subject had a “variant” of the severe phenotype, with the ability to sit with assistance but with lack of head control.

All 13 patients received prior and concomitant medications, the majority of which were for treatment of symptoms related to AADC deficiency (SoC), or prophylaxis for procedures.

6.1.10.1.3 Subject Disposition

All 13 patients in Study AADC-002 have completed the Trial Phase (8 weeks) (Table 3). One subject has discontinued the study (withdrawn consent) during the Extension Phase and has a total of 23 weeks of follow-up. One subject declined to enroll in the Long-Term Extension Phase of the study and has a total of 73 weeks of follow-up. One subject has discontinued the study (withdrawn consent) after the enrollment in the Long-Term Extension Phase and has a total of 71 weeks of follow-up. All other patients remained in the study as of the time of this submission.

Table 3 Summary of Subject Disposition in Study AADC-002

Variable	Study AADC-002 (N=13)
Number of screened patients	16
Number of screen failures	3
Number in safety population	13
Number of patients withdrawn from study^a	3
Subject completed Trial Phase n (%)	
Yes	13 (100)
Early discontinuation	0
Ongoing	0
Subject completed Extension Phase n (%)	
Yes ^b	8 (61.5)
Early discontinuation	1 (7.7)
Ongoing	3 (23.1)
Subject enrolled in Long-Term Extension Phase n (%)	
Yes	7 (53.8)
No	1 (7.7)
Subject completed Long-Term Extension Phase n (%)	
Yes	0
Early discontinuation	1 (14.3)
Ongoing	6 (85.7)

^a At the time of the last on-site visit or follow-up phone call, the 3 patients who discontinued the study did not report any safety concerns and there were no reports of SAEs, which include fatalities or life-threatening conditions.

^b Subject (b) (6) completed the Week 48 visit prior to the data cut and is still entering into the Long-Term Extension Phase of the study, but their disposition CRF was not completed prior to the data extract. This subject was not included in the count of "Yes" for Completed Extension Phase.

Note: Trial Phase=8 weeks after gene therapy, Extension Phase=9 to 48 weeks after gene therapy, Long-Term Extension Phase=49 weeks to 60 months after gene therapy.

Source: Adapted from BLA125722/0; Module 5.3.5.2 Interim Clinical Study Report of Study AADC-002, Table 5

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

The primary endpoint pre-specified in the protocol was CSF HVA change from baseline to Week 8. Please refer to clinical pharmacology and clinical reviews regarding the evaluation of the results for this endpoint.

6.1.11.2 Analyses of Secondary Endpoints

Motor Milestones

Patients treated with KEBILIDI acquired motor milestones, such as gaining head control, the ability to sit unassisted, and standing with support, beginning at Week 24 post-treatment. The numbers of patients who demonstrated a newly emerging skill or mastery of a skill cumulatively at Weeks 24, 48, 72, and 96 are summarized in Table 4.

Table 4 Summary of Motor Milestones Achieved^a at Each Visit (Efficacy Population N=13)

Motor Milestone^a (emerging skill or mastery)	Baseline^b N=12^c	Week 24 N=11^c	Week 48 N=12^c	Week 72 N=3^c	Week 96 N=3^c
Full head control	0	4	9	3	3
Sitting unassisted	0	3	4	0	2
Standing with support	0	2	2	0	0
Walking with assistance	0	0	2	0	0
Walk to a toy	0	0	2	0	0
Walking upstairs with support	0	0	2	0	0
Walking backwards using normal stride	0	0	2	0	0

Abbreviations: number of patients with a PDMS-2 score of 1 or 2 for that milestone; PDMS-2, Peabody Developmental Motor Scale, second edition

^a Motor milestones achieved means that patients demonstrated emerging skill or mastery, which are defined as earning a score of 1 or 2 on the PDMS-2, respectively.

^b Baselines values are only reported for patients who have post-baseline data.

^c The N for each timepoint represents the number of patients assessed at that timepoint.

