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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/0000326084

Note

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

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Table of contents

1. Introduction

On 29 January 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 submitted as part of the post-authorisation measure EMA/PAM/0000326084.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "Mortality Rates and Risk Factors among Patients with DS and LGS in the US using Komodo Claims Data" (RWE1609) is a stand-alone study.

The MAH stated that this study is not part of the Fintepla Paediatric Investigation Plan (001990-PIP01-16).

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.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- "Mortality Rates and Risk Factors among Patients with DS and LGS in the US using Komodo Claims Data" (RWE1609)

RWE1609 is a non-interventional retrospective cohort analysis using United State claims and fact-of death data to evaluate mortality rates and associated risk factors among patients diagnosed with Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS).

2.3.2. Study

RWE1609: "Mortality Rates and Risk Factors among Patients with DS and LGS in the US using Komodo Claims Data"

Description

Fenfluramine is currently licensed in the United States as well as the EU for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients from 2 years of age onwards. Fenfluramine is a serotonin-releasing agent and thereby stimulates multiple 5-hydroxytryptamine (5HT) receptor subtypes through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT1A, 5-HT1D, 5 HT2A, and 5-HT2C receptors, and by acting on the sigma-1 receptor. Patients treated with fenfluramine without concomitant stiripentol (STP) are titrated from 0.2 mg/kg/d to effect up to

the maximum maintenance dose of 0.7 mg/kg/d of fenfluramine (absolute maximum daily dose of 26 mg/d). With concomitant STP, patients are titrated from 0.2 mg/kg/d to the maximum dose of 0.4 mg/kg/d fenfluramine (absolute maximum daily dose of 17 mg/d).

Both DS and LGS are rare and severe treatment-resistant developmental and epileptic encephalopathies (DEEs) that are associated with high unmet need and an increased risk of mortality (Specchio et al, 2022; Zuberi et al, 2022). To date, limited data describing the use of fenfluramine for the treatment of epilepsy in a real-world setting have been published.

This study is a retrospective cohort study investigating mortality rates (primary objective) and patient demographic and clinical characteristics associated with mortality (secondary objective) among patients with developmental and epileptic encephalopathies (LGS and DS) using US claims data. The study period ran from 01 Jan 2015 to 31 Dec 2024, covering approximately 14 million active patient lives across the US with any seizure-related diagnosis. The primary outcomes were patient status alive (yes/no) from index date to end of study period and time to death from index date to end of study period. Secondary variables included demographics (age, sex, race, and ethnicity), social factors (Area Deprivation Index and insurance payer), clinical factors (treatment, comorbidity scores and comorbidities, and physician specialty tier), Healthcare Resource Utilisation (HCRU)-based severity score. Mortality rates per 1000 person years and standardised mortality ratios were estimated overall and stratified by paediatric versus adult status and by a HCRU-based severity score. Kaplan Meier methods described age specific survival, and Cox proportional hazards models assessed associations between mortality and demographic and clinical characteristics.

As available data on mortality rates in these populations, in particular in patients with LGS, are limited, study RWE1609 aims to fill the knowledge gaps regarding the mortality risks and disease characteristics of DS and LGS and thereby contribute to enhance the support systems for DS and LGS patients and their care teams.

Methods

Study participants

This retrospective cohort study used Komodo's open and closed longitudinal medical and pharmacy claims data, and Komodo's mortality database with a study period from January 1, 2015 to December 31, 2024.

The study population comprised 2 separate cohorts of LGS and DS patients who met the following inclusion and exclusion criteria:

- Cohort 1 – All LGS patients – patients with >2 LGS claims at least one month apart during the qualification period. Patients are required to have at least one LGS claim after Jan 1, 2018 (The first LGS claim can be before Jan 1, 2018 if they have at least one claim after Jan 1, 2018). Patients are required to have a 12 month baseline period of visibility in the database.
- Cohort 2 – All DS patients – patients with >2 DS claims at least one month apart during the qualification period. Patients are required to have at least one DS claim after Jan 1, 2018 (The first DS claim can be before Jan 1, 2018 if they have at least one claim after Jan 1, 2018). Patients are required to have a 12-month baseline period of visibility in the database.

Table 1: Specific diagnosis codes used

DEE	ICD-10-CM code
Dravet Syndrome	G40.83*
Lennox Gastaut Syndrome	G40.81*

*is a wildcard indicating any sub-variants of the diagnostic code

Identical study periods were used for the LGS and DS analyses:

- Study period: January 1, 2015 to Dec 31, 2024
    - Patient qualification period: January 1, 2015 to December 31, 2023

      -Index date: Jan 1, 2018 or the second DS or LGS claim, whichever occurs later.

      The rationale for this is that a patient is required to have two DEE claims to be included in the analysis. The patient would remain alive between the first and second DEE claim. Thus, using 1/1/2018 as the index date for these patients can introduce a bias.
    - Mortality outcome measurement-period: Index date to exit date which is date of death, date of last recorded claim (any claim) before December 31, 2024 or December 31,2024, whichever is first.
    - Pre-index period: 12 months of enrollment in the pre-index period required for the study objectives.

Treatments

Not applicable as RWE1609 is a non-interventional, retrospective cohort study.

Research Questions and Objectives

Research questions:

- What are the mortality rates in people with DS and LGS?
- What are the key patient demographic and clinical characteristics that are associated with mortality?

Objectives:

- Primary objective:
    - To investigate mortality among patients with DS and LGS.
- Secondary objective:
    - To evaluate key patient demographic and clinical characteristics that are associated with mortality.

Outcomes

Primary outcome variable definition and measurement

- Patient status alive (yes/no) – any cause during post-index period
- Time to mortality event from index date during post-index period

Secondary outcome variable definition and measurement

- Demographics
    - Age at index date
    - Sex (male, female, other)
    - Race and ethnicity
    - Area Deprivation Index as an indicator for disadvantaged neighborhoods. It is a rank between 1 to 100 with 100 being the most deprived/disadvantaged neighborhood. This is derived from the Neighborhood Atlas by the University of Madison Wisconsin.
    - The most common/modal pharmacy ZIP5 code for the patient will be chosen and the relevant Census Block Groups for that ZIP code will be identified. The average of the ADI for all census block groups that the ZIP5 is associated with will be calculated. The crosswalk from ZIP to census block groups will be derived from the HUD website.
    - Payer: If a patient has Medicaid as a payer on at least one claim during the covariate measurement period regardless of any other payer listed, they qualify as Medicaid patients. If the patient is not on Medicaid but has Medicare listed as Payer on at least one claim during the covariate measurement period, they qualify as Medicare patients. Lastly if the patient is not Medicaid or Medicare but has Commercial insurance listed as a payer on at least one claim during the covariate measurement period, they qualify as Commercial insurance.
- Clinical characteristics and treatment pattern:
    - DEE-related Treatments
        - Total and average number of ASMs used per month for the patient in the covariate measurement period. Complete list of ASMs provided in the Appendix.
        - Binary indicator for the patients who have had Vagus Nerve Stimulation, as identified by CPT codes for placement, interrogation, and programming
        - Binary indicator for the patients who have had Deep Brain Stimulation or Responsive Neurostimulation System, as identified by CPT codes for placement, interrogation, and programming
        - Binary indicator for the patients who have had Epilepsy Surgery, as identified by ICD-10 codes and CPT codes
        - Number of rescue medication claims. Rescue medications included are: a. lorazepam (IV, buccal, or rectal formulations) b. midazolam (IV, buccal, or rectal formulations) c. diazepam (IV, buccal, or rectal formulations) d. clonazepam as needed (buccal, oral, or rectal formulations)
    - DEE-related Comorbidities/Symptoms
        - Charlson comorbidity score
        - Germaine Smith epilepsy-specific comorbidity score
        - Specific comorbidities

