25 June 2026
EMADOC-1700519818-3456293
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Fintepla

Fenfluramine

Procedure no: EMA/PAM/0000339786

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

1. Introduction

On 30 March 2026, the MAH submitted a completed paediatric study for Fintepla, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also assessed as part of this post-authorisation measure EMA/PAM/0000339786.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that RWE1624: "Patient Characteristics, Treatment Patterns, and Healthcare Resource Utilization among Patients with CDKL5 Deficiency in US Claims Data" is not part of the Fintepla Paediatric Investigation Plan (001990-PIP01-16). A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Fintepla is only available as an oral solution containing fenfluramine with a concentration of 2.2 mg/ml. As they are easy to swallow and allow for straightforward dose adjustments, oral solutions are considered a suitable paediatric formulation.

However, the focus of this study was not to evaluate one specific medicinal product, but rather to describe certain characteristics and treatment patterns among patients with CDKL5 deficiency.

2.3. Clinical aspects

Introduction

The MAH submitted a final report for:

- RWE1624: Patient Characteristics, Treatment Patterns, and Healthcare Resource Utilization among Patients with CDKL5 Deficiency in US Claims Data

Clinical study

RWE1624: "Patient Characteristics, Treatment Patterns, and Healthcare Resource Utilization among Patients with CDKL5 Deficiency in US Claims Data"

Description

RWE1624 is a retrospective US claims analysis of patients with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD), which aimed to determine prevalence and incidence, treatment patterns, and healthcare resource utilisation (HCRU) among these patients.

CDD, a rare and severe developmental epileptic encephalopathy (DEE) caused by pathogenic variants in the CDKL5 gene, is characterised by early-onset, antiseizure medication (ASM)-resistant seizures and impaired neurological development with median age of seizure onset of 6 weeks, and 90% of cases having onset before 3 months (Zuberi et al., 2022). The clinical presentation of CDD also includes motor impairments, intellectual disabilities, cerebral visual impairment, sleep impairments, and microcephaly and CDD affects approximately 1 in 40,000 to 60,000 live births (Jakimiec et al.,

2020). Diagnosis is complicated and often delayed due to phenotypic variability, limited awareness and possible overlap with other epilepsy syndromes, including Lennox-Gastaut syndrome (LGS) and infantile epileptic spasms syndrome (IESS)/West syndrome. Specifically, up to 23% of patients with CDD may later develop to LGS, with CDKL5 identified as one of the most frequently involved genes in LGS cohorts (Kim et al., 2024; Daniels et al., 2024). Across multiple studies, CDD has been shown to disproportionately affect females, with a female-to-male ratio close to 4:1.

Although the CDKL5 gene was first identified as a cause of human disease in 2004, the term "CDKL5 deficiency disorder" did not appear in the medical literature until 2018 (Leonard et al., 2022). In November 2019 ICD-10 coding was assigned (G40.42), which enabled more accurate identification and tracking of affected individuals in administrative data. Healthcare resource utilisation (HCRU) in CDD is substantial, with hospitalisation being the most frequently reported burden.

As formal guidelines remain limited, treatment of CDD is primarily guided by expert consensus and often includes use of vigabatrin, steroids, ganaxolone and cannabidiol as well as ketogenic diet or vagus nerve stimulation (VNS) and corpus callosotomy. Fenfluramine (Fintepla ®) is also used based on clinical experience, but it is currently licensed in the United States as well as the EU only for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients from 2 years of age onwards. However, it was granted orphan drug designation for the treatment of CDD by FDA in June 2022 and by EMA in March 2023. As the first medicinal product authorised for the use in CDD, Ganoxolon (Ztalmy ®) was granted market authorisation by FDA in March 2022 and by EMA in July 2023 for the adjunctive treatment of epileptic seizures associated with cyclin dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 to 17 years of age.

Although increasing interest in therapeutic development and the unmet medical need in patients with CDD has been observed in recent years, real-world evidence describing the prevalence, clinical presentation, treatment approaches, and health care burden of CDD ~~in the US~~ remains limited. Therefore, this study aims to address existing knowledge gaps and to contribute to a deeper understanding of the burden of illness in order to inform future efforts in clinical care and research.

Methods

RWE1624 is a retrospective, non-interventional, longitudinal cohort analysis of CDD patients in the United States, utilising secondary healthcare open and closed claims data from Komodo claims database.

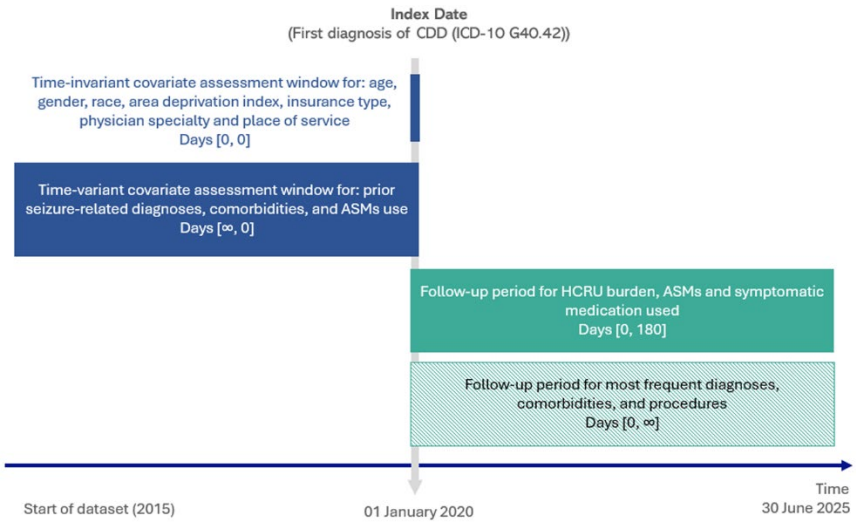

Figure 1: Schematic Study Design

Study participants

CDD cohort:

The CDD study cohort included all patients with at least 2 CDD claims (ICD-10 diagnosis of G40.42) 1 month apart from January 2020 through June 2025, with the first CDD claim occurring between Jan 2020 and Dec 2024 (patient selection period). The index date is defined as the first date of CDD diagnosis captured during the patient selection period. The cohort definition captured both prevalent cases (patients with CDD before 2020 who only become identifiable after the ICD-10 code was introduced) and incident cases (newly diagnosed during 2020–2024).

For the exploratory objective, 6 months of continuous enrollment post index date was required for patients aged 1 year and older, while for those under 1-year, continuous enrollment was not required because Komodo assigned January 1st of the birth year as the diagnosis date for all diagnoses in that year (including the index date), and so requiring enrollment would exclude infants born later in the year and introduce bias. Patients aged 1 year and older with less than 120 days of continuous enrollment during the 6-month period following the first CDD diagnosis date were excluded for the exploratory objective.

Non-CDD matched DS cohort:

The non-CDD DS cohort included matched patients with at least 2 DS claims (ICD-10 diagnosis of G40.83) 1 month part during the patient selection period of January 2020 to June 2025, with the first DS claim occurring between Jan 2020 and Dec 2024, excluding patients with any CDD claim. The index date is defined as the first date of Dravet diagnosis captured during the patient selection period. Patients with any CDD claim (ICD-10 of G40.42) from the DS cohort and patients not matched with CDD cohort were excluded.

Objectives

- Primary Objective:
    - (1) Estimate the prevalence and incidence of CDD between January 2020 and December 2024
- Secondary Objectives:
    - (2) Describe the sociodemographic and clinical characteristics of patients with CDD between January 2015 to June 2025
    - (3) Describe treatments patterns in patients with CDD over time
    - (4) Describe the top twenty-five most frequent diagnoses and top ten most frequent procedures for patients with CDD, from index date to June 30, 2025
- Exploratory Objective:
    - (5) Describe HCRU burden for patients with CDD vs non-CDD patients, from index date to 180 days post-index date.

Outcomes/endpoints

- Primary outcome variable definition and measurement

- The exposure variables in this study are claims of G40.42 (CDD cohort) and G40 (non-CDD cohort) regardless of whether it is the primary or and of the additional diagnoses on the claim.

