16 October 2025
EMADOC-1700519818-2837424
Human Medicines Division

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

Epidyolex

Cannabidiol

Procedure no: EMA/PAM/0000291080

Note

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

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1. Introduction

On 28 July 2025, the MAH submitted a prematurely terminated paediatric study for Epidyolex, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the following phase 3 study no. GWEP17005: '*An Open-label, Single-arm Study to Assess the Safety, Pharmacokinetics, and Efficacy of Adjunctive Cannabidiol Oral Solution (GWP42003-P) in Participants with Tuberous Sclerosis Complex (Age 1 Month to < 2 Years of Age), Dravet Syndrome (1 Year to < 2 Years of Age), or Lennox-Gastaut Syndrome (1 Year to < 2 Years of Age) who Experience Inadequately-controlled Seizures*' has been terminated, due to feasibility issues. The MAH stated that the GWEP17005 study was part of the clinical development program.

Approaches to improve recruitment and retention to the study have been attempted by changing the study to a single-arm study across all 3 indications (pooling data), with the primary endpoints being PK, safety and efficacy as well as extension of the timeline. Despite these changes the feasibility challenges have prevented the completion of the study (PIP modification EMEA-001964- PIP01-16-M04).

On 15th November 2024 the PDCO agreed to a PIP waiver (PIP modification EMA/PE/0000224912) for DS, LGS and TSC in the paediatric population from birth to less than 2 years of age. GWEP17005 has therefore been removed from the PIP and the final agreed Paediatric Investigation Plan has now been completed in full for Epidyolex.

The above study is the only concerned study.

The Sponsor plans to submit a Type II variation in Q3 2025 in order to appropriately update the paediatric wording in the SmPC to ensure alignment with the completed PIP and close PIP activities.

Overview over PIP-procedures:

Dravet Syndrome:

Area	Description
Quality-related studies	Not applicable.
Non-clinical studies	Not applicable.
Clinical studies	**Study 1 (GWEP1332)** Randomised double-blind placebo-controlled study to assess the efficacy and safety of cannabidiol, to investigate its pharmacokinetics and its effects on other anti-epileptic drugs in patients with DS. **Study 2 (GWEP1424)** Randomised double-blind placebo-controlled study to assess efficacy and safety of two doses of cannabidiol compared to placebo in patients with DS. **Study 5 (GWEP1415)** Open-label extension study to assess long-term safety of cannabidiol in patients with DS or LGS. **Study 8 (GWEP17006)** *Deleted in procedure EMEA-001964-PIP01-16-M04.* **Study 9 (GWEP17005)** *Deleted in procedure EMA/PE/0000224912 (15 Nov 2024).*
Extrapolation, modelling and simulation studies	**Study 10 (GWPP17025)** A physiological based PK model for cannabidiol (CBD) in a virtual patient population. **Study 11 (GWPP17004)** A joint population PK model for CBD, 7-OH CBD and 7-COOH CBD in healthy adult subjects to re-estimate exposure in PK evaluable patients with Lennox-Gastaut syndrome.
Other studies	Not applicable.
Other measures	Not applicable.

Lennox-Gastaut syndrome:

Area	Description
Quality-related studies	Not applicable.
Non-clinical studies	Not applicable.
Clinical studies	**Study 3 (GWEP1423)** Randomised double-blind placebo-controlled study to assess the efficacy and safety of cannabidiol in patients with LGS. **Study 4 (GWEP1414)** Randomised double-blind placebo-controlled study to assess efficacy and safety of two doses of cannabidiol in patients with LGS. **Study 5 (GWEP1415)** Open-label extension study to assess long-term safety of cannabidiol in patients with DS or LGS (same study as for the condition DS). **Study 8 (GWEP17006)** *Deleted in procedure EMEA-001964-PIP01-16-M04.*
	Study 9 (GWEP17005) *Deleted in procedure EMA/PE/0000224912 (15 Nov 2024).*
Extrapolation, modelling and simulation studies	**Study 10 (GWPP17025)** A physiological based PK model for CBD in a virtual patient population (same study as for the condition DS). **Study 11 (GWPP17004)** A joint population PK model for CBD, 7-OH CBD and 7-COOH CBD in healthy adult subjects to re-estimate exposure in PK evaluable patients with Lennox-Gastaut syndrome (same study as for the condition DS).
Other studies	Not applicable.
Other measures	Not applicable.

Tuberous sclerosis complex:

Area	Description
Quality-related studies	Not applicable.
Non-clinical studies	Not applicable.
Clinical studies	**Study 6 (GWEP1521)** Randomised, placebo-controlled, double-blind parallel-group comparison of two doses of cannabidiol as add-on therapy in patients with TSC, with a one year open-label safety extension. **Study 9 (GWEP17005)** *Deleted in procedure EMA/PE/0000224912 (15 Nov 2024).*
Extrapolation, modelling and simulation studies	**Study 10 (GWPP17025)** A physiological based PK model for CBD in a virtual patient population (same study as for the condition DS). **Study 11 (GWPP17004)** A joint population PK model for CBD, 7-OH CBD and 7-COOH CBD in healthy adult subjects to re-estimate exposure in PK evaluable patients with Lennox-Gastaut syndrome (same study as for the condition DS).
Other studies	Not applicable.
Other measures	Not applicable.

