Amsterdam, 20 May 2021
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Human Medicines Division

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

Epidyolex

cannabidiol

Procedure no: EMEA/H/C/004675/P46/008

Note

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

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1. Introduction

Epidyolex was approved, via the European Union centralised procedure by the Committee for Medicinal Products for Human Use (CHMP), with European Commission decision issued on 19th September 2019 for the following 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."

The intent of this paediatric study was to evaluate the long-term safety and efficacy of Epidyolex (cannabidiol oral solution [CBD-OS]) in 681 patients aged 2 years and above (≥104 weeks after Visit 1). The study comprised an open-label extension study in children and adults as part of a paediatric investigational plan as approved by the European Medicines Agency's Paediatric Committee (PDCO).

No unexpected or new clinically significant safety findings were noted. Therefore, no regulatory consequences were identified by the Marketing Authorisation Holder (MAH).

1.1. Steps taken for the assessment

Submission date:	09 March 2021
Start of procedure:	22 March 2021
Rapporteur's preliminary assessment report circulated on:	22 April 2021
Rapporteur's updated assessment report circulated on:	N/A
CHMP adoption of conclusions:	20 May 2021

2. Summary of data submitted

2.1. Study design and methodology

2.1.1. Study design

This was a multi-center, open-label extension (OLE) study for participants with DS or LGS who had completed the double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies). The study consisted of a titration period and a maintenance period, followed by a 10-day taper period.

2.1.2. Methods

Participants could receive treatment for up to a maximum of 6 years, depending on the country. Information on seizures was recorded weekly using an interactive voice response system. All participants titrated up to 10 to 20 mg/kg/day GWP42003-P using a recommended titration schedule. The participants continued at this dose during the maintenance period. However, investigators could decrease or increase (upon discussion with medical monitor) the dose if a participant experienced intolerance or for additional seizure control. The maximum dose patients could receive was 30 mg/kg/day.

2.1.3. Objective

Primary Objective:

The purpose of this study was to evaluate the long-term safety and tolerability of GWP42003-P, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS.

Secondary Objectives:

All Participants:

Evaluated the effect of GWP42003-P, as adjunctive treatment, on:

- Quality of life.
- Adaptive behaviour.
- Need for hospitalizations due to epilepsy.
- Usage of rescue medication.
- Maintenance of seizure frequency reduction and freedom from seizures during the OLE study.
- Frequency of total and subtypes of seizures.
- Change in duration of subtypes of seizures.
- Number of episodes of *status epilepticus*.
- Cognitive function.
- Growth and development.
- Menstruation cycles (in females).
- Signals indicating drug abuse liability of GWP42003-P.

DS Participants Only:

Evaluated the effect of GWP42003-P, as adjunctive treatment, on:

- Total convulsive seizure frequency.
- Total non-convulsive seizure frequency.
- Number of participants convulsive seizure-free.
- Responder rate (defined in terms of percentage reduction in total convulsive seizure frequency).

LGS Participants Only:

Evaluated the effect of GWP42003-P, as adjunctive treatment, on:

- Drop seizure frequency.
- Non-drop seizure frequency.
- Number of participants drop seizure-free.
- Responder rate (defined in terms of percentage reduction in drop seizure frequency).

2.1.4. Study Population

Participants aged 2 years and above with DS or LGS who had completed the double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies) were included in this study.

2.1.5. Treatment

GWP42003-P oral solution was presented as an oily solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavouring.

Dosage: Participants were titrated up to 10 to 20 mg/kg/day GWP42003-P. Participants then remained at this dose until the 'End of Treatment' visit, with the option for doses to be increased (up to 30 mg/kg/day, maximum) or decreased, if deemed necessary by the Investigator. Following the 'End of Treatment'/Withdrawal visit, doses of IMP were down-titrated at home (10% per day for 10 days) until the 'End of Taper Period' visit.

Investigational medicinal product was to be taken twice daily (morning and evening) immediately after the participant's usual antiepileptic drug (AED) administration, or as GW Pharma (International) B.V otherwise specified by the investigator.

2.1.6. Outcomes/Endpoints

Primary Endpoint:

The safety of GWP42003-P was assessed by the adverse event (AE) profile and by evaluating changes in the following, relative to the pre-randomisation baseline of the Core Study: vital signs, physical examination (including height and body weight), 12-lead ECG, Columbia Suicide Severity Rating Scale (C-SSRS) (The Children's C-SSRS for participants 6 to 18 years of age and C-SSRS for participant's 19 years and above), Cannabis Withdrawal Scale (CWS) (for participants older than 18 years), Pediatric Cannabinoid Withdrawal Scale (PCWS) (for participants 4 to 17 years of age), Clinical laboratory parameters.