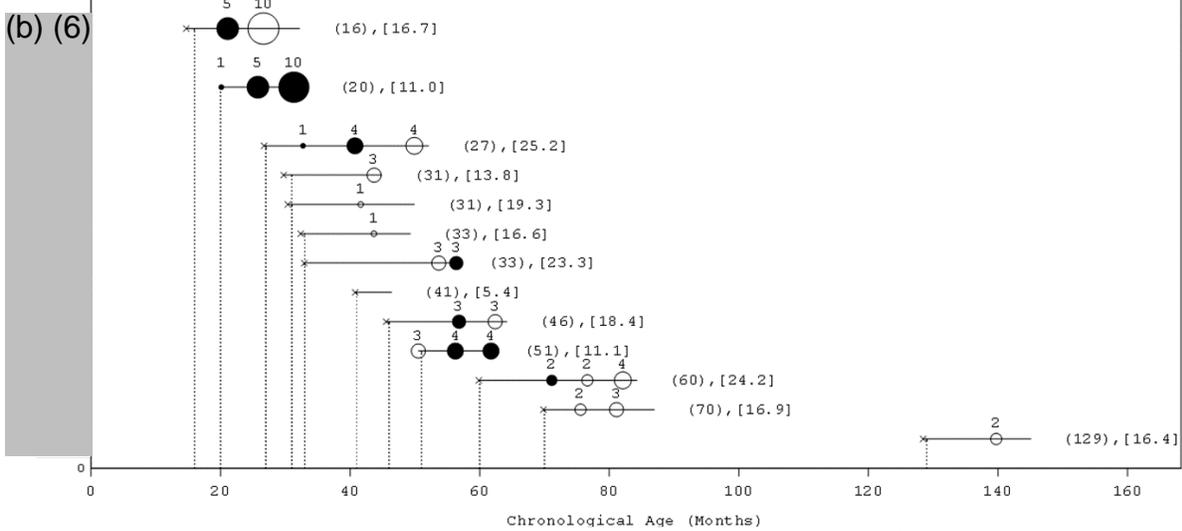
Note: Motor milestones are acquired sequentially, i.e., in the following order: full head control, sitting, standing, and walking. The study is still ongoing with only 3 patients having motor assessment at Week 72 and Week 96 Visit by May 20, 2024.

Source: Adapted from BLA125722/0; Module 1.11.4 Response to FDA Information Request received May 20, 2024, Table 5.

Figure 1 and Figure 2 display the gross motor milestone achievement results for the KEBILIDI treated patients and the NHDB untreated patients, respectively. The

KELBILIDI treated patients presented apparent motor milestone achievements visually when compared to the untreated patients.

Figure 1 Highest Motor Milestone Achieved at a Visit After Treatment with Eladocagene Exuparvovec in Study AADC-002



Solid circle: Mastering (PDMS-2 score of 2); **Hollow circle:** Emerging (PDMS-2 score of 1). The vertical dashed lines indicate age at the time of treatment (in months) for each subject.

The horizontal lines start from baseline PDMS-2 assessment up to last available follow-up time or data cutoff date (01 March 2024), whichever is earlier. Age at treatment in months is shown in parentheses (); The duration of follow-up in months is shown in brackets [].

Motor milestones: x =no motor milestone achieved; 1 =Partial head control (Sta Q5); 2 =Head control (Sta Q10); 3 =Sitting with assistance (Sta Q11); 4 =Sitting unassisted (Sta Q14); 5 =Standing with support (Loc Q28); 6 =Standing away from Support (Loc Q31); 7 =Walking with assistance (Loc Q34); 8 =Walking to Toy (Loc Q35); 9 =Walking Up Stairs With Support (Loc Q40); 10 =Walking Backward using Normal Stride (LOC Q44).

Source: Adapted from BLA125722/0; Module 1.11.4 Response to FDA IR #35 received October 04, 2024; Figure 1.