- Secondary outcome variable definition and measurement (obtained from Komodo database)
  - patient sociodemographic characteristics: age, sex, race and ethnicity, area deprivation index, and payer type
  - patient clinical characteristics: prior and concomitant diagnoses, comorbidities, physician tier and specialty, and place of service at the first CDD diagnosis
  - treatment patterns (ASM and Other Rx Outcome Variables): type and number of anti-seizure medication (ASM) use, persistency of ASMs, treatment procedures and diagnosis, medication use for other comorbidities or symptoms
  - HCRU burden: number of all claims seizure-related claims, status epilepticus claims, office visits, ER visits and seizure related ER visits, inpatient days, inpatient hospital admissions, rescue medication claims, ambulance use

Data source and measurement

The only data source used in this study is Komodo claims data (US, open and closed claims, Jan 2015 to June 2025). Komodo covers 75-80% of the US claims and 65-75% of the Pharmacy Claims that represent a large portion of US market including capture of CDD claims. Like other claims data sources, not all payers (i.e. all US population) are represented in Komodo data and some fields may not be populated well due to reporting problems such as dose information, age, gender, etc.

Statistical Methods

All variables were summarized using descriptive statistics. For continuous variables, summary statistics were tabulated. Categorical variables were summarized by the absolute and relative frequency of patients and the proportion of patients in each category.

Primary outcome variables:

For objective 1, annual prevalence of CDD was computed as:

$$= \frac{\text{Number of CDD patients in the given year}}{\text{US Population} * \text{Komodo Capture Rate}}$$

Komodo's capture rate varies by year and for open vs closed claims data. We used 50% as the default for the main analysis and provide ranges of prevalence using the 40% and 60% metric.

In addition to a population-level prevalence analysis, we also examined the prevalence of CDD among all epilepsy patients captured in Komodo data for that year and report that as a %.

The formula is:

$$= \frac{\text{Number of CDD patients in the given year} * 100}{\text{Number of CDD patients} + \text{Number of non} - \text{CDD Epilpesy patients}}$$

The denominator is a sum of the CDD and non-CDD cohort included in the study.

To calculate the annual incidence of CDD, we used this equation:

$$= \frac{\text{Newly diagnosed CDD patients in the given year}}{\text{US Population} * \text{Komodo Capture Rate}}$$

Secondary and exploratory outcome variables:

For objectives 2 to 4, descriptive analyses were conducted to summarize the study data. For continuous variables, summary measures including the count, mean, standard deviation, median, and range were reported. Categorical variables were presented as frequencies and corresponding percentages.

For Objective 5, we compare CDD patients to a matched cohort of DS patients and compare HCRU outcomes between the two groups. For comparing HCRU outcomes between the two matched groups, t-tests have been applied, and nominal p-values have been reported.

Subgroup analyses:

For all the Objectives, subgroup analyses were conducted by age groups.

Age groups were defined as age 0, 1 to 2, 3 to 11, 12 to 17, and 18+. Out of research interest, a subgroup analysis were conducted among patients aged ≥ 45 years.

Sensitivity analysis:

- CDD sensitivity analysis analytical set 1(Excluding age outliers) for all Objectives
    - Patients who are an outlier on age based on the box plot analysis being excluded from the study.
    - The reason for this sensitivity analysis is that clinically there are no patients older than 60 diagnosed with CDD but in secondary data sources, patients up to the age of 80 are diagnosed with CDD. The outlier analysis lent more credibility to prevalence and treatment patterns analyses.
- CDD sensitivity analysis analytical set 2 (One CDD claim only) for all Objectives
    - Patients with at least 1 CDD claim (G40.42) and an ASM prescription and an Intellectual Development Disorder/Developmental Disorder diagnosis claim during the January 2020 – December 2024 period.
    - The reason for this sensitivity analysis is that the main analysis is quite restrictive in its definition of CDD patients and may underestimate the prevalence.
- CDD sensitivity analysis analytical set 3 (Closed claims only) for all Objectives
    - Use closed claims data to identify CDD patients who had at least 2 CDD claims (G40.42) 1 month apart during the period from January 2020 to June 2025, with the first CDD claim occurring between Jan 2020 and Dec 2024.
    - The reason for this sensitivity analysis is that open claims do not provide a complete picture of comorbidities, treatment patterns and HCRU.
- Non-CDD sensitivity analysis analytical set 1 for exploratory objective only
    - At least 2 DS claims (G40.83) 1 month apart.
    - Exclude patients with any CDD claim (G40.42)
    - 6-month continuous enrollment in post period with <= 60-day gap
    - Propensity score matching on state, insurance type, and year of Dx
- Non-CDD sensitivity analysis analytical set 2 for exploratory objective only
    - At least 2 G40 claims 1 month apart.

    - Exclude patients with any DEEs claim (G40.42, G40.81, G40.82, G40.83, G40.803, G40.844, G93.45, Q85.1, Q93.51, F78.A1)
    - 6-month continuous enrollment in post period with <= 60-day gap
    - 1:2 Matching with CDD cohort: exact matching on sex, insurance and year of diagnosis, and propensity score matching including on age, US Census region of residence, area deprivation index, and diagnosis quarter.
- Non-CDD sensitivity analysis analytical set 3 for exploratory objective only
    - At least 2 Juvenile Myoclonic epilepsy claims (G40.B*).
    - Exclude patients with any CDD claim (G40.42)
    - For patients aged 1 year and older, require continuous enrollment 6 months post index date, allowing for 60 days gaps.
- Non-CDD sensitivity analysis analytical set 4 for exploratory objective only
    - At least 2 Juvenile Myoclonic epilepsy claims (G40.B*).
    - Exclude patients with any CDD claim (G40.42)
    - For patients aged 1 year and older, require continuous enrollment 6 months post index date, allowing for 60 days gaps.
    - 1:2 Matching with CDD cohort: exact matching on sex, insurance and year of diagnosis, and propensity score matching including on age, US Census region of residence, area deprivation index, and diagnosis quarter.

Results

Participants

Patients with at least 2 CDD claims (G40.42) 1 month apart during the Jan 2020 – June 2025 period, with the first CDD claim occurring between Jan 2020 and Dec 2024.

In total, 584 patients were included in the study. For the final research question, applying a 6-month continuous enrollment requirement reduced the analytic sample to 574 patients (see Table 1).

Table 1: Study size

Analytical sets	Patient Counts in Komodo Database
CDD (G40.42) 2+ claims 1 month apart. (Objective 1-4)	584
CDD (G40.42) 2+ claims 1 month apart; For patients aged 1 year and older, require continuous enrollment 6 months post index date, allowing for 60 days gaps. (Objectives 5)	574

DS (G40.83) 2+ claims 1 month apart; Exclude patients with ANY CDD claim (G40.42); For patients aged 1 year and older, require continuous enrollment 6 months post index date, allowing for 60 days gaps. (Only for objective 5)	1,136

General patient characteristics

Most of the 584 patients with CDD were female (415, 71.1%), with males comprising 164 (28.1%) and 5 (0.9%) having unknown sex (see Table 2). Age at index date was broadly distributed, with the largest groups ages 2 to 5 years (122, 20.9%) and 6 to 11 years (121, 20.8%), followed by 45 years or older (96, 16.5%) and 12 to 17 years (92, 15.8%). Mean age was 19.1 years (95% CI, 17.2, 21.1), median age is 10 years. Race and ethnicity was predominantly White (229, 53.9%), and Neighborhood deprivation, measured by Area Deprivation Index (ADI), clustered around the mid-range, with the highest proportion in ADI 40 to 49 (120, 22.0%), indicating many patients lived in moderately disadvantaged areas. Coverage was primarily Medicaid (274, 50.3%), followed by commercial insurance (182, 33.4%) and Medicare (89, 16.3%).

Table 2: Descriptive summary statistics (N=584 patients)

		Patients Counts	Percentage
Gender			
	Female	415	71.1%
	Male	164	28.1%
	Unknown	5	0.9%
Age at index date			
	<1	29	5.0%
	1	49	8.4%
	2-5	122	20.9%
	6-11	121	20.8%
	12-17	92	15.8%
	18-24	45	7.7%
	25-34	22	3.8%
	35-44	7	1.2%
	45+	96	16.5%
Race/Ethnicity			
	White	229	53.9%
	Hispanic or Latino	79	18.6%
	Black or African American	54	12.7%
	Unknown	29	6.82%
	Asian or pacific islander	19	4.47%
	Other	15	3.53%
ADI score			
	0-9	30	5.5%
	10-19	49	9.0%
	20-29	68	12.5%
	30-39	66	12.1%
	40-49	120	22.0%
	50-59	63	11.6%
	60-69	62	11.4%
	70-79	58	10.6%
	80-89	20	3.7%
	90-100	9	1.7%
Payers			
	Medicaid	274	50.3%
	Commercial	182	33.4%
	Medicare	89	16.3%

Main results

CDD epidemiology was summarised using annual prevalence and incidence, reported as estimated rates per million in the U.S. population under assumed Komodo coverage.