- Developmental impairments
- Behavioral disorders
- Wheelchair use
- Other mobility dysfunction excluding wheelchair use
- Respiratory/CV complications
- Sleep apnea or use of continuous positive airway pressure (CPAP)/Bilevel positive airway pressure (BiPAP)
- Other sleep disturbances excluding sleep apnea
- GI disorders

- Physician Specialty: If a patient has ever seen an Epileptologist at a Level 4 accredited National Association of Epilepsy Centers (NAEC) center during the study period, then the Physician Specialty tier assigned is 1. If they have not qualified for Tier 1 but have seen an epileptologist (outside of a Center of Excellence) during the study period, they are classified as Tier 2. If they do not qualify for Tier 1 or 2 but have seen a Neurologist/Pediatric Neurologist during the study period, they are assigned a Tier 3. If they haven't seen any of the mentioned specialists during the study period, they are classified as Tier 4.
- Severity score: Risk/severity score is a weighted composite score based on the number of ER visits, hospitalizations, generalized tonic-clonic seizure (GTCS) claims, status epilepticus claims, and number of rescue medications. The weights assigned are as follows:
    - ER Visit: 10 points per ER visit
    - Inpatient admissions: 5 points per day of length of stay
    - Any Generalized tonic clonic seizure claim: 4 points per GTCS claims
    - Any status epilpeticus claims: 5 points per SE claim. (Note: If a patient has an ER visit for SE, the points for both the ER visits and the SE claim will be counted)
    - Anti-seizure medication: 2 points for every distinct ASM molecule
    - Rescue medication: 4 points for every claim of rescue medication

  The severity score is measured as an average across all years of enrollment after the index date and before the end of study period. This score hasn't been validated in any previous study.

Data sources and measurements

This study used Komodo's integrated longitudinal claims database that spans from January 1st, 2015, through December 31st, 2024, covering approximately 14 million active patient lives across the United States with any seizure related diagnosis.

Komodo's dataset is a nationally representative, de-identified, comprehensive, open and closed claims database that includes medical, hospital, prescription, and specialty pharmacy claims captured across

the healthcare system. Komodo sources its data directly from payers, health systems, pharmacies, clearinghouses and switches.

Komodo data is sourced from 150+ payer complete datasets (a high number of diverse payers) and the data is well distributed by geography and patient demographics. It has near census-level coverage across geographies to minimize biases (see Table 2).

Table 2: Regional distribution of Komodo data

U.S. Region	Komodo Data	CDSC NHIS of insured patients
Northeast	19%	17%
South	38%	37%
Midwest	21%	22%
West	22%	24%

Komodo data included claims data for patients covered by Commercial Insurance (77%), Medicare (16%), as well as Medicaid (7%).

Komodo's mortality data is sourced from Government public records (e.g. Social Security Administration), claims, as well as Obituaries and includes over 1.6M death records for patients with any seizure related claim or any claim for an anti-epilepsy drug from 2018 to present. Komodo's mortality data covers over 78% of deaths in the United States since 2018. The mortality data is linked to the claims data using deterministic algorithms as part of the tokenization process. Komodo's race and ethnicity data from a variety of sources including clinical electronic health records, patient intake forms, and payer enrollment files. Komodo also utilizes data from consumer reporting agencies to increase overall coverage where statistically reliable.

Bias

As a claims-based study, RWE1609 is subject to various biases including selection and confounding biases, as well as time-related issues.

Selection bias: Cohort entry requirement (≥2 LGS or DS claims ≥1 month apart) may exclude true cases with limited healthcare engagement, potentially selecting for individuals with higher disease severity and healthcare use.

Confounding: Despite adjustment for demographic and clinical covariates and comorbidity indices, unmeasured/residual confounding remains (e.g., genetic risk, lifestyle, environmental factors, detailed seizure physiology), potentially biasing hazard ratios in either direction.

Time-related biases: Calendar-time confounding (e.g., COVID-19 period effects on care access and mortality) could influence both outcomes and covariate capture; annual SMRs and sensitivity analyses partially mitigate this but may not fully eliminate bias.

Study size

On the basis of a feasibility check of the underlying database, the following numbers of patients meet the inclusion criteria.

- DS patients:
    - Living or lost to follow-up as of 12/31/2024: 2,734

- Deceased as of 12/31/2024: 65

- LGS patients:
  - Living or lost to follow-up as of 12/31/2024: 31,271
  - Deceased as of 12/31/2024: 2,367

On the basis of the above reported data crude mortality rates were calculated for each cohort:

Table 3: Crude mortality rates for DS and LGS

Cohort	Sample size	Assumed probability (crude mortality rate) according to observed data in database
DS	2,799	65/2799=0,023
LGS	33,638	2367/33638=0,070

The probabilities of observing at least one death assuming a distribution for rare events in a cohort and the precision of a 95% confidence interval (C.I.) were derived in Query 8 in order to provide a justification for the expected sample size.

Cohort DS:

For a sample size of 2799, the probability of observing at least one event will be 1 when the probability of an event is 0.023. A two-sided 95% confidence interval for a crude mortality rate using the large sample normal approximation will extend 0.006 from the observed mortality rate for an expected mortality rate of 0.023 (95% C.I: [0.017;0.029]).

Cohort LGS:

For a sample size of 33638, the probability of observing at least one event will be 1 when the probability of an event is 0.07. A two-sided 95% confidence interval for a crude mortality rate using the large sample normal approximation will extend 0.003 from the observed mortality rate for an expected mortality rate of 0.070 (95% C.I: [0.067;0.073]).

Statistical Methods

Primary outcome variables

The mortality rates per 1000 patient-years (PY) were calculated for the LGS and DS cohorts. The standardized mortality ratio (SMR) was computed separately for the LGS and DS cohorts and stratified by paediatric (<18 years of age at index date) versus adult (≥18 years of age at index date) status and by a Healthcare Resource Utilization (HCRU)-based severity score (defined as a weighted pre-index severity score [not validated] based on emergency room and in-patient utilization, generalized tonic-clonic seizure [GTCS], status epilepticus, anti-seizure medication [ASMs], and rescue medications). In addition to mortality rates, Kaplan-Meier methods were used to describe age-specific survival for the DS and LGS cohorts.