Figure 2 Highest Motor Milestone Achieved at a Visit in NHDB Cohort

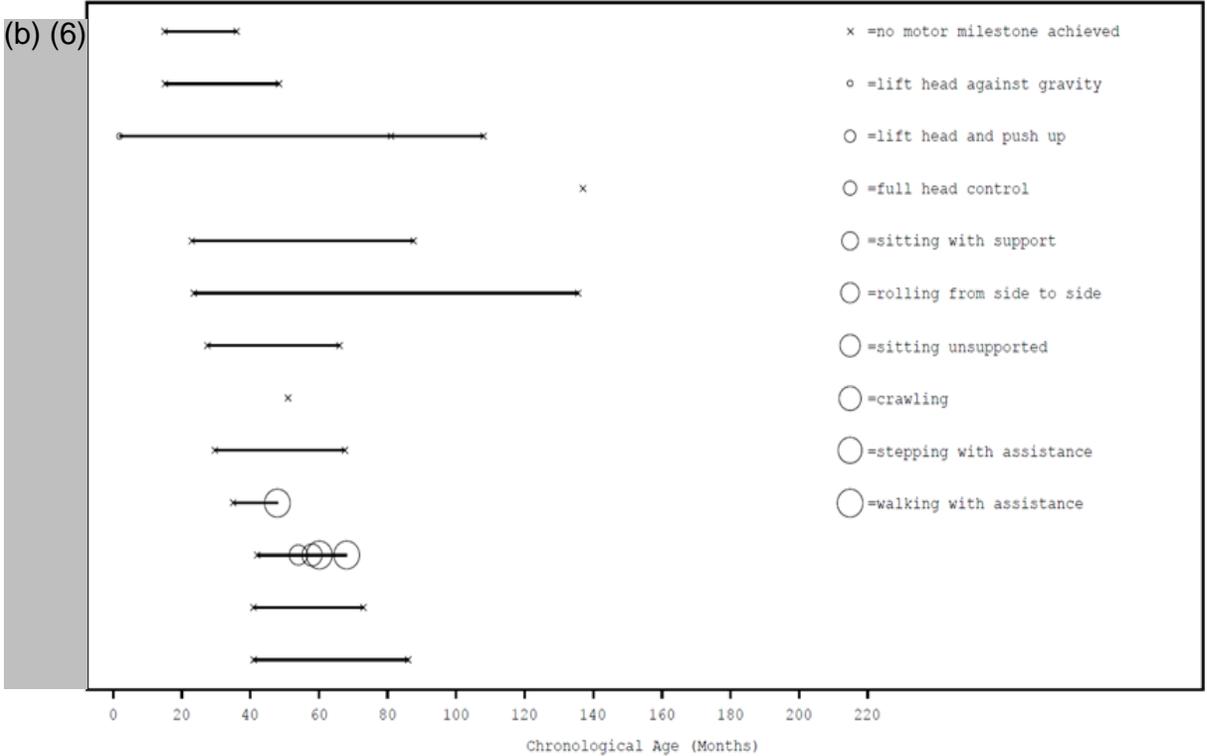
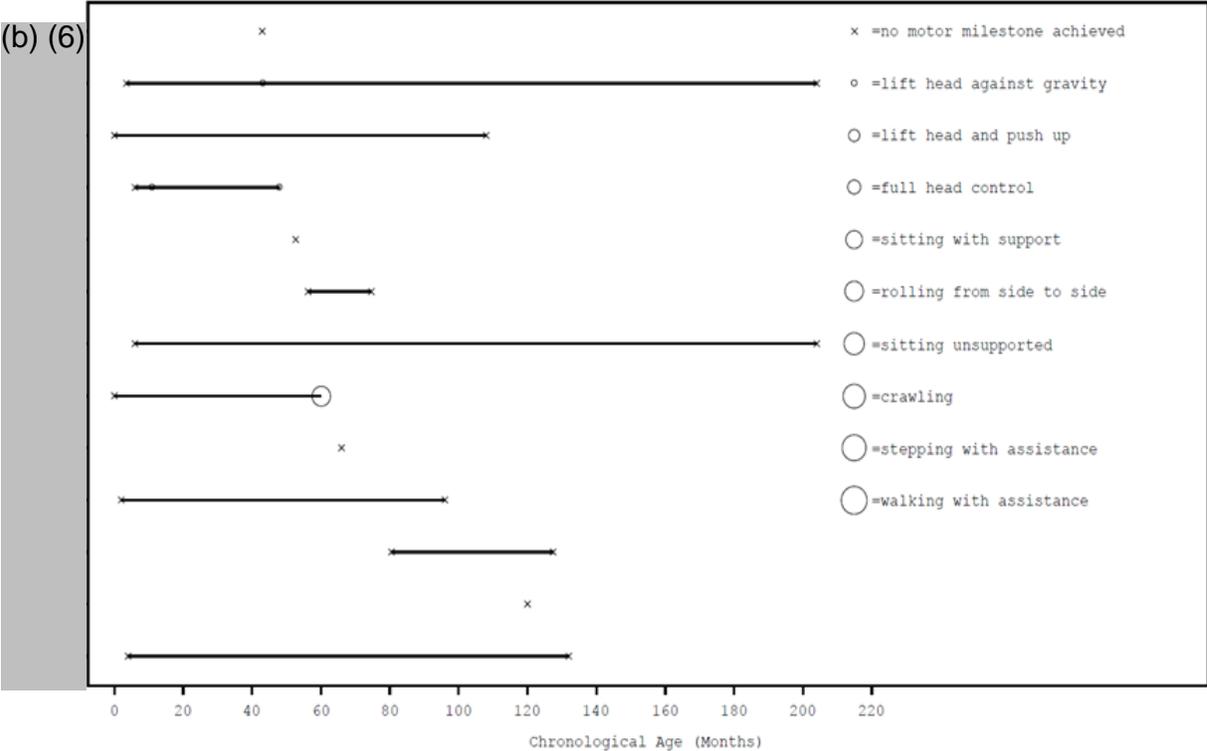