Clinical characteristics at diagnosis were described using place of service, provider tier, and physician specialty. Clinical burden was assessed via seizure related diagnoses and key comorbidities before and after CDD diagnosis, along with treatment patterns for anti seizure medications, rescue medications, and selected procedures.

Health outcomes were evaluated using follow up HCRU, reported as per month per patient measures for seizure related claims, status epilepticus claims, ER visits, inpatient admissions and days, office visits, ambulance use, and rescue medication claims; average concomitant ASMs was calculated as the number of unique ASM molecules per patient over the 6 month follow up period rather than a monthly rate.

Prevalence and incidence

The prevalence and incidence of CDD patients in the Komodo database were reported as patient counts and estimated rates per million in the U.S. population under three assumed coverage scenarios (40%, 50%, and 60%; see Table 3).

A steady increase of prevalent counts from 53 in 2020 to 562 in 2024 was observed, with prevalence estimates rising from 0.40 to 4.13 per million at 40% coverage (0.27 to 2.75 per million at 60% coverage).

Regarding incidence, a peak of counts was observed in 2021 and 2022 (182 and 170 cases respectively), which may reflect a catch up effect following the introduction of the CDD-specific ICD-10 code in 2020, as previously diagnosed patients began to be newly captured under the new code.

Table 3: Prevalence and incidence of CDD patients among U.S. population

	Year	Patients Counts	Prevalence (per million): 40% coverage*	Prevalence (per million): 50% coverage*	Prevalence (per million): 60% coverage*
Prevalence					
	2020	53	0.4	0.32	0.27
	2021	229	1.72	1.38	1.15
	2022	393	2.94	2.35	1.96
	2023	500	3.71	2.97	2.47
	2024	562	4.13	3.31	2.75
Incidence					
	2020	53	0.4	0.32	0.27
	2021	182	1.37	1.1	0.91
	2022	170	1.27	1.02	0.85
	2023	111	0.82	0.66	0.55
	2024	68	0.5	0.4	0.33

*Note: assuming Komodo's coverage is 40%, 50%, or 60% of US population

CDD prevalence was stratified by sex and age group, using an assumed 50% Komodo coverage for the U.S. population (see Table 4).

The prevalence per million increased over time across all strata, with consistently higher rates observed among females aged ≤17 years (rising from 1.7 per million in 2020 to 17.3 per million in 2024) compared with males aged ≤17 years (0.4 to 5.0 per million) and adults aged >17 years (females 0.2 to 1.4 per million, males 0.1 to 0.9 per million).

Compared to the total population with epilepsy, CDD accounted for a small proportion overall (generally ≤0.3%), with the disease occurring mainly in patients aged ≤17 years, particularly females. Within the DEE population, CDD accounted for a larger share than in the broader epilepsy population, again highest among females aged ≤17 years (1.2% to 2.9% across 2020 to 2024).

*Table 4: Prevalence of CDD in the U.S. population, epilepsy population, and DEE population, stratified by sex and age group**

Year	Female age<=17	Female age>17	Male age<=17	Male age>17
U.S. population (per million)				
2020	1.7	0.2	0.4	0.1
2021	7.6	0.4	2.5	0.3
2022	12.1	0.8	3.9	0.6
2023	15.2	1.2	4.8	0.8
2024	17.3	1.4	5.0	0.9
Epilepsy population (%)				
2020	0.1%	0.0%	0.0%	0.0%
2021	0.2%	0.0%	0.1%	0.0%
2022	0.3%	0.0%	0.1%	0.0%
2023	0.2%	0.0%	0.1%	0.0%
2024	0.2%	0.0%	0.1%	0.0%
DEE population (%)				
2020	1.2%	0.6%	0.2%	0.2%
2021	2.7%	0.8%	0.8%	0.5%
2022	3.0%	1.2%	0.9%	0.8%
2023	3.0%	1.3%	0.8%	0.9%
2024	2.9%	1.4%	0.7%	0.8%

*Note: assuming Komodo's coverage is 50% of US population

Clinical and sociodemographic characteristics of patients with CDD

Care setting and provider characteristics

According to the RWE1624 Study Report, among the 584 patients in the CDD cohort, most diagnoses occurred in outpatient settings (324, 55.5%), while smaller proportions were recorded in inpatient (73, 12.5%), and emergency care (60, 10.3%); telehealth accounted for 33 diagnoses (5.7%), and other settings each contributed less than 3% (see Table 5).

Provider tier at diagnosis was predominantly Tier 4 (297, 67.2%), followed by Tier 1 (83, 18.8%), Tier 3 (40, 9.0%), and Tier 2 (22, 5.0%).

In terms of physician specialty, pediatrics (88, 19.9%) and child neurology (68, 15.4%) were the most common, followed by epileptology (56, 12.7%) and family doctors (49, 11.1%); other specialties including neurology, physical therapy, internal medicine, cardiovascular disease, emergency medicine, and medical genetics each represented under 5% of diagnoses.

However, there are some uncertainties regarding the figures presented. The sum of the absolute numbers for the different variables in the three categories (place of service, the physician tier and physician specialty) does not equal the total count of CDD patients (N=584). Furthermore, the percentages presented do not add up to 100%. The MAH is therefore kindly requested to explain more clearly in future submissions how figures are derived and to use clear and unambiguous formulations.

Table 5: Characteristics of patients with CDD (N = 584) at diagnosis by place of service, physician tier, and physician specialty

		Patients Counts	Percentage
Place of service at CDD Dx			
	Outpatient	324	55.5%
	OTHER (not report)	82	14.0%
	Home	73	12.5%
	Inpatient	73	12.5%
	Emergency	60	10.3%
	Telehealth	33	5.7%
	SNF	17	2.9%
	Lab	15	2.6%
	Hospice	8	1.4%
	ASC	2	0.3%
Physician Tier* at CDD Dx			
	Tier1	83	18.8%
	Tier2	22	5.0%
	Tier3	40	9.0%
	Tier4	297	67.2%
Physician Specialty at CDD Dx			
	noPediatrics	88	19.9%
	Child neurology	68	15.4%
	Epileptologist	56	12.7%
	Family medicine	49	11.1%
	Neurology	21	4.8%
	Physical therapy	20	4.5%
	Internal medicine	18	4.1%
	Cardiovascular disease	16	3.6%
	Emergency medicine	11	2.5%
	Medical genetics	10	2.3%

*Note: Tier 1: Epileptologist at Level 4 NAEC; Tier 2: Epileptologists outside of Level 4 NAEC; Tier 3: Neurologist and Child Neurologist; Tier 4: Others including Pediatrics

Diagnoses and comorbidities

Seizure related diagnoses and comorbidities among patients with CDD (N = 584) before and after the CDD diagnosis are summarised in Table 6.

Most common diagnoses before the first CDD diagnosis were infantile spasms (32.0%), Rett syndrome (29.5%), cerebral palsy (29.3%), and Lennox Gastaut syndrome (24.7%). An increase of several conditions was observed post CDD diagnosis, including cerebral palsy (32.4% vs 29.3%), LGS (29.1% vs 24.7%), sodium voltage-gated channel alpha subunit 8 (SCN8A) related DEE (3.6% vs 2.4%), and other DEE (6.3% vs 0.2%). In contrast, Rett syndrome (21.4% vs 29.5%) and infantile spasms (27.7% vs 32.0%) dropped after CDD diagnosis.

Both before and after CDD diagnosis, gastrointestinal issues (69.2% in both periods), respiratory issues (64.0% pre and 61.3% post), and developmental delay (65.6% and 71.7%) were the most common comorbidities. Additional commonly observed comorbidities included sleep problems (33.0% pre and 33.7% post), communication issues (40.2% and 38.0%), behavioral disorders (39.7% and 34.1%), scoliosis (22.1% and 28.9%), and intellectual or developmental disability (25.9% and 30.0%).