- Mortality Rate:
  - Mortality rate per 1000 patient years will be calculated separately for all three DEEs included as well as for all three DEEs combined. The formula is:

    $$total\ number\ of deaths\ in\ the\ data\ among\ DEE\ population * 1000\ /\ Total\ DEE\ patients\ in\ the\ data * Mean\ follow-up\ length\ for\ each\ patient\ in\ the\ data$$

- All patients diagnosed with the DS or LGS during the study period will serve as the first element in the denominator for the crude mortality rate calculations.
- The second element in the denominator will be the mean follow-up length for the patients included in the analysis. The follow-up period is defined as $Exit\ date - Index\ date$. The index date is the first DEE diagnosis date within the study period and the exit date is the date of mortality or date of censoring. Censoring data could be the date the patient was lost to follow up in the dataset or the end of the study period i.e. 12/31/2024.
- The numerator will be the total number of deaths during the study period among the patient population in the denominator.
- The numerator will be divided by the denominator and multiplied by 1000 to arrive at the crude mortality rate per 1000 at-risk patients.
- The uncertainty of the rates will be estimated by computing a 95% confidence interval (CI).

- Adjusted mortality rate
  - To calculate adjusted mortality rate, the mortality capture rate in the Komodo mortality dataset will be taken into account. Komodo mortality data claims a capture rate of ~78% compared to deaths captured by the CDC.
  - Adjusted mortality rate per 1000 patient years will be calculated separately for all three DEEs included as well as for all three DEEs combined.
  - The uncertainty of the rates will be estimated by computing a 95% confidence interval.
- Standardized Morality Ratio
  - A standardized mortality ratio (SMR) describes whether a population with a specific DEE are more, less or equally as likely to die than a standard/ reference population (US general population).
  - SMR uses age-specific rates for the study population as well as the reference population to compute observed and expected deaths for each group and these are then combined into one rate based on the proportion of the study population in each group.
  - SMR will be calculated separately for all three DEEs included as well as for all three DEEs combined.
  - The age specific expected deaths will be derived by summing the age specific actuarial death probabilities in the US census data from the Social Security Administration website for each DEE patient.
  - The SMRs will be computed separately for each DEE, for each age group (Pediatric i.e.=18 years of age at index date) and for each year in the study period.
- Survival Analysis:
  - In addition to mortality rates and case fatality rates, survival analysis using the Kaplan Meir method will be conducted to calculate and compare longitudinal survival probabilities among DEE patients.

- The Kaplan–Meier method is a more sophisticated method of summarizing survival data, which uses all the cases in a series, not just those followed up until the selected cut-off. It also has the advantage of displaying survival over time/age, which is unlike the mortality rate which can only present a snapshot in time. . Besides the Kaplan-Meier estimates inclusive 95% C.I. for the time to death per each of the three DEE cohorts the Kaplan Meier Curves will be provided.
- For the purpose of the survival analysis, a patient is considered to be censored as of a particular point before the end of the study period (12/31/2024) if they have no more medical or pharmacy claims in the claims data (including open and closed claims) after that point.
- For the purpose of the survival analysis, the entry date is the latter of Jan 1, 2018 or the second Dx code for the DEE.
- Delayed entry adjustment will be used to control for left truncation and inverse probability of censoring weights to control for loss to follow-up.

Secondary outcome variables

Cox proportional hazards (Cox PH) models assessed associations between mortality and demographic and clinical characteristics for the DS and LGS cohorts combined, as well as separately.

- Descriptive Statistics:
  - Descriptive statistics for all continuous variables (n, mean, standard deviation, Q1, median, Q3, interquartile range, minimum and maximum) will be provided for each cohort separately and for overall. For all categorical variables absolute and relative frequencies will be provided for each cohort separately and for overall. Hereby, each of the three DEE cohorts will be broken down by living and deceased patients.
  - In addition, the missingness (n and %) for each variable in the analyses will be reported.
- Cox Proportional Hazards Multivariate Regression Model:
  - A Cox Proportional hazards model will be estimated to address the secondary objective. The outcome variable is time to death. The model will evaluate the association between the outcome variable and demographic and clinical characteristics (Defined in the Variables Section).
  - The CPH model evaluates time to mortality from index date to exit date. The exit date would be the earliest of date of death, date of censoring (if patient is no longer available in the data before end of study period), or end of study period i.e. 12/31/2024.
  - The same model will be estimated for each DEE separately (conditional on sample size and number of mortality events for each DEE) as well as for all DEEs combined.
  - The proportional hazards assumption will be tested using Schoenfeld residuals. If the proportionality assumption is not met, the specific covariates that violate this assumption will be further investigated and actions including adding interaction terms or conducting subgroup analyses will be considered.

Sensitivity analysis

All the analyses will be replicated for a mortality outcome assessment period starting 1/1/2020 instead of 1/1/2018 as in the main analysis. The end of study period will still be 12/31/2024. In this case, the index date would be the latter of 1/1/2020 or the second DEE diagnosis claim.

Additionally, sensitivity analyses with a 6-month baseline period instead of a 12-month baseline period.

Lastly, sensitivity analysis by calculating the denominator for the SMR across all age groups and not be specific age group. Thus, the denominator for the SMR would be Crude mortality rate for the standard US population across all age group* Sample size for each cohort.

The rationale for doing is the above sensitivity analyses to be able to compare mortality rates published in the study examining mortality rates among Dravet Syndrome patients using Anovo specialty pharmacy database.

In case of fewer than 3 deaths in a subgroup/analytical cohort (for instance in a particular year for the annual SMR calculation, the SMR values will only be repeated for the entire study period combined and not separately for each year.

Results

Participants and patients' characteristics

Patients were included if they had ≥2 DS (ICD-10, G40.83) or LGS (ICD-10, G40.81) claims ≥1 month apart in the patient qualification period (1/1/2015–12/31/2023) and 12 months of pre index data.

In total, there are **2,781 DS** patients and **33,404 LGS** patients included in this study.

DS

The cohort was balanced by sex overall, but deaths were more common among females. Most patients were covered by Medicaid, with a higher proportion of Medicare coverage among those who died. Patients who died also resided in more deprived neighborhoods as reflected by higher mean Area Deprivation Index (ADI). Across clinical factors, the deceased group showed a consistently higher burden of medical complexity, including more sleep apnea, feeding tube or gastrostomy, gastrointestinal conditions, cardiopulmonary complications, and mobility related impairment. This pattern was supported by higher comorbidity scores (Charlson and Germaine Smith), greater treatment intensity (more unique ASMs and rescue medication claims), and higher HCRU severity scores among patients who died. This suggests that mortality in DS is concentrated among individuals with greater baseline comorbidity burden and healthcare utilisation.