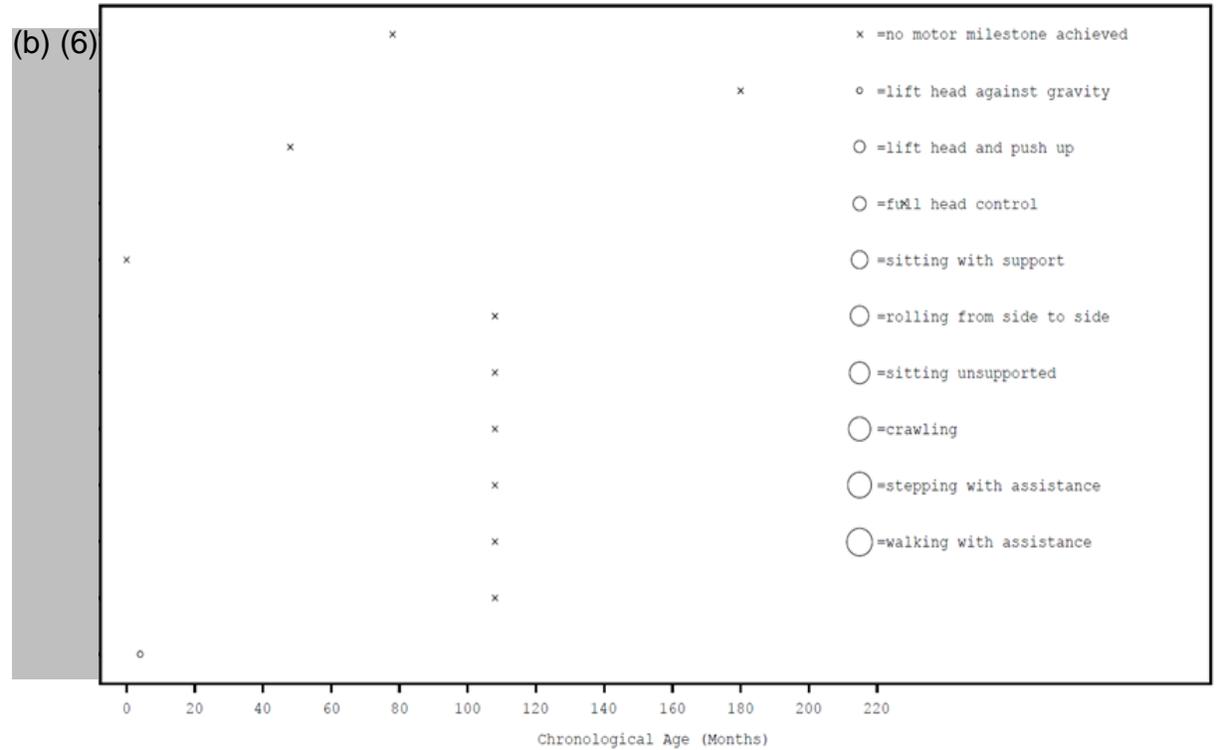
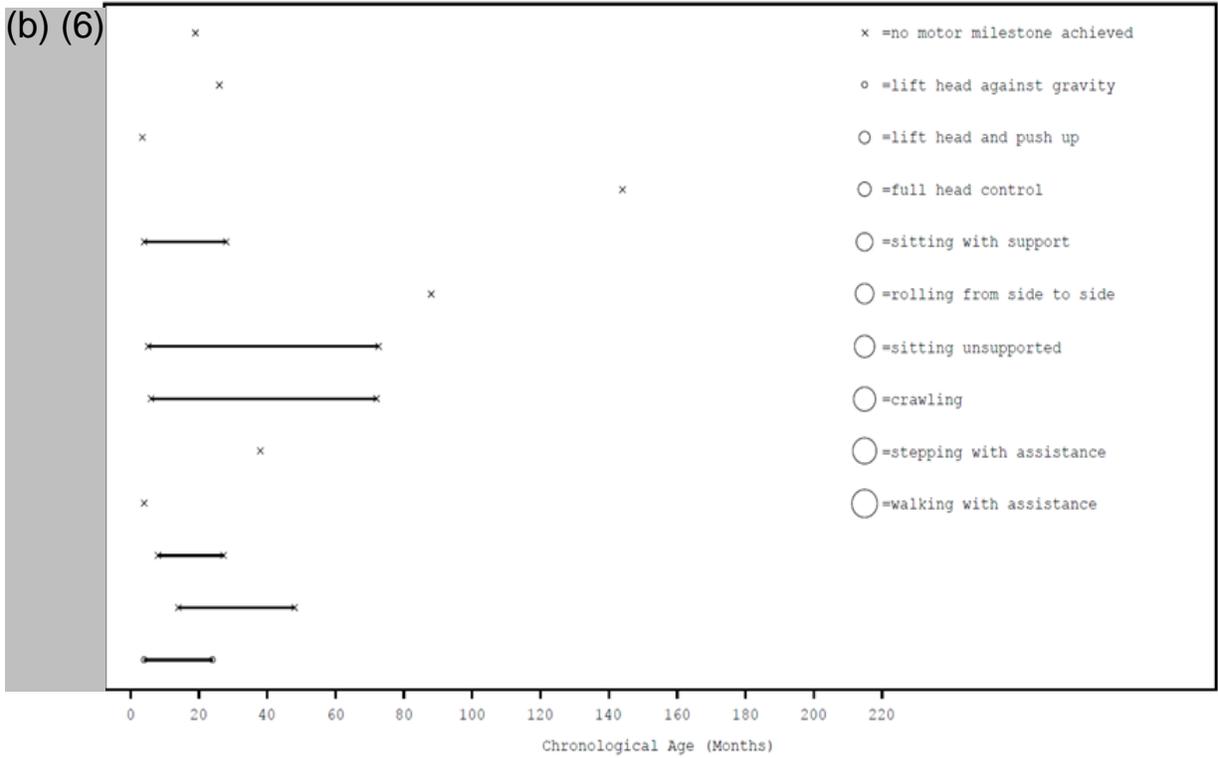