Table 6: Seizure-related diagnoses and comorbidities among patients with CDD (N = 584) before and after diagnosis

	Prior to CDD Dx		Post CDD Dx	
	Patients Counts	Percentage	Patients Counts	Percentage
Seizure-related diagnoses				
DS	3	0.5%	5	0.9%
LGS	144	24.7%	170	29.1%
Rett	172	29.5%	125	21.4%
Angelman	4	0.7%	3	0.5%
Infantile spasms	187	32%	162	27.7%
TSC	1	0.2%	0	0%
SYNGAP1 related DEE	0	0%	0	0%
KCNQ2 related DEE	0	0%	2	0.3%
SCN8A related DEE	14	2.4%	21	3.6%
Other DEE	1	0.2%	37	6.3%
Cerebral palsy	171	29.3%	189	32.4%
Other epilepsy (not reported)	147	25.2%	207	35.4%
Comorbidities				
IDD	151	25.9%	175	30.0%
DD	383	65.6%	419	71.7%
Autism	87	14.9%	89	15.2%
Vision impairment	95	16.3%	119	20.4%
Movement disorder	110	18.8%	80	13.7%
Microencephaly	44	7.5%	32	5.5%
Sleep	193	33%	197	33.7%
GI issues	404	69.2%	404	69.2%
Scoliosis	129	22.1%	169	28.9%
Respiratory issues	374	64%	358	61.3%
Cardiac arrythmias	181	31%	157	26.9%
Communication issues	235	40.2%	222	38%
Behavioral disorders	232	39.7%	199	34.1%
Other cardiac abnormality	102	17.5%	83	14.2%

Most Common Dx and Procedure Codes

The most frequent diagnosis in both periods (before and after CDD diagnosis) was unspecified convulsions (R56.9; 74% pre and 60% post), highlighting the central role of seizure related clinical encounters. Table 7 lists the top 10 most common diagnoses recorded before and after CDD diagnosis. Beyond seizures, the most common codes reflected neurodevelopmental impairment and multisystem complications.

Prior to CDD diagnosis, frequent diagnoses included lack of expected normal development in childhood (R62.50, 58%), genetic susceptibility to other disease (Z15.89, 45%), gastro esophageal reflux disease (K21.9, 44%), chromosome abnormalities (Q99.8, 39%), and feeding related conditions such as feeding difficulties (R63.3, 38%) and gastrostomy status (Z93.1, 31%).

After CDD diagnosis, a similar pattern persisted, with high prevalence of genetic susceptibility (Z15.89, 58%) and developmental disorder related codes (for example F88, 57%, and R62.50, 56%), along with continued gastrointestinal and nutrition related diagnoses including gastrostomy status (Z93.1, 41%) and GERD (K21.9, 39%).

Overall, seizures, developmental delay, feeding and GI issues, and neurologic complications are more concentrated in CDD patients' diagnostic profile before and after CDD diagnosis.

Table 7: Top 10 most common diagnoses before and after CDD diagnosis

Rank	Prior to CDD Dx			Post CDD Dx		
	ICD10 Code	Description	N (%)	ICD10 Code	Description	N (%)
1	R569	Unspecified convulsions	432 (74%)	R569	Unspecified convulsions	350 (60%)
2	R6250	Unspecified lack of expected normal physiological development in childhood	338 (58%)	Z1589	Genetic susceptibility to other disease	337 (58%)
3	Z1589	Genetic susceptibility to other disease	263 (45%)	F88	Other disorders of psychological development	330 (57%)
4	K219	Gastro-esophageal reflux disease without esophagitis	258 (44%)	R6250	Unspecified lack of expected normal physiological development in childhood	329 (56%)
5	Q998	Other specified chromosome abnormalities	227 (39%)	Z931	Gastrostomy status	241 (41%)
6	R633	Feeding difficulties	224 (38%)	K219	Gastro-esophageal reflux disease without esophagitis	227 (39%)
7	M6281	Muscle weakness (generalized)	187 (32%)	R6330	Feeding difficulties, unspecified	200 (34%)
8	Z931	Gastrostomy status	182 (31%)	M6281	Muscle weakness (generalized)	173 (30%)
9	F82	Specific developmental disorder of motor function	156 (27%)	F82	Specific developmental disorder of motor function	142 (24%)
10	R6251	Failure to thrive (child)	150 (26%)	G809	Cerebral palsy, unspecified	136 (23%)

Supportive and diagnostic services accounted for the majority of procedures. In both periods physical therapy was the most frequent procedure (40.2% pre and 39.7% post) and EEG including video EEG remaining common (26.7% pre and 26.2% post). Several rehabilitation services were consistently observed, including speech therapy (23.1% pre and 23.5% post) and occupational therapy (21.4% pre and 18.2% post). After CDD diagnosis, cardiac ultrasound increased (17.1% post vs 19.7% pre is slightly lower, but it remained among the most common), and new frequent items appeared in the top 10 such as spine imaging X ray (18.5%) and evaluation for wheelchair (14.2%).

Overall, the procedure profile highlights continued use of neurologic testing, imaging, and multidisciplinary therapy services before and after diagnosis.

Treatment patterns

In order to evaluate treatment patterns among patients with CDD (N = 584), medication use (anti-seizure medications, symptomatic medications, diagnostic and Non-Rx treatment procedures) was compared prior to CDD diagnosis, post CDD diagnosis, and across the full study period (see Table 8).

Levetiracetam, clobazam, and clonazepam were the most commonly used anti seizure medications in both the pre and post periods (for example, levetiracetam 40.4% pre and 33.9% post, clobazam 33.9% pre and 33.0% post, clonazepam 28.9% pre and 29.8% post). An increase in uptake post diagnosis was seen for ganaxolone (27.1% post vs 3.6% pre), fenfluramine (5.8% post vs 0.7% pre), and cenobamate (4.3% post vs 1.0% pre), while some commonly used agents such as levetiracetam, prednisone, and topiramate were less frequent post diagnosis than pre diagnosis.

Symptomatic medication use was also common, with rescue medications increasing from 39.9% prior to diagnosis to 46.7% post diagnosis, and 56.2% across the study period.

Genetic testing was more commonly recorded prior to diagnosis than after diagnosis (18.0% pre vs 2.9% post), whereas vagus nerve stimulation or deep brain stimulation was more frequent post diagnosis (14.7% post vs 9.4% pre).

Table 8: Anti-seizure medications, symptomatic medications, and diagnostic and non-prescription treatment procedures before and after CDD diagnosis, and across the study period

	Prior to CDD Dx		Post CDD Dx		Across study period	
	Patients Counts	Percentage	Patients Counts	Percentage	Patients Counts	Percentage
Anti-seizure Medication						
LEVETIRACETAM	236	40.4%	198	33.9%	286	49.0%
CLOBAZAM	198	33.9%	193	33.0%	252	43.2%
CLONAZEPAM	169	28.9%	174	29.8%	234	40.1%
PREDNISONE	154	26.4%	131	22.4%	219	37.5%
TOPIRAMATE	109	18.7%	71	12.2%	135	23.1%
VIGABATRIN	91	15.6%	92	15.8%	121	20.7%
VALPROATE	74	12.7%	61	10.4%	100	17.1%
PHENOBARBITAL	73	12.5%	47	8.0%	88	15.1%
LAMOTRIGINE	69	11.8%	58	9.9%	89	15.2%
LACOSAMIDE	67	11.5%	69	11.8%	98	16.8%
OXCARBAZEPINE	65	11.1%	26	4.5%	74	12.7%
CANNABIDIOL (CBD)	59	10.1%	71	12.2%	97	16.6%
RUFINAMIDE	59	10.1%	45	7.7%	79	13.5%
PERAMPANEL	54	9.2%	50	8.6%	77	13.2%
ZONISAMIDE	54	9.2%	44	7.5%	72	12.3%
FELBAMATE	27	4.6%	24	4.1%	36	6.2%
GANAXOLONE	21	3.6%	158	27.1%	162	27.7%
ACTH	20	3.4%	3	0.5%	23	3.9%
BRIVARACETAM	13	2.2%	22	3.8%	30	5.1%
CARBAMAZEPINE	7	1.2%	2	0.3%	8	1.4%
CENOBAMATE	6	1.0%	25	4.3%	26	4.5%
ACETAZOLAMIDE	4	0.7%	5	0.9%	7	1.2%
FENFLURAMINE	4	0.7%	34	5.8%	34	5.8%
Symptomatic Medication						
Rescue med	233	39.9%	273	46.7%	328	56.2%
SSRIS	66	11.3%	56	9.6%	92	15.8%
Gabapentin	63	10.8%	66	11.3%	98	16.8%
Clonidine	52	8.9%	66	11.3%	87	14.9%
Antipsychotics	47	8.0%	43	7.4%	66	11.3%
Sleep drugs	35	6.0%	39	6.7%	57	9.8%
Ataluren	0	0.0%	0	0.0%	0	0.0%
Chloral hydrate	0	0.0%	0	0.0%	0	0.0%
Diagnostic & Non-Rx Treatment Procedures						
Genetic test	105	18.0%	17	2.9%	119	20.4%
VNS OR DBS	55	9.4%	86	14.7%	97	16.6%
Epilepsy surgery	7	1.2%	4	0.7%	11	1.9%

HCRU Analyses

The monthly per patient healthcare resource utilisation (HCRU) of patients with CDD (N = 368) was compared with those of matched patients with DS (N = 638; see Table 9).