Table 4: Descriptive Summary Statistics for DS Patients (N= 2,781 patients)

	Overall	Alive	Dead
Gender			
Male	50.7%	50.9%	42.4%
Female	49.2%	49.1%	57.6%
Race/Ethnicity			
Non-Hispanic White	40.5%	40.4%	44.1%
Asian or Pacific Islander	4.1%	4.1%	5.1%
Hispanic or Latino	14.1%	14.2%	6.8%
Black or African American	7.9%	7.8%	13.6%
HCP Tier			
1 - COE	46.7%	46.7%	45.8%
2 - Epileptologist	19.3%	19. 3%	16.9%
3 - Neurology / Child Neurology	22.5%	22.5%	20.3%
4 - Other	10.6%	10.5%	16.9%
Insurance			
Medicaid	70.3%	70.3%	71.2%
Medicare	4.1%	3.9%	11.9%
Commercial and other	24.7%	24.9%	16.9%
Area Deprivation Index	46.3	46.2	54.1
Clinical variables			
Sleep Apnea (Yes)	12.3%	12.1%	20.3%
Other Sleep Comorbidities (Yes)	7.8%	7.6%	16.9%
Feeding Tube/Gastrostomy (Yes)	17.7%	17.2%	42.4%
Other GI Comorbidities (Yes)	38.8%	38.4%	57.6%
Behavioral Comorbidities (Yes)	31.7%	31.6%	39.0%
Cardiovascular Respiratory Comorbidities (Yes)	53.0%	52.7%	71.2%
Wheelchair Use (Yes)	1.3%	1.2%	6.8%
Other Mobility Disorders (Yes)	19.6%	19.4%	28.8%
Developmental Disorders (Yes)	68.9%	68.9%	67.8%
Vagus Nerve Stimulation/Deep Brain Stimulation	15.2%	15.2%	15.3%
Epilepsy Surgery	0.6%	0.6%	0.0%
HCRU Severity Score	132.1	131.8	147.2
Charlson Comorbidity Index (CCI)	0.29	0.28	0.97
Germaine Smith Index (GSI)	0.4	0.4	1.2
Number of unique ASMs in the baseline period	2.3	2.3	3.0
Average number of rescue medication claims in baseline period	2.2	2.1	2.9

LGS

The population was predominantly male and the population was largely Medicaid insured, with a higher share of Medicaid and Medicare coverage among patients who died and a markedly lower proportion with commercial coverage. As seen in patients with DS, decedents also lived in more deprived neighborhoods, as indicated by higher mean Area Deprivation Index, and differed by race and ethnicity distribution, with a higher proportion of non-Hispanic White patients among those who died. Clinically, mortality was concentrated among patients with greater medical complexity, including higher prevalence of sleep apnea, feeding tube or gastrostomy, gastrointestinal conditions, cardiopulmonary complications, and mobility related impairment. Consistent with this, patients who died had higher comorbidity indices, higher HCRU severity scores, and modestly higher treatment intensity (more unique ASMs and rescue medication use), indicating that baseline comorbidity burden and healthcare utilization are key differentiators between survivors and decedents in LGS.

Table 5: Descriptive Summary Statistics for LGS Patients (N=33,404 patients)

	Overall	Alive	Dead
Gender			
Male	56.4%	56.4%	56.2%
Female	43.6%	43.6%	43.8%
Race/Ethnicity			
Non-Hispanic White	43.5%	42.7%	55.3%
Asian or Pacific Islander	3.0%	3.1%	1.5%
Hispanic or Latino	14.8%	15.2%	8.8%
Black or African American	9.8%	9.9%	9.4%
HCP Tier			
1 - COE	38.3%	38.4%	37.4%
2 - Epileptologist	19.6%	19.7%	18.1%
3 - Neurology / Child Neurology	27.8%	27.5%	32.0%
4 - Other	13.6%	13.7%	12.5%
Insurance			
Medicaid	74.3%	74.2%	76.1%
Medicare	10.3%	9.9%	16.3%
Commercial and other	14.7%	15.2%	7.4%
Area Deprivation Index	48.0	47. 7	52.7
Clinical variables			
Sleep Apnea (Yes)	20.4%	19.8%	29.6%
Other Sleep Comorbidities (Yes)	8.0%	8.0%	7.7%
Feeding Tube/Gastrostomy (Yes)	35.4%	33.8%	58.9%
Other GI Comorbidities (Yes)	54.6%	53.5%	72.2%
Behavioral Comorbidities (Yes)	30.0%	29.8%	32.3%
Cardiovascular Respiratory Comorbidities (Yes)	53.8%	52.8%	69.2%
Wheelchair Use (Yes)	6.4%	6.1%	11.7%
Other Mobility Disorders (Yes)	20.3%	20.2%	21.4%
Developmental Disorders (Yes)	74.3%	74.0%	79.5%
Vagus Nerve Stimulation/Deep Brain Stimulation	17.2%	17.0%	19.2%
Epilepsy Surgery	1.0%	1.0%	0.5%
HCRU Severity Score	101.6	98.7	145.4
Charlson Comorbidity Index (CCI)	0.8	0.8	1.3
Germaine Smith Index (GSI)	0.7	0.7	1.4
Number of unique ASMs in the baseline period	2.2	2.2	2.5
Average number of rescue medication claims in baseline period	0.9	0.8	1.0

Safety results – Outcome data

Mortality rates per patient years

In **DS**, mortality was evaluated overall and within paediatric (1 to 17 years; n = 2,045) and adult (18 years and older; n = 736) subgroups, and further stratified by HCRU severity (low n = 1,391; high n = 1,390; quartiles Q1 n = 711, Q2 n = 680, Q3 n = 700, Q4 n = 690).

Within this study mortality rate for DS was **7.3 per 1000 PY** overall, with higher rates in adults (9.1) than paediatric patients (6.7). Mortality rates were higher for those with greater HCRU burden, demonstrating a consistent increase in mortality across HCRU severity score quartiles (4.3 in quartile 1 to 10.5 in quartile 4). The results from RWE1609 indicate that DS mortality rate is higher in adults and among patients with greater HCRU-based severity.

Table 6: Mortality rates per 1000 patient years among patients with DS

		Patient counts	Mortality rate per 1000 PY (95% CI)
DS	Total	2,781	7.3 (5.6, 9.4)
	Age 1-17	2,045	6.7 (4.8, 9.1)
	Age 18+	736	9.1 (5.5, 14.2)
	Low severity score	1,392	4.8 (2.8, 7.5)
	High severity score	1,389	9.6 (6.9, 13.0)
	Severity score Q1	712	4.3 (1.9, 8.5)
	Severity score Q2	680	5.2 (2.5, 9.6)
	Severity score Q3	699	8.6 (5.1, 13.6)
	Severity score Q4	690	10.5 (6.7, 15.7)

In **LGS**, outcomes were similarly assessed overall and by age (pediatric n = 16,984; adult n = 16,420) and HCRU severity (low n = 16,987; high n = 16,417; quartiles Q1 n = 8,662, Q2 n = 8,325, Q3 n = 8,246, Q4 n = 8,171).

For LGS, mortality rate was **14.2 per 1000 PY** overall and also higher in adults (16.3) than paediatric patients (12.1). As seen in patients with DS, rates increased with increasing HCRU severity, from 9.7 in quartile 1 of the severity score to 22.6 in quartile 4. The results from this study indicate that LGS mortality rate is higher in adults and among patients with greater HCRU-based severity. Overall, LGS mortality is higher than DS mortality across age and severity score strata.