Figure 2 Highest Motor Milestone Achieved at a Visit in NHDB Cohort (Continued)



Note: Eight patients marked in grey were decided to be excluded from the NHDB control group by FDA (b) (6) (b) (6).

Source: Adapted from BLA125722/0; Module 1.11.4 Figure 1 in Response to FDA IR #30 received October 04, 2024; Figure 1.

Furthermore, Table 5 presents the Week 48 motor milestone assessments in the KELBILIDI treated patients, compared to the highest motor milestones among all available assessments in the 43 untreated patients, for whom assessments were performed at the median age of 7.2 years (range 2 to 19 years).

In Study AADC-002, 8 (67%) of the 12 treated patients with the severe phenotype (no motor milestone achievement at baseline) achieved a new gross motor milestone at Week 48: 8 (67%) achieved full head control, 5 (42%) achieved sitting with assistance, 4 (33%) achieved sitting without assistance, and 2 (17%) achieved walking backwards. In contrast, none of the 43 untreated pediatric patients with the severe phenotype had documented motor milestone achievement.

Reviewer’s comments:

- *As a post hoc exploratory analysis and under a strong assumption that the two groups were comparable, the difference in the proportion of patients achieving full head control between the KELBILIDI treated patients (8/12 [67%]) and untreated patients (0/43 [0%]) would reach statistical significance at a one-sided 2.5% level.*
- *However, because of the limited availability of the data among the NHDB patients with highly variable time spans between the first and last reported motor milestone assessments (e.g., some did not have data at earlier age), it is difficult to match patients on an individual level and properly compare the motor milestone achievement at comparable time points. Specifically, KEBILIDI-treated patients were assessed at 48 weeks post-treatment while the NHDB patients were often assessed only across longer time spans.*
- *Without long-term data, there is limited statistical evidence for the conclusion that the observed motor milestone achievements at Week 48 in the treated patients is reasonably likely to predict clinical benefit KEBILIDI in a longer term. However, based on the clinical context (per discussion with the clinical review team) and submitted clinical data, this conclusion is supportable.*

Table 5 Cumulative Key Motor Milestones Achieved up to Week 48 compared to Natural History Database

	Study AADC-002 Patients (N=12)	NHDB Patients (N=43)	
Motor Milestone at Mastery Level^a	n(%)	n(%)	p-value^b
Full head control	8 (67)	0 (0)	<0.0001
Sitting with assistance	5 (42)	0 (0)	0.0002
Sitting unassisted	4 (33)	0 (0)	0.0015
Standing with support	2 (17)	0 (0)	0.0444
Walking with assistance	2 (17)	0 (0)	0.0444

a. Based on PDMS-2 score of 2 (Mastery)

b. One-sided Fisher Exact test at the 2.5% level. The motor milestones were tested sequentially (from “full head control” to “walking with assistance”) and would only continue to test the next motor milestone when the current test showed significant results. The recorded p-values in the table were just for reference, not representing the true test procedure.

Source: FDA Statistical reviewer’s analysis

Motor Development Tests: PDMS-2

Beginning at Week 24, the first post-treatment assessment for PDMS-2, all patients showed an increase from baseline in PDMS-2 total score. As shown in Table 6, the mean (SD) change from baseline at Week 24 (n=11) was 50.8 points (53.6), and 69.5 (67.8) at Week 48 (n=12).

Table 6 Change from Baseline in PDMS-2 Total Score (Efficacy Population N=13)

Visit	N	Mean (SD)	Change from Baseline (mean [SD])
Baseline	13	14.5 (11.65)	-
Week 24	11	65.8 (62.45)	50.8 (53.60)
Week 48	12	84.1 (75.51)	69.5 (67.79)
Week 72	3	79.0 (25.24)	67.0 (28.62)
Week 96	3	99.3 (10.69)	88.3 (17.16)

Abbreviations: N, number of patients; SD, standard deviation

Source: Adapted from BLA125722/0; Module 1.11.4 Response to FDA Information Request received May 20, 2024, Table 6.

Cognition and Language Scores: Bayley-III

From Table 7, patients treated with KEBILIDI showed improvement in Bayley-III total scores beginning at Week 24 post-treatment and increasing over time; a mean change from baseline of 7.7 was seen at Week 24 (n=9) and increased to 19.6 at Week 48 (n=12).