It was observed that patients with CDD had higher monthly seizure related claims (11.77 versus 7.69) as well as higher all cause office visits (1.37 versus 0.85) and seizure related office visits (0.58 versus 0.40).

In contrast, patients with Dravet syndrome had higher monthly all cause ER visits (0.18 versus 0.12), seizure related ER visits (0.14 versus 0.08), ambulance utilisation (0.07 versus 0.02), and rescue medication claims (0.21 versus 0.09).

Monthly status epilepticus claims, inpatient admissions, inpatient days, and average concomitant ASM use were generally comparable between the two groups.

Table 9: HCRU comparisons between patients with CDD (N = 368) and patients with matched DS (N = 638)

HCRU Variable*	CDD patients Mean (95% CI)	DS patients Mean (95% CI)	P value
Seizure-related claims (number of claims)	11.77 (10.11, 13.43)	7.69 (6.66, 8.72)	0.000
Status epilepticus claims (number of claims)	1.53 (1.01, 2.05)	1.85 (1.43, 2.27)	0.342
All-cause ER visits (number of claim days)	0.12 (0.10, 0.15)	0.18 (0.16, 0.20)	0.001
Seizure-related ER visits (number of claim days)	0.08 (0.06, 0.09)	0.14 (0.12, 0.16)	0.000
All-cause inpatient (IP) admissions	0.12 (0.10, 0.14)	0.11 (0.09, 0.13)	0.262
Seizure-related IP admissions	0.10 (0.09, 0.12)	0.10 (0.09, 0.12)	0.884
All-cause IP days	0.63 (0.41, 0.85)	0.54 (0.35,0.73)	0.560
Seizure-related IP days	0.56 (0.34, 0.77)	0.45 (0.30, 0.61)	0.438
All-cause office visits (number of claim days)	1.37 (1.12, 1.61)	0.85 (0.74, 0.96)	0.000
Seizure-related office visits (number of claim days)	0.58 (0.45, 0.71)	0.40 (0.35, 0.45)	0.010
Ambulance utilization count (number of claim days)	0.02 (0.01, 0.04)	0.07 (0.06, 0.09)	0.000
Average concomitant ASMs (number of unique molecules)	1.91 (1.74, 2.08)	1.85 (1.74, 1.97)	0.562
Number of rescue medication claims (number of claims)	0.09 (0.07, 0.12)	0.21 (0.18, 0.24)	0.000

*Note: HCRU outcomes are reported per month per patient. Average concomitant ASMs is the number of unique ASM molecules per patient over the 6 month follow up period (not monthly), because it represents medication types and is not meaningful to divide by month.

Subgroup analyses

For all the Objectives, subgroup analyses were conducted by age groups (age 0, 1 to 2, 3 to 11, 12 to 17, and 18+).

Prevalence

The estimated prevalence of CDD showed an increase across all age groups from 2020 to 2024 (see Table 10). Under the 50% coverage assumption, prevalence rose from 1.08 to 16.04 per million among infants, from 2.10 to 25.17 per million among toddlers, from 1.25 to 10.72 per million among children aged 3 to 11 years, from 0.31 to 6.91 per million among adolescents, and from 0.12 to 1.16 per million among adults. The fact that a similar upward pattern was observed under the 40% and 60% coverage assumptions indicates that the trend was consistent regardless of the assumed level of Komodo coverage.

The highest prevalence was observed among toddlers, followed by infants and children. Among adolescents and adults the prevalence was substantially lower. In 2024, estimated prevalence under the 50% coverage assumption reached 25.17 per million in toddlers, 16.04 per million in infants, and 10.72 per million in children, compared with 6.91 per million in adolescents and 1.16 per million in adults.

These findings suggest that CDD is identified most frequently in younger age groups, particularly during early childhood, while prevalence estimates remain comparatively low in older populations.

Overall, the age stratified results show both a marked increase over calendar time and a clear concentration of CDD prevalence in paediatric populations.

Table 10: Prevalence of CDD patients among U.S. population, stratified by age group

	Year	Patients Counts	Prevalence (per million): 40% coverage*	Prevalence (per million): 50% coverage*	Prevalence (per million): 60% coverage*
Infant (age 0)					
	2020	2	1.35	1.08	0.90
	2021	11	7.70	6.16	5.13
	2022	18	12.23	9.78	8.15
	2023	26	17.79	14.23	11.86
	2024	29	20.05	16.04	13.37
Toddler (age 1 and 2)					
	2020	8	2.63	2.10	1.75
	2021	36	12.03	9.63	8.02
	2022	65	22.13	17.71	14.76
	2023	82	27.84	22.28	18.56
	2024	94	31.46	25.17	20.97
Children (age 3-11)					
	2020	23	1.56	1.25	1.04
	2021	103	7.07	5.66	4.71
	2022	148	10.22	8.17	6.81
	2023	175	12.11	9.69	8.08
	2024	193	13.40	10.72	8.93
Adolescents (age 12-17)					
	2020	4	0.38	0.31	0.25
	2021	35	3.34	2.67	2.23
	2022	63	6.02	4.81	4.01
	2023	81	7.75	6.20	5.17
	2024	90	8.64	6.91	5.76
Adults (age 18+)					
	2020	16	0.16	0.12	0.10
	2021	44	0.43	0.34	0.28
	2022	98	0.94	0.75	0.63
	2023	135	1.28	1.02	0.85
	2024	155	1.45	1.16	0.97

*Note: assuming Komodo's coverage is 40%, 50%, or 60% of US population

General characteristics of patients with CDD

Of the 583 patients included in the CDD cohort, the largest proportion were children aged 3 to 11 years (34.0%), followed by adults aged 18 years or older (29.2%), toddlers aged 1 and 2 years (16.1%), adolescents aged 12 to 17 years (15.8%), and infants aged 0 years (5.0%) (see Table 11).

Females accounted for the majority of patients in every age group, ranging from 58.8% among adults to 87.0% among adolescents.

White patients represented the largest proportion in all age groups, increasing from 24.1% among infants to 50.0% among adults, while Hispanic or Latino patients accounted for 6.9% to 18.2%, and Black or African American patients accounted for 6.1% to 11.8% across groups. Insurance coverage also varied by age group with commercial insurance and Medicaid being the most common payer types among pediatric patients. Medicaid was the largest category among toddlers (51.1%), children (56.6%), and adolescents (66.3%), whereas nearly half of adults were covered by Medicare (47.6%).

Overall, these results suggest that the CDD population at diagnosis was predominantly female, largely paediatric, and showed age related differences in insurance coverage patterns.

Table 11: Social characteristics of patients with CDD (N = 583) at diagnosis, stratified by age group

Age group	Infant (age 0)	Toddler (age 1 and 2)	Children (age 3-11)	Adolescents (age 12-17)	Adults (age 18+)
Total count	29 (5.0%)	94 (16.1%)	198 (34.0%)	92 (15.8%)	170 (29.2%)
Sex					
Female	23 (79.3%)	67 (71.3%)	145 (73.2%)	80 (87.0%)	100 (58.8%)
Male	6 (20.7%)	27 (28.7%)	50 (25.3%)	12 (13.0%)	68 (40.0%)
Race/ ethnicity					
Asian or pacific islander	0 (0.0%)	3 (3.2%)	7 (3.5%)	3 (3.3%)	6 (3.5%)
Black or African American	2 (6.9%)	10 (10.6%)	12 (6.1%)	10 (10.9%)	20 (11.8%)
Hispanic or Latino	2 (6.9%)	9 (9.6%)	30 (15.2%)	7 (7.6%)	31 (18.2%)
White	7 (24.1%)	23 (24.5%)	74 (37.4%)	39 (42.4%)	85 (50.0%)
Other/unknown	2 (6.9%)	7 (7.4%)	15 (7.6%)	7 (7.6%)	13 (7.6%)
Insurance					
Commercial	3 (10.3%)	41 (43.6%)	74 (37.4%)	29 (31.5%)	34 (20.0%)
Medicaid	0 (0.0%)	48 (51.1%)	112 (56.6%)	61 (66.3%)	53 (31.2%)
Medicare	0 (0.0%)	3 (3.2%)	5 (2.5%)	0 (0.0%)	81 (47.6%)

Clinical and sociodemographic characteristics of patients with CDD

Care setting and provider characteristics

Table 9-12 of the study report (see Table 12 of this Assessment Report) shows the place of service, the physician tier and physician specialty at CDD diagnosis stratified by age group.