Table 7: Mortality rates per 1000 patient years among patients with LGS

		Patient counts	Mortality rate per 1000 PY (95% CI)
LGS	Total	33,404	14.2 (13.6, 14.8)
	Age 1-17	16,984	12.1 (11.3, 12.9)
	Age 18+	16,420	16.3 (15.4, 17.2)
	Low severity score	17,001	10.1 (9.4, 19.9)
	High severity score	16,403	18.3 (17.3, 19.3)
	Severity score Q1	8,667	9.7 (8.7, 10.8)
	Severity score Q2	8,334	10.5 (9.5, 11.6)
	Severity score Q3	8,053	14.0 (12.8, 15.2)
	Severity score Q4	8,350	22.6 (21.1, 24.2)

These data are extracted from section 10.4.1 of the MAH Study Report, which provides an overview of the results concerning mortality rates per patient years. The heading of Table 10-4-1-1 in the study report also states that the mortality rates per 1,000 patient years are presented, as shown in Table 6 and Table 7 of this AR. However, the heading of the last column in Table 10-4-1-1 in the study report is labelled 'SMR' instead of 'Mortality rates per 1,000 patient years'. The MAH is requested to clarify whether this is a typo and, whether the figures presented are mortality rates per 1000 PY or standardised mortality rates. (**RSI**).

Standardised mortality rate (SMR)

Patients with DS experienced substantial excess mortality compared to the general population (overall SMR 8.3, where the general population reference SMR is 1.0). Relative risk was especially elevated in paediatric patients (SMR 27.3) compared with adults (SMR 3.4), indicating that even if the absolute number of deaths is lower in children than adults, children with DS have a much higher mortality risk than other children of the same age in the general population. Similar to mortality rates, SMRs were also higher among those with higher HCRU severity, rising from 3.9 in the low severity group to 16.1 in the high severity group and increasing stepwise across HCRU quartiles (2.6 in Q1 to 18.5 in Q4).

Table 8: Standardised mortality ratios among patients with DS

		Patient counts	SMR (95% CI)
DS	Total	2,781	8.3 (6.3-10.7)
	Age 1-17	2,045	27.3 (19.5-37.1)
	Age 18+	736	3.4 (2.0-5.2)
	Low severity score	1,391	3.9 (2.3-6.2)
	High severity score	1,390	16.1 (11.6-21.9)
	Severity score Q1	711	2.6 (1.1-5.1)
	Severity score Q2	680	6.8 (3.2-12.4)
	Severity score Q3	700	13.8 (8.2-21.9)
	Severity score Q4	690	18.5 (11.8-27.8)

LGS similarly showed marked excess mortality (overall SMR 8.0). As in DS, paediatric patients had a much higher relative risk versus the general population (SMR 36.8) than adults (SMR 5.1), reinforcing that paediatric LGS represents a high-risk subgroup in relative terms. SMRs were higher in the high versus low HCRU severity group (10.2 vs 5.7) and increased across quartiles (5.2 in Q1 to 12.8 in Q4), indicating a severity associated increase in excess mortality (see Table 9).

Together with the mortality rate results, the SMR results clarify that age patterns differ for absolute versus relative risk. Adults generally have higher mortality rates, but paediatric patients show higher SMRs because expected mortality in the general paediatric population is very low.

In both DS and LGS, the alignment between rising mortality rates and rising SMRs across HCRU severity strata strengthens the fact that the HCRU-based severity score is associated with mortality risk and may help identify patients with the greatest excess mortality burden.

Table 9: Standardised mortality ratios among patients with LGS

		Patient counts	SMR (95% CI)
LGS	Total	33,404	8.0 (7.6-8.3)
	Age 1-17	16,984	36.8 (34.4-39.3)
	Age 18+	16,420	5.1 (4.8-5.4)
	Low severity score	16,987	5.7 (5.3-6.1)
	High severity score	16,417	10.2 (9.7-10.8)
	Severity score Q1	8,662	5.2 (4.7-5.8)
	Severity score Q2	8,325	6.2 (5.6-6.9)
	Severity score Q3	8,246	7.8 (7.1-8.5)
	Severity score Q4	8,171	12.8 (11.9-13.7)

Kaplan Meier analysis

The Kaplan–Meier curves show higher survival for DS than LGS patients across most of the age range (see Figure 1). Among patients with LGS an earlier and more pronounced decline in survival probability was observed. Detailed values (see Table 10) indicate that survival remains high in childhood for both DS and LGS but is consistently lower for LGS at each milestone age (for example, 88% vs 98% at age 5 and 66% vs 80% at age 30 for LGS vs DS). Overall, these results suggest a persistently greater mortality burden over the observed age range in LGS compared with DS. However, the relatively smaller sample size for DS patients compared to LGS patients may be driving these results.

Table 10: Kaplan–Meier survival results by age for DS and LGS patients

Patient age (in years)	DS (N at risk)	DS survival probability	LGS (N at risk)	LGS survival probability
5	378	98%	2,306	88%
10	415	95%	4,647	83%

15	281	91%	4,347	78%
20	255	88%	4,370	74%
25	161	87%	3,035	70%
30	66	80%	2,733	66%
35	44	80%	1,749	62%
40	23	80%	1,571	58%
45	13	77%	947	54%
50		77%	744	47%
55		55%	584	42%
60		47%	567	36%
65		47%	286	30%
70		47%	172	23%

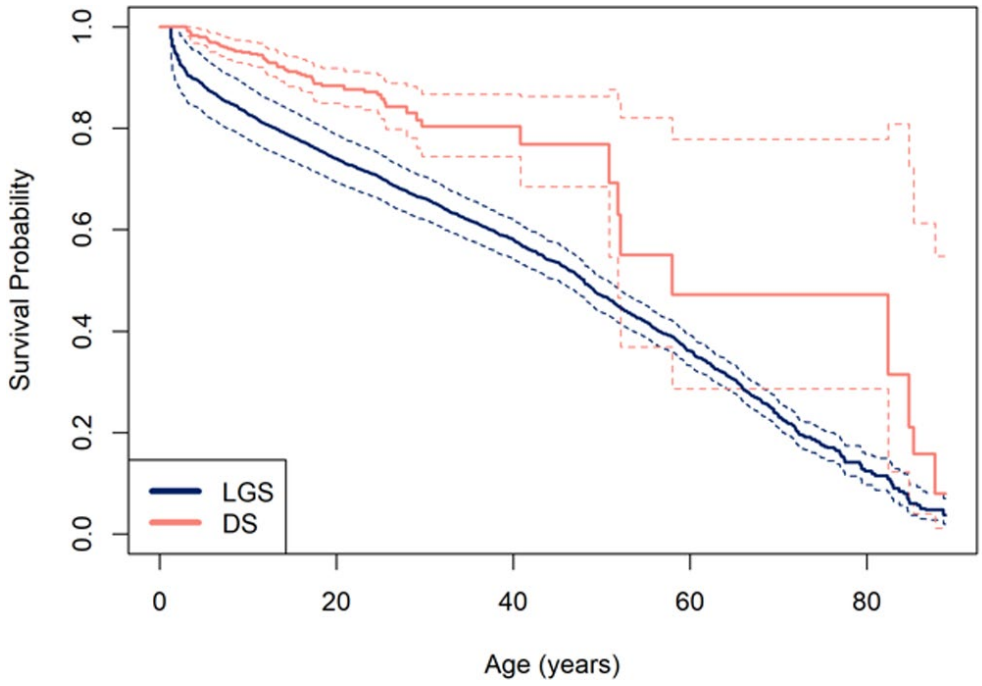

Figure 1: Kaplan–Meier survival by age for LGS and DS patients

Cox proportional hazards model

Cox models estimate hazard ratios (HRs) for death above 1.0 indicate higher mortality risk, and HRs below 1.0 indicate lower risk.