2.2. Information on the pharmaceutical formulation used in the study

The Investigational Medicinal Product (GWP42003-P, Epidyolex, cannabidiol oral solution [CBD-OS]) is a clear, colourless to yellow solution containing 100 mg/mL CBD dissolved in the following excipients: sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose [0.5 mg/mL]) and strawberry flavouring (0.2 mg/mL).
Mode of administration is oral. Dosing via a gastrostomy (G)/nasogastric (NG) tube (as required) is an option.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **GWEP17005** '*An Open-label, Single-arm Study to Assess the Safety, pharmacokinetics, and Efficacy of Adjunctive Cannabidiol Oral Solution (GWP42003-P) in Participants with Tuberous Sclerosis Complex (Age 1 Month to < 2 Years of Age), Dravet Syndrome (1 Year to < 2 Years of Age), or Lennox-Gastaut Syndrome (1 Year to < 2 Years of Age) who Experience Inadequately-controlled Seizures*'

Study Initiation Date:	12 May 2021 (first participant signed informed consent)
Early Study Termination Date:	28 Jan 2025 (last participant last visit) The analyses presented in this report are based on a database lock date of 24 Mar 2025.
Primary Completion Date:	28 Jan 2025 (last participant last visit) The analyses presented in this report are based on a database lock date of 24 Mar 2025.

2.3.2. Clinical study

GWEP17005

Description

An Open-label, Single-arm Study to Assess the Safety, pharmacokinetics, and Efficacy of Adjunctive Cannabidiol Oral Solution (GWP42003-P) in Participants with Tuberous Sclerosis Complex (Age 1 Month to < 2 Years of Age), Dravet Syndrome (1 Year to < 2 Years of Age), or Lennox-Gastaut Syndrome (1 Year to < 2 Years of Age) who Experience Inadequately-controlled Seizures

Methods

Study participants

Up to 27 participants were planned for assignment to receive the study intervention to achieve 18 evaluable participants, which was considered sufficient to characterize PK in children < 2 years of age. Enrollment was stratified to ensure that at least 5 participants each with Lennox-Gastaut syndrome and Dravet syndrome (1 to < 2 years of age) and 8 participants with Tuberous sclerosis complex (4 participants < 1 year of age and 4 participants aged 1 to < 2 years) would be included in this study.

Treatments

Oral Cannabidiol twice daily: 2 weeks fixed titration period and hereafter investigator driven titration depending on symptoms till 52 weeks treatment. Hereafter a taper period.

Objectives

Primary Objectives:

- To evaluate the safety and tolerability of adjunctive CBD-OS assessed during the 52-week treatment period.
- To investigate the exposure of CBD-OS and its major metabolites following single and multiple doses of CBD-OS.
- To evaluate the efficacy of CBD-OS in reducing the frequency of indication-specific countable seizures.

Secondary Objectives:

- To evaluate the efficacy of CBD-OS in reducing the frequency of total countable seizures.
- To assess the retention of participants receiving CBD-OS.

Exploratory Objectives:

- To evaluate the efficacy of CBD-OS based on VEEG.
- To evaluate the effects of CBD-OS on QoL.
- To evaluate time of dosing relative to food intake time.

Outcomes/endpoints

Sample size

Five participants were enrolled into the study, with 2 screen failures.
Three participants had study intervention dosing ranging from 27 to 192 days.

Randomisation and blinding (masking)

No randomization or blinding

Statistical Methods

No formal testing of statistical hypotheses was planned in this study, and thus, no formal sample size calculation was performed. Analysis and reporting of the primary safety and PK endpoint parameters were to include descriptive statistical summaries of each element at Baseline and Follow-up Visits

Results

Participant flow

Please see results

Recruitment

Despite a diligent and comprehensive approach towards study recruitment across multiple years, recruitment and retention have not been possible. After 4 years of active recruitment only 4 participants were screened across 11 sites.

Baseline data

Number analysed

N/A

Efficacy results

N/A

Safety results

An independent safety monitoring committee was constituted to evaluate participant safety.

Safety data were submitted individually. Adverse events assessed by the investigator to be related to study intervention were the following:

SAE (moderate) 2 episodes: change in seizure presentation, hospitalization.

SAE (mild) one episode: change in seizure presentation. It is noted that the event lead to hospitalization.

One patient experienced a SAE of change in seizure presentation leading to hospitalization, but assessed by the investigator not to be related to study intervention.

In one patient elevated liver enzymes (increased ALAT, ASAT, GGT) were found and assessed to be related to study intervention.

Two participants withdrew from the study due to physician decision to terminate treatment (day 221, day 27). One patient withdrew from the study as the patient switched to a commercially available product.

No TEAEs led to discontinuation of study intervention.
No fatal TEAEs were reported during the study.

2.3.3. Discussion on clinical aspects

The GWEP17005 study is an Open-label, Single-arm Study to Assess the Safety, pharmacokinetics, and Efficacy of Adjunctive Cannabidiol Oral Solution (GWP42003-P) in children below 2 years of age with Tuberous Sclerosis Complex, Dravet Syndrome or Lennox-Gastaut Syndrome who experience inadequately-controlled Seizures. This study did not have a formal testing of hypothesis and was not designed to demonstrate efficacy or safety.

The number of patients (n=3) is too low to make conclusions regarding efficacy, safety and PK.

Epidyolex already holds the indication:

Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older. Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older

Regarding safety data no new or concerning AE's were detected. The reported SAE's hepatocellular injury with elevated liver enzymes as well as increased seizure frequency are described in section 4.4 'Special warnings and precautions for use' of the SmPC for the use of Epidyolex in patients above 2 years of age.

The presented data is limited and does not necessitate any changes in the current SmPC for Epidyolex

3. Rapporteur's overall conclusion and recommendation

☒**Fulfilled:**

No regulatory action required.