Table 7 Change from Baseline in Bayley-III Total Score (Efficacy Population N=13)

Visit	N	Mean (SD)	Change from Baseline (mean [SD])
Baseline	11	29.5 (10.07)	-
Week 24	9	39.8 (18.03)	7.7 (16.05)
Week 48	12	47.1 (20.40)	19.6 (17.06)
Week 72	4	48.5 (6.35)	18.7 (1.53)
Week 96	3	54.0 (2.65)	23.0 (2.83)

Abbreviations: N, number of patients; SD, standard deviation

Source: Adapted from BLA125722/0; Module 1.11.4 Response to FDA Information Request received May 20, 2024, Table 7.

6.1.11.3 Subpopulation Analyses

The Majority (76.9%) of patients are Asian in this study. Due to the limited sample size, no formal statistical subgroup analysis was conducted.

6.1.11.4 Dropouts and/or Discontinuations

There was one subject dropped out of the study (withdrawn consent) prior to Week 48 with a total of 23 weeks of follow-up, so only 12 patients had gross motor milestone achievement assessed at Week 48.

6.1.12 Safety Analyses

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data. The safety analysis set in this section includes a total of 13 treated patients. The median duration of follow-up was 72 weeks (range 23 to 109 weeks).

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 241 TEAEs were recorded, the majority of which were determined to be unrelated to treatment. The most common TEAEs were pyrexia (in 11 patients) and dyskinesia (in 10 patients) (Table 8). Pyrexia was the most frequently reported TEAE considered related to surgery (4 subjects). Ten subjects experienced a TEAE considered related to gene therapy, the most frequent of which was dyskinesia in 10 subjects. The majority of TEAEs were of mild or moderate intensity and resolved. No subject discontinued due to TEAEs.

Table 8 Summary of Treatment-Emergent Adverse Events by Preferred Term Reported in ≥ 2 Patients (Safety Population)

Adverse Event Category	Number (%) of Patients (N=13)
Pyrexia	11 (84.6)
Dyskinesia	10 (76.9)
Hypotension	4 (30.8)
Anaemia	4 (30.8)
Salivary hypersecretion	3 (23.1)
Hypokalaemia	3 (23.1)
Hypophosphataemia	3 (23.1)
Insomnia	3 (23.1)
Hypomagnesaemia	2 (15.4)
Procedural complications*	2 (15.4)

* Procedural complications included respiratory and cardiac arrest.

Note: All listed TEAE occurred within 120 days after treatment.

Adapted from IND19653; Module 1.14.4 Investigator's Brochure Version 6.0, Table 28.

6.1.12.5 Adverse Events of Special Interest (AESI)

The protocol-specified AESIs of dyskinesia, AEs specifically related to the neurosurgical procedure, and CSF leaks were assessed. There were no AEs of CSF leaks reported, and no evidence found in brain imaging assessments. Of the 13 patients treated in the study, 10 (76.9%) experienced dyskinesia, most mild or moderate in severity. One event of dyskinesia was considered severe and reported as an SAE. The median time to onset of dyskinesia was 27.5 days after gene therapy. Dyskinesia was ongoing in 1 subject at the time of the BLA submission.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary evidence to support the efficacy and safety of KEBILIDI comes from data in the pivotal study PTC-AADC-GT-002 (referred to as AADC-002 hereafter). Data in an external untreated natural history cohort (referred to as “Natural History Database” [NHDB]) were also used as reference in the efficacy evaluation. Study AADC-002 is an ongoing open-label, multicenter, single arm study aiming to evaluate the efficacy and safety of KEBILIDI in pediatric patients with genetically confirmed AADC deficiency (severe phenotype) who had achieved full skull maturity. Thirteen pediatric patients aged 1.3 to 10.8 years (median: 2.8 years) were administered a total dose of 1.8×10^{11} vg KEBILIDI in a single neurosurgical procedure.