According to the Study Report "Outpatient diagnosis ranged from 51.0% among children aged 3 to 11 years to 79.3% among infants. Infants had a notably higher proportion of diagnoses occurring in inpatient (48.3%) and emergency settings (34.5%) than older age groups, suggesting that diagnosis in infancy may more often occur during acute or hospital based care. In contrast, diagnoses among toddlers, children, adolescents, and adults were less frequently identified in inpatient or emergency settings and were more commonly observed in outpatient, home, or other nonreported settings."

Physician tier at CDD diagnosis also showed differences across age groups, with Tier 1 physicians accounting for nearly half of diagnoses among infants (48.3%) but a much smaller proportion in older groups, declining to 4.1% among adults. In contrast, the proportion of diagnosing providers who were Tier 4 physicians rose with age, increasing from 31.0% in infants to 65.3% in adults. Among toddlers, children, and adolescents, Tier 4 physicians consistently accounted for the largest proportion of diagnoses, followed by Tier 1 physicians. These findings suggest that infants were more likely to receive a CDD diagnosis from higher specialty neurologic providers, whereas diagnoses in older patients were more often made by broader provider groups, showing that adults are likely to be managed by less specialized providers.

A similar age related pattern was observed for physician specialty. Among infants, pediatrics (37.9%), child neurology (41.4%), and epileptologists (27.6%) were the most common specialties involved at diagnosis. In toddlers, children, and adolescents, pediatric and neurology related specialties remained prominent, including pediatrics, child neurology, and epileptologists. In adults, however, the

distribution shifted toward family medicine (22.4%), internal medicine (10.6%), cardiovascular disease (9.4%), and neurology (5.3%), while pediatrics, child neurology, and epileptologists accounted for relatively small proportions.

Table 12: Clinical characteristics of patients with CDD (N = 583) at diagnosis, stratified by age group

	Infants (age 0)	Toddlers (age 1 and 2)	Children (age 3-11)	Adol. (age 12-17)	Adults (age 18+)
Place of service at CDD Dx					
Outpatient	23 (79.3%)	51 (54.3%)	101 (51.0%)	53 (57.6%)	96 (56.5%)
OTHER (not report)	2 (6.9%)	16 (17.0%)	33 (16.7%)	5 (5.4%)	25 (14.7%)
Home	2 (6.9%)	9 (9.6%)	23 (11.6%)	16 (17.4%)	23 (13.5%)
Inpatient	14 (48.3%)	15 (16.0%)	29 (14.6%)	9 (9.8%)	6 (3.5%)
Emergency	10 (34.5%)	11 (11.7%)	27 (13.6%)	7 (7.6%)	5 (2.9%)
Telehealth	4 (13.8%)	6 (6.4%)	13 (6.6%)	8 (8.7%)	2 (1.2%)
SNF	0 (0.0%)	2 (2.1%)	3 (1.5%)	1 (1.1%)	11 (6.5%)
Lab	1 (3.4%)	2 (2.1%)	2 (1.0%)	0 (0.0%)	10 (5.9%)
Hospice	0 (0.0%)	1 (1.1%)	1 (0.5%)	1 (1.1%)	5 (2.9%)
ASC	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.6%)
Physician Tier* at CDD Dx					
Tier1	14 (48.3%)	16(17.0%)	27 (13.6%)	19 (20.7%)	7 (4.1%)
Tier2	2 (6.9%)	4 (4.3%)	8 (4.0%)	5 (5.4%)	3 (1.8%)
Tier3	2 (6.9%)	7 (7.4%)	14 (7.1%)	4 (4.3%)	13 (7.6%)
Tier4	9 (31.0%)	44(46.8%)	85 (42.9%)	47 (51.1%)	111 (65.3%)
Physician Specialty at CDD Dx					
Pediatrics	11 (37.9%)	16 (17.0%)	33 (16.7%)	24 (26.1%)	4 (2.4%)
Child neurology	12 (41.4%)	12 (12.8%)	24 (12.1%)	13 (14.1%)	7 (4.1%)
Epileptologist	8 (27.6%)	12 (12.8%)	15 (7.6%)	15 (16.3%)	6 (3.5%)
Family medicine	3 (10.3%)	2 (2.1%)	6 (3.0%)	0 (0.0%)	38 (22.4%)
Neurology	0 (0.0%)	2 (2.1%)	9 (4.5%)	1 (1.1%)	9 (5.3%)
Physical therapy	3 (10.3%)	4 (4.3%)	7 (3.5%)	1 (1.1%)	5 (2.9%)
Internal medicine	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (10.6%)
Cardiovascular disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (9.4%)
Emergency medicine	0 (0.0%)	2 (2.1%)	6 (3.0%)	2 (2.2%)	1 (0.6%)
Medical genetics	2 (6.9%)	3 (3.2%)	3 (1.5%)	1 (1.1%)	1 (0.6%)

*Note: Tier 1: Epileptologist at Level 4 NAEC; Tier 2: Epileptologists outside of Level 4 NAEC; Tier 3: Neurologist and Child Neurologist; Tier 4: Others including Pediatrics

However, there are some uncertainties regarding the figures presented. The sum of the absolute numbers for the different variables in the three categories (place of service, the physician tier and physician specialty) does not equal the total count for the respective age group provided in Table 9–11 of the Study Report. Furthermore, the percentages presented do not add up to 100%. The Study Report also states that "Outpatient diagnosis ranged from 51.0% among children aged 3 to 11 years to 79.3% among infants." and on the same time that "Infants had a notably higher proportion of diagnoses occurring in inpatient (48.3%) and emergency settings (34.5%) than older age groups, suggesting that diagnosis in infancy may more often occur during acute or hospital based care.", which is considered contrary. This contradiction is further substantiated by the statement that "In contrast, diagnoses among toddlers, children, adolescents, and adults were less frequently identified in inpatient or emergency settings and were more commonly observed in outpatient, home, or other nonreported settings.". The MAH is therefore kindly requested to explain more clearly in future submissions how figures are derived and to use clear and unambiguous formulations.

Diagnoses and comorbidities

The profile of seizure related diagnoses among patients with CDD differed by age group and also changed before versus after CDD diagnosis (see Table 13).

Among infants, several conditions were more frequently documented, including infantile spasms (69.0%), Rett syndrome (10.3%), cerebral palsy (10.3%), other epilepsy (17.2%), LGS (10.3%), SCN8A related DEE (3.4%), DS (3.4%), and other DEE (13.8%).

In toddlers, infantile spasms remained common both before and after diagnosis (45.7% and 61.7%), while Rett syndrome, cerebral palsy, other epilepsy, and LGS also increased after diagnosis.

Among children aged 3 to 11 years, infantile spasms were common before diagnosis (52.0%) but less frequent after diagnosis (31.8%), whereas other epilepsy increased from 18.2% to 24.2% and LGS increased from 34.3% to 41.9%.

In adolescents, Rett syndrome (55.4% before and 38.0% after), cerebral palsy (65.2% and 54.3%), and LGS (50.0% and 47.8%) were among the most common seizure-related diagnoses, while in adults, other epilepsy was the dominant category and increased markedly after diagnosis (42.4% to 68.8%).