The Cox PH model for the combined cohort highlights that specific clinical factors are associated with higher mortality risk, with the largest and statistically significant effects observed for feeding tube or gastrostomy, sleep apnea, wheelchair use, gastrointestinal comorbidities, and cardiovascular or respiratory complications (see Table 11). Higher comorbidity burden (Charlson Comorbidity Index (CCI) and Germaine Smith index (GSI)), higher area deprivation index (ADI), and greater ASM exposure were also associated with increased risk.

The LGS only cohort shows a similar pattern, with elevated mortality risk associated with feeding tube or gastrostomy and sleep apnea as the most prominent predictors, alongside other medical complexity markers such as wheelchair use, gastrointestinal comorbidities, and cardiopulmonary complications.

Comorbidity indices and neighborhood deprivation remained positively associated with mortality. Cox PH analyses were not conducted for a DS-only cohort due to a much smaller sample size for the DS-only cohort.

Overall, these findings align with the descriptive and stratified findings above, showing that mortality concentrates in patients with higher HCRU-based severity and greater baseline clinical complexity, and they provide complementary evidence by isolating independent correlates of risk.

Table 11: Cox proportional hazards model for mortality; selected variables with HR >1

	DS + LGS patients		LGS patients only	
Variable	Hazard_Ratio	P_Value	Hazard_Ratio	P_Value
COMORBID_GI_GASTROSTOMY	2.3 (2.1, 2.6)	0.0	2.3 (0.0, 2.1)	0.0
COMORBID_SLEEP_APNEA	1.8 (1.5, 2.2)	0.0	1.9 (0.0, 1.6)	0.0
COMORBID_WHEELCHAIR	1.2 (1.1, 1.4)	0.0	1.2 (0.0, 1.0)	0.0
COMORBID_GI_OTHER	1.2 (1.1, 1.4)	0.0	1.2 (0.0, 1.1)	0.0
COMORBID_RESPIRATORY_CV	1.2 (1.0, 1.3)	0.0	1.2 (0.0, 1.0)	0.0
HCP_TIERTIER 3 - NEUROLOGY / CHILD NEUROLOGY	1.1 (1.0, 1.2)	0.0	1.1 (0.1, 1.0)	0.1
INSMEDICARE	1.1 (1.0, 1.3)	0.1	1.1 (0.2, 1.0)	0.2
CCI	1.1 (1.1, 1.1)	0.0	1.1 (0.0, 1.0)	0.0
GSI	1.1 (1.1, 1.1)	0.0	1.1 (0.0, 1.1)	0.0
ADI_TEN	1.1 (1.1, 1.1)	0.0	1.1 (0.0, 1.1)	0.0
HCP_TIERTIER 4 - OTHER	1.1 (0.9, 1.3)	0.4	1.0 (0.6, 0.9)	0.6
RX_ASM_MOL_COUNT	1.1 (1.0, 1.1)	0.0	1.0 (0.0, 1.0)	0.0

Sensitivity analyses

- Sensitivity analysis with closed claims only

For DS cohort, the closed claims only sensitivity analysis (N = 630) produced mortality patterns consistent with the primary analysis, with higher mortality in adults than paediatric patients and higher mortality with greater HCRU severity. The overall mortality rate was 11.1 per 1000 person years, with rates of 9.1 in paediatric patients and 17.6 in adults. Mortality also increased from the low severity group (8.1) to the high severity group (13.1), and quartile estimates generally suggested higher mortality in the highest severity stratum (Q4 16.7), although confidence intervals were wide across quartiles due to smaller sample sizes. Excess mortality remained substantial, with an overall SMR of 11.6, particularly elevated in paediatric patients (37.2) compared with adults (5.5), and increasing with severity (low 4.9 vs high 25.4, with the highest SMR in Q4 at 35.5).

Table 12: Results of sensitivity analysis with closed claims only: ***Patients with DS***

		Patient counts	Mortality rate per 1000 PY (95% CI)	SMR (95% CI)
DS	Total	630	11.1 (6.9-17.0)	11.6 (7.2-17.8)
	Age 1-17	470	9.1 (4.8-15.5)	37.2 (19.8-63.6)
	Age 18+	160	17.6 (7.6-34.6)	5.5 (2.4-10.8)
	Low severity score	267	8.1 (3.0-17.7)	4.9 (1.8-10.8)
	High severity score	363	13.1 (7.3-21.6)	25.4 (14.2-41.9)
	Severity score Q1	104	14.6 (4.0-37.3)	5.6 (1.5-14.3)
	Severity score Q2	163	4.3 (0.5-15.5)	4 (0.5-14.5)
	Severity score Q3	177	9.1 (3.0-21.2)	16.2 (5.3-37.9)
	Severity score Q4	186	16.7 (8.0-30.8)	35.5 (17.0-65.2)

For LGS cohort, the closed claims only sensitivity analysis (N = 4,894) similarly supported the robustness of the main findings, showing higher mortality in adults and a clear gradient by HCRU severity. The overall mortality rate was 17.5 per 1000 person years, with higher rates in adults (21.0) than paediatric patients (14.4). Mortality increased markedly by severity, from 12.0 in the low severity group to 21.3 in the high severity group, and rose across quartiles, reaching 25.3 in Q4. Standardized mortality remained elevated overall (SMR 10.9) and was substantially higher in paediatric patients (45.7) than adults (6.9), with higher SMRs in the high severity group (14.4) compared with the low severity group (6.7), consistent with excess mortality being concentrated among patients with greater utilisation burden.

Table 13: Results of sensitivity analysis with closed claims only: ***Patients with LGS***

		Patient counts	Mortality rate per 1000 PY (95% CI)	SMR (95% CI)
LGS	Total	4,894	17.5 (15.7-19.5)	10.9 (9.8-12.1)
	Age 1-17	2,592	14.4 (12.2-16. 9)	45.7 (38.7-53.6)
	Age 18+	2,302	21.0 (18.2-24.1)	6.9 (6.0-7.9)
	Low severity score	1,981	12.0 (9.7-14.6)	6.7 (5.4-8.2)
	High severity score	2,913	21.3 (18.8-24.2)	14.4 (12.7-16.3)
	Severity score Q1	721	12.1 (8.3-16.8)	14.6 (4.0-37.3)
	Severity score Q2	1,260	12.0 (9.2-15.3)	4.3 (0.5-15.5)
	Severity score Q3	1,402	17.2 (14.0-20.9)	9.1 (3.0-21.2)
	Severity score Q4	1,511	25.3 (21.4-29.7)	16.7 (8.0-30.8)

Similarly, in the closed claims only sensitivity analysis, the Kaplan–Meier curves continue to show lower survival for LGS than DS across most of the age range (see Figure 2). Survival declines earlier and more steadily in LGS, whereas DS maintains higher survival through early and mid adulthood, with wider uncertainty bands at older ages consistent with smaller numbers at risk in the DS cohort. Overall, this sensitivity analysis supports the primary finding of a greater mortality burden over the life

course in LGS compared with DS, while highlighting reduced precision at later ages for DS in the closed claims subset.