The applicant proposed to use a biomarker of cerebrospinal fluid (CSF) homovanillic acid (HVA), as a surrogate endpoint to support an application for accelerated approval. CSF HVA change from baseline to Week 8 was designated as the primary efficacy endpoint in Study AADC-002 for the purpose of this application. Please refer to the reviews by the clinical pharmacology and clinical reviewers regarding the evaluation of this biomarker as a surrogate endpoint to reasonably likely predict the clinical benefit of KEBILIDI. The review team concluded that the submitted evidence was inadequate to support the surrogacy of this biomarker endpoint.

The secondary efficacy endpoints related to clinical outcomes in Study AADC-002 included long-term motor milestone achievement, Peabody Developmental Motor Scale, Second Edition (PDMS-2) score, and Bayley-III scores through 60 months post treatment. The efficacy endpoint of motor milestone achievement was planned to be compared to the untreated pediatric patients with severe AADC deficiency and at least one motor milestone assessment after 2 years of age in the NHDB. However, up to the 01 March 2024 data cut, the median duration of follow-up among the treated patients was 82 weeks (range 23 to 109 weeks). All patients (except for one subject who withdrew at 23 weeks) reached 48 weeks of follow-up. Consequently, the assessments on motor milestone achievement at Week 48 in these patients are used instead as an intermediate clinical efficacy endpoint to support accelerated approval in FDA’s review of the application.

Among 12 treated patients with the severe phenotype, defined as no motor milestone achievement and no clinical response to standard of care therapy at baseline, 8 (67%) achieved a new gross motor milestone at Week 48: 8 (67%) achieved full head control, 5 (42%) achieved sitting with assistance, 4 (33%) achieved sitting without assistance, and 2 (17%) achieved walking backwards. In contrast, among 43 untreated subjects for whom the assessments were performed at the median age of 7.2 years (range 2 to 19 years), none of the 43 untreated pediatric patients with the severe phenotype had documented motor milestone achievement.

The comparison of above motor milestone achievement results between the treated and untreated patients was performed in a descriptive manner. As a post hoc exploratory analysis and under a strong assumption that the two groups were comparable, the

difference in the proportion of patients achieving full head control between the KELBILIDI treated patients (8/12 [67%]) and untreated patients (0/43 [0%]) would reach statistical significance at a one-sided 2.5% level. However, because of the limited availability of the data among the NHDB patients with highly variable time spans between the first and last reported motor milestone assessments (e.g., some did not have data at earlier age), it is difficult to match patients on an individual level and properly compare the motor milestone achievement at comparable time points. Specifically, KEBILIDI-treated patients were assessed at 48 weeks post-treatment while the NHDB patients were often assessed only across longer time spans.

Without long-term data, there is limited statistical evidence for the conclusion that the observed motor milestone achievements at Week 48 in the treated patients is reasonably likely to predict clinical benefit KEBILIDI in a longer term. However, based on the clinical context and submitted clinical data, this conclusion is supportable due to the following considerations:

- The enrolled population had severe disease – all were at least two years old at baseline with no or poor head control and no clinical response to standard of care therapies. Their prognosis for achieving major motor milestones was poor.
- Some treated patients achieved motor milestones by Week 48 that are beyond what would be expected based on the natural course of the disease.
- The observed effect size for proportion of treated patients achieving minimum motor milestone (i.e., full head control) was high (8/12 [67%] for treated patients at Week 48 compared to 0/43 [0%] among untreated patients over a longer time span). Such a large effect size may be robust to uncertainty or possible sources of bias in the comparison and may be more likely to ensure preservation of a meaningful positive effect at later timepoints.

Regarding safety, in Study AADC-002, the most common TEAEs were pyrexia (in 11 patients, 4 related to surgery) and dyskinesia (in 10 patients, 10 related to treatment). The majority of TEAEs were of mild or moderate intensity and resolved. No subject discontinued due to TEAEs. No deaths occurred during the study.

10.2 Conclusions and Recommendations

In conclusion, based on the findings stated above and in consideration of the rarity of the disease and clear unmet need for the indicated AADC deficiency population, I recommend granting accelerated approval of KEBILIDI for treatment of AADC deficiency.