Table 13: Seizure-related diagnoses among patients with CDD (N = 583) before and after diagnosis, stratified by age group

	Infants (age 0)		Toddlers (age 1 and 2)		Children (age 3-11)		Adol. (age 12-17)		Adults (age 18+)	
	Pri	Post	Pri	Post	Pri	Post	Pri	Post	Pri	Post
Seizure-related diagnoses										
Infantile spasms	0 (0.0%)	20 (69.0%)	43 (45.7%)	58 (61.7%)	103 (52.0%)	63 (31.8%)	30 (32.6%)	19 (20.7%)	11 (6.5%)	2 (1.2%)
Rett	0 (0.0%)	3 (10.3%)	6 (6.4%)	10 (10.6%)	85 (42.9%)	56 (28.3%)	51 (55.4%)	35 (38.0%)	30 (17.6%)	21 (12.4%)
Cerebral palsy	0 (0.0%)	3 (10.3%)	5 (5.3%)	17 (18.1%)	66 (33.3%)	83 (41.9%)	60 (65.2%)	50 (54.3%)	40 (23.5%)	36 (21.2%)
Other_epilepsy	0 (0.0%)	5 (17.2%)	33 (35.1%)	23 (24.5%)	36 (18.2%)	48 (24.2%)	5 (5.4%)	13 (14.1%)	72 (42.4%)	117 (68.8%)
Lgs	0 (0.0%)	3 (10.3%)	3 (3.2%)	19 (20.2%)	68 (34.3%)	83 (41.9%)	46 (50.0%)	44 (47.8%)	27 (15.9%)	21 (12.4%)
Scn8a_related_dee	0 (0.0%)	1 (3.4%)	2 (2.1%)	6 (6.4%)	6 (3.0%)	8 (4.0%)	4 (4.3%)	6 (6.5%)	2 (1.2%)	0 (0.0%)
Angelman	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (1.1%)	1 (1.1%)	3 (1.8%)	1 (0.6%)
DS	0 (0.0%)	1 (3.4%)	1 (1.1%)	0 (0.0%)	1 (0.5%)	2 (1.0%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (0.6%)
TSC	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other DEE	0 (0.0%)	4 (13.8%)	0 (0.0%)	11 (11.7%)	1 (0.5%)	14 (7.1%)	0 (0.0%)	7 (7.6%)	0 (0.0%)	1 (0.6%)
SYNGAP1 related DEE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
KCNQ2 related DEE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)

Regarding comorbidities (see Table 14), developmental delay was one of the most common comorbidities across all pediatric age groups, increasing from 89.7% to 96.6% in infants, 56.4% to 88.3% in toddlers, 91.9% to 89.9% in children, and 94.6% to 89.1% in adolescents, but was less common in adults (35.9% before and 29.4% after diagnosis). Furthermore, GI issues (55.2% of infants, 67.0% of toddlers, 77.3% of children, and 88.0% of adolescents after diagnosis), respiratory issues, communication issues, sleep problems, and behavioral disorders were also frequently observed, particularly in paediatric patients.

The comorbidity pattern among adults differed slightly from the paediatric groups. While GI issues (72.4% before and 52.9% after), respiratory issues (74.1% and 57.1%), behavioral disorders (66.5% and 58.2%), and cardiac arrhythmias (48.8% and 30.6%) remained common, developmental and communication related comorbidities were less frequent than in paediatric groups. Adults also had relatively high frequencies of abnormality related diagnoses, including other cardiac abnormality (34.7% before and 27.6% after), idiopathic developmental disability (30.0% and 26.5%), and movement disorder (20.0% and 11.8%).

Across nearly all age groups, many comorbidities were already present before CDD diagnosis and often remained highly prevalent afterward, highlighting the substantial multisystem clinical burden associated with CDD and the broad range of neurologic, developmental, gastrointestinal, respiratory, musculoskeletal, and behavioral conditions affecting these patients.

Table 14: Seizure-related comorbidities among patients with CDD (N = 583) before and after diagnosis, stratified by age group

	Infants (age 0)		Toddlers (age 1 and 2)		Children (age 3-11)		Adol. (age 12-17)		Adults (age 18+)	
	Pri	Post	Pri	Post	Pri	Post	Pri	Post	Pri	Post
Comorbidities										
GI issues	0 (0.0%)	16 (55.2%)	42 (44.7%)	63 (67.0%)	164 (82.8%)	153 (77.3%)	74 (80.4%)	81 (88.0%)	123 (72.4%)	90 (52.9%)
DD	0 (0.0%)	26 (89.7%)	53 (56.4%)	83 (88.3%)	182 (91.9%)	178 (89.9%)	87 (94.6%)	82 (89.1%)	61 (35.9%)	50 (29.4%)
Respiratory issues	0 (0.0%)	13 (44.8%)	36 (38.3%)	59 (62.8%)	146 (73.7%)	138 (69.7%)	65 (70.7%)	50 (54.3%)	126 (74.1%)	97 (57.1%)
Communication issues	0 (0.0%)	12 (41.4%)	21 (22.3%)	46 (48.9%)	125 (63.1%)	104 (52.5%)	46 (50.0%)	38 (41.3%)	43 (25.3%)	22 (12.9%)
Behavioral disorders	0 (0.0%)	5 (17.2%)	12 (12.8%)	15 (16.0%)	63 (31.8%)	56 (28.3%)	43 (46.7%)	23 (25.0%)	113 (66.5%)	99 (58.2%)
Sleep	0 (0.0%)	4 (13.8%)	7 (7.4%)	25 (26.6%)	73 (36.9%)	81 (40.9%)	49 (53.3%)	41 (44.6%)	64 (37.6%)	45 (26.5%)
Cardiac arrythmias	0 (0.0%)	9 (31.0%)	10 (10.6%)	25 (26.6%)	59 (29.8%)	47 (23.7%)	28 (30.4%)	23 (25.0%)	83 (48.8%)	52 (30.6%)
IDD	0 (0.0%)	0 (0.0%)	2 (2.1%)	14 (14.9%)	53 (26.8%)	70 (35.4%)	45 (48.9%)	46 (50.0%)	51 (30.0%)	45 (26.5%)
Scoliosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (10.6%)	44 (22.2%)	76 (38.4%)	51 (55.4%)	57 (62.0%)	34 (20.0%)	26 (15.3%)
Movement disorder	0 (0.0%)	2 (6.9%)	12 (12.8%)	8 (8.5%)	40 (20.2%)	32 (16.2%)	24 (26.1%)	18 (19.6%)	34 (20.0%)	20 (11.8%)
Other cardiac abnormality	0 (0.0%)	1 (3.4%)	7 (7.4%)	7 (7.4%)	27 (13.6%)	15 (7.6%)	8 (8.7%)	12 (13.0%)	59 (34.7%)	47 (27.6%)
Vision impairment	0 (0.0%)	4 (13.8%)	3 (3.2%)	25 (26.6%)	49 (24.7%)	50 (25.3%)	32 (34.8%)	29 (31.5%)	11 (6.5%)	11 (6.5%)
Autism	0 (0.0%)	4 (13.8%)	1 (1.1%)	6 (6.4%)	40 (20.2%)	45 (22.7%)	27 (29.3%)	19 (20.7%)	19 (11.2%)	15 (8.8%)
Microencephaly	0 (0.0%)	0 (0.0%)	3 (3.2%)	1 (1.1%)	20 (10.1%)	17 (8.6%)	11 (12.0%)	7 (7.6%)	10 (5.9%)	7 (4.1%)

Treatment patterns

The use of anti seizure medication use was common across all age groups, although the specific treatment patterns varied by age.

The most frequently used anti seizure medication overall was levetiracetam (reported in 72.4% of infants, 71.3% of toddlers, 53.5% of children, 32.6% of adolescents, and 35.9% of adults). Other commonly used ASMs were clobazam, clonazepam, prednisone and ganaxolone. Several other anti seizure medications, including topiramate, vigabatrin, valproate, lamotrigine, lacosamide, oxcarbazepine, cannabidiol, rufinamide, perampanel, and cenobamate, were used less often but showed variation across age groups, with some medications such as lamotrigine and cenobamate appearing more frequently in older children, adolescents, and adults.

Symptomatic medications were also used across the study population, with rescue medications being less frequent in adults (28.2%) compared to paediatric patients (increasing from 51.7% in infants to 75.0% in adolescents).

Other symptomatic medications such as SSRIs, gabapentin, antipsychotics, and sleep drugs were more commonly used in older age groups, especially adults, among whom SSRIs, gabapentin, antipsychotics, and sleep drugs were reported in 40.0%, 29.4%, 25.9%, and 27.6%, respectively.

Diagnostic and non prescription treatment procedures were less frequent than medication use overall, although genetic testing was reported across all age groups and was most common among children (30.8%). Other procedures such as vagus nerv stimulation (VNS) or deep brain stimulation (DBS) was more frequently reported among older children and adolescents, with proportions of 22.2% and 27.2%, respectively, while epilepsy surgery was uncommon in all age groups.

Overall, these results suggest substantial treatment burden among patients with CDD throughout the study period, with broad use of anti-seizure medications in all age groups and greater use of symptomatic medications and device related procedures in older patients.

Discussion on clinical aspects

The study included a total of 584 patients with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD). The study population was predominantly paediatric (70.9% <18 years) and female (71.1%), which supports the previously made observation that CDD more commonly affects female paediatric patients.