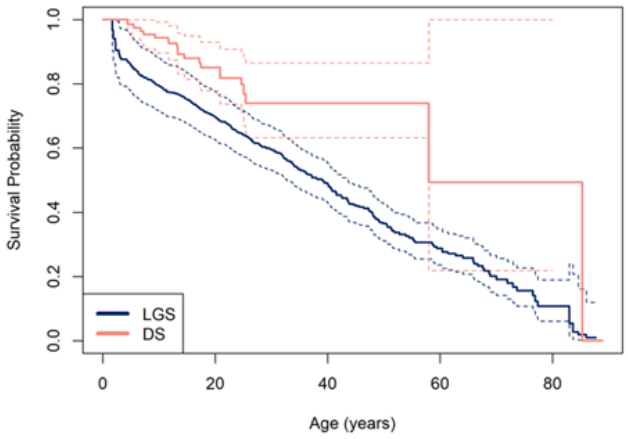

Figure 2: Kaplan–Meier survival by age for LGS and DS (closed claims only)

Also, the Cox model for the combined DS and LGS cohort in the sensitivity analyses showed similar patterns of mortality correlates as were seen in the main analyses with the largest statistically significant associations observed for markers of medical fragility and functional impairment such as sleep apnea and feeding tube or gastrostomy.

- Sensitivity analysis with restricted study period (from July 2020 through March 2024)

As an additional sensitivity analysis data were analysed using a shorter observation window from July 2020 through March 2024.

For DS cohort, mortality rates and standardized mortality rates remained higher in adults than paediatric patients and increased with higher HCRU severity. The DS overall mortality rate was 8.1 per 1000 person years. As observed in the main analysis and the sensitivity analysis with closed claims only, mortality was higher in adults (10.9) than in paediatric patients (7.1). A similar severity pattern was observed, with higher mortality in the high severity group (11.1) than the low severity group (4.6) and generally higher rates in higher severity quartiles. Standardized mortality rates in DS were directionally consistent with these patterns.

For LGS cohort, mortality remained consistently higher than DS across comparable strata and showed a clear gradient by age and severity. The overall LGS mortality rate was 14.7 per 1000 person years, increasing from 12.2 in paediatric patients to 17.2 in adults. Higher utilisation based severity was associated with increased mortality, which rose from 10.9 in the low severity group to 18.6 in the high severity group, and increased stepwise across quartiles, reaching 23.6 in Q4. Standardised mortality rates showed the same pattern, with higher values in adults than paediatric patients and the highest standardised mortality rates in the highest severity strata.

Overall, compared with the main analysis, results from this shorter study period broadly reinforce the key conclusions.

2.3.3. Discussion on clinical aspects

Primary objective of study RWE1609 was to investigate mortality among patients with Dravet syndrome and Lennox-Gastaut syndrome.

Both DS and LGS were associated with a substantial mortality burden, with higher all-cause mortality rates observed in LGS (14.2 per 1000 PY) than DS (7.3 per 1000 PY). A marked excess mortality compared to the general population was observed in both groups within this study, with overall standardised mortality rates (SMRs) of 8.3 for DS and 8.0 for LGS.

Comparing adults with paediatric patients, it could be observed that the absolute mortality rate was higher in adults than in paediatric patients in both DS (9.1 vs. 6.7) and LGS (16.3 vs. 12.1). In contrast, paediatric patients had higher SMRs than adults (DS: 27.3 vs. 3.4; LGS: 36.8 vs. 5.1), reflecting the very low expected mortality in age-matched general populations. Healthcare Resource Utilisation (HCRU) served as a proxy for underlying disease severity and medical complexity. Within this study it was observed that higher HCRU-based severity was associated with higher mortality rates and standardised mortality rates in both DS and LGS, indicating that excess mortality was concentrated among patients with a greater acute care burden. Sensitivity analyses involving closed claims only and a shortened observation period supported the main analysis's findings, showing that mortality is concentrated among patients with higher HCRU-based severity and greater baseline clinical complexity.

Although there is preliminary evidence suggesting an increased mortality in patients with DS and LGS in comparison to the general population, robust epidemiological data on background mortality rates for developmental epileptic encephalopathies (DEEs), such as DS and LGS, is limited. Estimates are further complicated by the heterogeneity of the diseases and the diagnostic challenges, particularly in patients with LGS. The mortality rate observed in patients with DS within this study (7.3 per 1000 PY) is consistent with previously reported estimates (Donnan et al., 2023: 8.6 per 1000 PY), as well as with the results from PASS EP0241 (8.02 per 1000 PY), which assessed mortality in DS and LGS patients associated with fenfluramine utilising the database of US pharmacy AnovoRx (currently under assessment via procedure EMA/PAM/0000323622). For patients with LGS receiving at least one dose of fenfluramine, PASS EP0241 reported a higher mortality rate (30.71 per 1000 PY) compared to the overall mortality rate for LGS patients in this study (14.2 per 1000 PY). It should be noted, that fenfluramine is an add-on therapy, indicating that patients receiving fenfluramine exhibit a higher severity of illness and medical complexity than the general LGS population. When mortality rates are compared among LGS patients with greater HCRU-based severity (mortality rate in quartile 4 of HCRU-based severity: 22.6 per 1000 PY in quartile 4), which is considered to better represent fenfluramine users with LGS, the difference in mortality rates becomes less pronounced. Chin et al. (2021) reported a lower mortality rate among patients with LGS (6.1 per 1000 PY). The results of this study should be interpreted with caution, as the underuse of LGS-specific diagnosis codes in general practice records has likely led to the under-identification of cases and consequently an underestimation of mortality rates. The results of this study (RWE1609) contribute to the suggestion that the mortality rate reported by Chin et al. is underestimated.

The secondary objective of study RWE1609 was to evaluate key patient demographic and clinical characteristics that are associated with mortality. Across descriptive comparisons and multivariable survival models, strong associations for feeding tube or gastrostomy, sleep apnea, cardiopulmonary complications, gastrointestinal conditions, wheelchair use, as well as social vulnerability (captured by neighborhood deprivation), and higher comorbidity burden were found, which indicates that the mortality risk is closely tied to medical complexity and functional impairment.