According to the RWE1624 study report, CDD is diagnosed most frequently in the outpatient setting by a paediatrician or a paediatric neurologist. Although the findings on care setting are not considered safety-relevant, certain uncertainties and potential inconsistencies have been identified in the information and data presented with regard to "care setting and provider characteristics". The MAH is therefore kindly requested to explain more clearly in future submissions how figures are derived and to use clear and unambiguous formulations.

The primary objective of study RWE1624 was to estimate the **prevalence and incidence** of CDD. Across the study period (2020 to 2024), the number of prevalent CDD patients observed in this study increased from 53 to 562, whereas the incident cases increased from 2020 to 2021 (53 to 182) before subsequently declining to 68 new cases in 2024. Using an assumed Komodo coverage for the U.S. population of 50%, the prevalence steadily increased from 0.32 (2020) to 3.31 (2024). The consistent increase in documented prevalence, together with a peak in incidence shortly after 2020, supports the conclusion that improved recognition and coding adoption contributed materially to observed trends.

Furthermore, it was observed that the prevalence was concentrated among female children, reaching 17.3 per million (assuming 50% Komodo coverage for the U.S. population) in females aged ≤17 years in 2024 compared to 5.0 per million in males aged ≤17 years. In addition, CDD constituted a larger proportion of the developmental and epileptic encephalopathy (DEE) population than of the overall epilepsy population. This is in line with the clinical profile of CDD as a rare developmental epileptic encephalopathy typically recognised in childhood and predominantly affecting females.

As a secondary objective, the study aimed to describe the **clinical characteristics** and **treatment patterns** of patients with CDD. Prior to diagnosis, patients commonly presented with multiple comorbidities, including infantile spasms, Rett syndrome, cerebral palsy, other epilepsies, and Lennox–Gastaut syndrome (LGS), with post diagnosis increases in other epilepsy (35.4%), LGS (29.1%), and other DEE (6.3%) and decreases in Rett syndrome (21.4%) and infantile spasms (27.7%). A variety of different anti-seizure medications (ASMs) and rescue medications was used by the patients included in

the CDD cohort in both the pre and post periods, with levetiracetam (34%), clobazam (33%), and clonazepam (30%) being the most commonly used ASMs post CDD diagnosis. After the CDD diagnosis had been made, an increase in uptake was seen for ganaxolone (+23%), fenfluramine (+5%), and cenobamate (+4%). The high frequency of seizure and neurodevelopmental diagnoses and the extensive use of ASMs, rescue medications, rehabilitation services, and EEG emphasize the substantial and multisystem care needs of this population.

As an exploratory objective, **healthcare resource utilisation** (**HCRU) burden** for patients with CDD vs non-CDD patients should be described. When comparing the CDD cohort with the matched DS cohort, CDD patients were shown to have higher monthly seizure related claims (11.77 vs 7.69) and office visits (1.37 vs 0.85) than matched DS, which is expected given the higher seizure frequency reported in CDD. Given the generally higher incidence of status epilepticus in Dravet syndrome, the higher monthly status epilepticus claims observed in patients with DS (1.85 vs 1.53) were also expected. Overall, the analysis of HCRU patterns suggests that CDD is associated with higher ongoing seizure related healthcare utilisation and routine care utilisation compared to DS.

Furthermore, **subgroup analyses** stratified by age (age group 0, 1 to 2, 3 to 11, 12 to 17, and 18+) were conducted. The results of these subgroup analyses support the main analyses' findings, confirming a CDD population at diagnosis that was predominantly paediatric and female, with a clear concentration of prevalence among females and paediatric populations. Furthermore, the age-stratified analyses underscore the substantial multisystem clinical burden and treatment burden associated with CDD, demonstrating widespread use of antiseizure medications across all age groups and increased use of symptomatic medications and device-related procedures among older patients.

The results of this study should be seen in light of the associated limitations, which hinder a meaningful conclusion from being drawn. As the identification of CDD relied on the presence of the CDD specific ICD 10 code, which was introduced in 2020, early increases in incidence and prevalence likely reflect evolving uptake of the new code and catch-up capture of previously diagnosed patients rather than true changes in disease occurrence. The reliance on the Komodo database as the data source limits the generalisability of the results both to the overall United States population and to regions outside the United States, including Europe. As observed counts were translated to population rates using assumed coverage levels, the absolute prevalence and incidence estimates are sensitive to coverage assumptions and may not be directly comparable to published estimates derived from other data sources. Furthermore, HCRU comparisons were observational and may be influenced by residual confounding (for example seizure severity, developmental level, caregiver resources) and differential access to care, and coding practices.

Despite these limitations, study RWE1624 provides valuable insights into the epidemiology, clinical characteristics, treatment patterns and healthcare resource utilisation of patients with Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in the United States. The findings reinforce previous evidence indicating that CDD disproportionately affects female paediatric patients and demonstrates that CDD imposes a substantial and sustained burden on patients, which emphasizes the need for more effective and disease-targeted therapeutic options.

3. Rapporteur's overall conclusion and recommendation

Study RWE1624 aimed to further characterise the epidemiology, clinical characteristics, treatment patterns, and HCRU of patients with Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in the United States.

Over the study period, the number of prevalent CDD patients increased continuously from 53 (2020) to 562 (2024), whereas incident cases increased from 2021 to 2022 (182 to 170) before declining by

2024, which supports the conclusion that improved recognition and coding adoption contributed materially to observed trends.

Furthermore, the results of study RWE1624 suggest that the CDD population at diagnosis was predominantly female, largely paediatric, which is supported by the results of the subgroup analyses conducted. The study showed that CDD is often diagnosed in the outpatient setting by a paediatrician or a pediatric neurologist, which is in line with the clinical profile of CDD as a rare developmental and epileptic encephalopathy (DEE) typically recognised in childhood. In addition, the results suggest that patients with CDD experience a substantial treatment burden, characterised by the presence of multiple comorbidities both before and after CDD diagnosis and by extensive use of antiseizure medications across all age groups. Together, these findings emphasize the considerable and multisystem healthcare needs associated with this patient population.

As this study relied solely on routinely collected claims data from the United States, the study is subject to several limitations inherent to this data source. These limitations restrict the ability to draw definitive conclusions and limit the generalisability of the findings to populations outside the United States, including Europe.

No new safety data for fenfluramine were generated, since the study objectives were descriptive in nature and not designed to evaluate safety of specific treatment options. Therefore, no further actions regarding fenfluramine are deemed necessary.

☒ **Fulfilled:**

No regulatory action required.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Fintepla Active substance: Fenfluramine

Study title	Study number	Date of completion	Date of submission of final study report
Dose range-finding juvenile toxicity study (9000468)	Study 3	20 June 2016	05 February 2019 with SN0000
Definitive juvenile toxicity study (9000406)	Study 4	21 June 2016	05 February 2019 with SN0000

Clinical studies

Product Name: Fintepla Active substance: Fenfluramine

Study title	Study number	Date of completion	Date of submission of final study report
Randomized, double-blind, placebo-controlled, parallel group trial of two fixed doses of fenfluramine as adjunctive therapy in peadiatric patients from 2 years to less than 18 years of age with Dravet syndrome (ZX008-Study 1)	Study 5	27 April 2018	05 February 2019 with SN0000
2-cohort trial to first assess the pharmacokinetics and safety profile of a single dose of fenfluramine when added to standard of care, followed by a randomised, double-blind, placebo-controlled, parallel group evaluation of the efficacy, safety and tolaribility of fenfluramine as adjunctive therapy to stiripentol treatment in peadiatric patients from 2 years to less than 18 years of age with Dravet syndrome (ZX008 1504)	Study 8	21 December 2018	05 February 2019 with SN0000
Randomized, double-blind, placebo-controlled, parallel group trial of two fixed doses of fenfluramine as adjunctive therapy in peadiatric patients from 2 years to less than 18 years of age with Dravet syndrome (ZX008-Study 3 (Old Study 2))	Study 6	12 November 2021	04 April 2022 with SN0035
Open-label extension trial to assess the long term safety of fenfluramine (ZX008-1503)	Study 7	18 July 2023	27 July 2023 with SN0074
Open-label, single-arm trial to assess safety, tolerability and pharmacokinetics of fenfluramine in patients from 1 year to less	Study 10	Study ongoing	N/A

than 2 years of age with Dravet syndrome (ZX008-2201) This study was added as a result of procedure EMEA-001990-PIP01-16-M04			