However, these findings should be interpreted in light of the inherent limitations of administrative claims data. The quality of the claims data used in this study is subject to coding errors and inconsistencies, as coding protocols may not always be applied correctly by HCPs. Variations in coding practices, was well as potential up-coding or down-coding can skew data analysis and lead to imprecise

conclusions. Aspects of patient care that are provided outside of traditional healthcare settings are not captured by claims data, which could downplay the severity of LGS/DS. Given that open claims data are not collected directly from the insurance provider, not all claims for a patient may be captured. Furthermore, not all deceased LGS and DS patients may be included in the mortality data (deaths have not been publicly recorded through a public announcement or government notice of death) leading to a possible underestimation of mortality rate. Despite controlling for many known confounders, residual or unmeasured confounding remains a possibility. Factors such as genetic predispositions, lifestyle choices, and environmental influences were not accounted for, affecting observed associations. Furthermore, clinical severity and cause-specific mortality are not directly observed, as HCRU is merely a proxy for underlying disease severity and medical complexity. Associations may also be influenced by residual confounding and reverse causation. While data from the Komodo database may be generalisable at the US level, generalisability to other regions (e.g. Europe) is limited due to differences in healthcare systems and the availability and funding of treatment options. Nevertheless, the trends observed within this study are generally considered to be applicable to other regions too.

In conclusion, study RWE1609 highlighted the relationship between age as well as higher HCRU severity score and higher mortality, and identified patient-related sociodemographic and clinical characteristics associated with mortality among LGS and DS patients. Overall, LGS mortality is higher than DS mortality across age and severity score strata. The mortality rates observed in this study are generally comparable to previously reported estimates. However, comparisons with previously estimated mortality rates are difficult due to the different populations under examination across studies, country specific healthcare systems, and different time periods, emphasizing the need for further data to characterise mortality in DS and LGS.

Nevertheless, this study provides some new insights into mortality rates and factors associated with mortality among patients with DS and LGS. The data retrieved within this study can help to inform risk stratification, care planning, and targeted treatment and support strategies for LGS and DS patients and their care teams.

3. Rapporteur's overall conclusion and recommendation

This study aimed to evaluate mortality rates, as well as key patient demographic and clinical characteristics that are associated with mortality, among patients with Dravet syndrome and Lennox-Gastaut syndrome.

The study indicates that both DS and LGS are associated with a substantial mortality burden compared to the general population. While the absolute risk of mortality increased with age, relative excess mortality was particularly pronounced in paediatric patients.

Overall, the mortality rate for LGS (overall 14.2 per 1000 PY) within this study is higher than for DS (overall 7.3 per 1000 PY) across age and severity score strata. The mortality rates reported in this study are generally consistent with data from other publications, although the available mortality data are relatively heterogeneous, particularly with regard to LGS. With regard to the mortality data presented in the Study Report, the MAH was requested to clarify whether the figures reported in Table 10-4-1-1 represent mortality rates per 1,000 patient-years or standardised mortality rates. The MAH provided a satisfactory clarification, confirming that the heading of the final column in Table 10-4-1-1 is incorrectly labelled as "SMR" (standardised mortality rates), whereas the values shown correspond to mortality rates per 1,000 patient-years.

It should be noted that comparisons with previously estimated mortality rates are difficult due to the different populations under examination across studies, country specific healthcare systems, and different time periods, emphasizing the need for further data to characterise mortality in DS and LGS.

Study RWE1609 highlights an association between a higher HCRU severity score and a higher mortality. It also showed that certain patient-related sociodemographic and clinical characteristics, which are indicative of medical complexity, functional impairment and social vulnerability (feeding tube or gastrostomy, sleep apnea, gastrointestinal comorbidities, wheelchair use, cardiovascular or respiratory complications, higher comorbidity burden and higher Area Deprivation Index) are associated with mortality among LGS and DS patients.

As the data were taken from a US claims database, the results cannot be directly compared to the situation in the EU due to differences in healthcare systems, as well as the availability and funding of treatment options in different regions (Europe, United States). However, the main trends observed within this study are generally considered to be applicable to other regions too. Furthermore, these findings should be interpreted in light of the study's inherent limitations, such as coding errors, incomplete capture of claims and deceased patients, the merely indirect capture of clinical severity and residual or unmeasured confounding.

Nevertheless, this study provides some new insights into mortality rates and factors associated with mortality among patients with DS and LGS. The data retrieved within this study can help to inform risk stratification, care planning, and targeted treatment and support strategies for LGS and DS patients and their care teams.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

- The heading of Table 10-4-1-1 in the study report states that the mortality rates per 1,000 patient years are presented, as shown in Table 6 and Table 7 of this AR. However, the heading of the last column in Table 10-4-1-1 in the study report is labelled 'SMR' instead of 'Mortality rates per 1,000 patient years'. The MAH is requested to clarify whether this is a typo and, whether the figures presented are mortality rates per 1000 PY or standardised mortality rates.

The timetable is a 30 day response timetable without clock stop.

MAH responses to Request for supplementary information

Question 1:

The heading of Table 10-4-1-1 in the study report states that the mortality rates per 1,000 patient years are presented, as shown in Table 6 and Table 7 of this AR. However, the heading of the last column in Table 10-4-1-1 in the study report is labelled 'SMR' instead of 'Mortality rates per 1,000 patient years'. The MAH is requested to clarify whether this is a typo and, whether the figures presented are mortality rates per 1000 PY or standardised mortality rates.

Summary of the MAH's response

The MAH confirmed that this is a typographical error and that the heading of the last column in Table 10-4-1-1 of the study report is incorrectly labelled as "SMR" (standardised mortality rates). Furthermore, the MAH confirmed that the data presented in this column correspond to mortality rates per 1,000 patient-years. No SMRs are presented in table below.

The table heading has been corrected accordingly. The corrected version of Table 10-4-1-1 is provided below.

Table 10-4-1-1: Mortality rates per 1000 patient years among DS and LGS patients, stratified by age group, low versus high HCRU severity score, and HCRU severity score quartiles

		Patient counts	**Mortality rate per 1000 PY** (95% CI)
DS	Total	2,781	7.3 (5.6, 9.4)
	Age 1-17	2,045	6.7 (4.8, 9.1)
	Age 18+	736	9.1 (5.5, 14.2)
	Low severity score	1,392	4.8 (2.8, 7.5)
	High severity score	1,389	9.6 (6.9, 13.0)
	Severity score Q1	712	4.3 (1.9, 8.5)
	Severity score Q2	680	5.2 (2.5, 9.6)
	Severity score Q3	699	8.6 (5.1, 13.6)
	Severity score Q4	690	10.5 (6.7, 15.7)
LGS	Total	33,404	14.2 (13.6, 14.8)
	Age 1-17	16,984	12.1 (11.3, 12.9)
	Age 18+	16,420	16.3 (15.4, 17.2)
	Low severity score	17,001	10.1 (9.4, 19.9)
	High severity score	16,403	18.3 (17.3, 19.3)
	Severity score Q1	8,667	9.7 (8.7, 10.8)
	Severity score Q2	8,334	10.5 (9.5, 11.6)
	Severity score Q3	8,053	14.0 (12.8, 15.2)
	Severity score Q4	8,350	22.6 (21.1, 24.2)

Assessment of the MAH's response

The MAH satisfactorily clarified that the heading of the last column in Table 10-4-1-1 of the study report is incorrectly labelled as "SMR" (standardised mortality rates), but the data presented correspond to mortality rates per 1,000 patient-years.

Issue resolved.

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 than 2 years of age with Dravet syndrome (ZX008-2201) This study was added as a result of procedure EMEA-001990-PIP01-16-M04	Study 10	Study ongoing	N/A