Secondary Endpoints:

All Participants:

• Change in quality of life was measured with QOLCE if 18 years of age or younger, or QOLIE if 19 years of age or older, relative to the pre-randomisation baseline of the Core Study, if assessed during the Core Study.

• Change in Subject/Caregiver Global Impression of Change (S/CGIC), relative to the pre-randomisation baseline of the Core Study.

• Change in adaptive behaviour was measured with the Vineland Adaptive Behaviour Scales, Second Edition (Vineland-II), relative to the pre-randomisation baseline of the Core Study, if assessed during the Core Study.

• Change in the number of inpatient epilepsy-related hospitalizations (number of hospitalizations due to epilepsy in each 28-day period), relative to the pre-randomisation baseline of the Core Study.

• Change in the use of rescue medication (number of days used in each 28-day period), relative to the pre-randomisation baseline of the Core Study.

• Maintenance of seizure frequency reduction and freedom from seizures during the OLE study.

• Percentage change in the frequency of the total seizures, relative to the pre-randomisation baseline of the Core Study.

• Number of participants considered treatment responders, defined as those with a ≥25%, ≥50%, ≥75%, or 100% reduction in total seizures, relative to the pre-randomisation baseline of the Core Study.

• Number of participants who experienced a >25% worsening, −25% to +25% no change, 25% to 50% improvement, 50% to 75% improvement or >75% improvement in total seizures, relative to the pre-randomisation baseline of the Core Study.

• Percentage change in the frequencies of subtypes of seizures, relative to the pre-randomisation baseline of the Core Study.

• Changes in duration of seizure subtypes as assessed by the S/CGICSD, relative to the pre-randomisation baseline of the Core Study.

• Change in the number of episodes of *status epilepticus*, relative to the pre-randomisation baseline of the Core Study.

• Change in cognitive function was measured with a cognitive assessment battery, relative to the pre-randomisation baseline of the Core Study, if assessed during the Core Study.

• Change in growth and development for participants less than 18 years of age by measurement of height, weight, IGF-1 levels, and Tanner Staging (for participants aged 10 to 17 [inclusive], or earlier if clinically indicated by onset of menarche or other signs of precocious puberty), relative to the pre-randomisation baseline of the Core Study.

• Effects on menstruation cycles (in females).

• Drug abuse liability was measured by AEs of abuse potential, drug accountability and Study Medication Use and Behaviour Survey in participants aged 12 and older.

<u>DS Participants only:</u>

• Percentage change in total convulsive seizure frequency, relative to the pre-randomisation baseline of the Core Study.

• Percentage change in total non-convulsive seizure frequency, relative to the pre-randomisation baseline of the Core Study.

• Number of participants considered treatment responders, defined as those with a ≥25%, ≥50%, ≥75%, or 100% reduction in convulsive seizures, relative to the pre-randomisation baseline of the Core Study.

• Number of participants experiencing a >25% worsening, −25% to +25% no change, 25% to 50% improvement, 50% to 75% improvement or >75% improvement in convulsive seizures, relative to the pre-randomisation baseline of the Core Study.

<u>LGS Participants Only:</u>

• Percentage change in the number of drop seizures, relative to the pre-randomisation baseline of the Core Study.

• Percentage change in the number of non-drop seizures, relative to the pre-randomisation baseline of the Core Study.

• Number of participants considered treatment responders, defined as those with a ≥25%, ≥50%, ≥75%, or 100% reduction in drop seizures, relative to the pre-randomisation baseline of the Core Study.

• Number of participants experiencing a >25% worsening, −25% to +25% no change, 25% to 50% improvement, 50% to 75% improvement or >75% improvement in drop seizures, relative to the pre-randomisation baseline of the Core Study.

2.1.7. Statistical Methods

All data collected during this study were summarised across time, using appropriate statistical methods. Where baseline data were available from the Core Studies (seizure information, C-SSRS, quality of life assessments, Vineland-II, cognitive assessment battery, other measures of safety [vital signs, clinical laboratory samples]), changes from baseline were also presented. Summaries were presented overall as well as for the different etiologies (DS and LGS) separately. Descriptive statistical methods were used throughout. There was no formal hypothesis testing.

CHMP comments

The present study was designed as a multi-center, open-label extension (OLE) study for patients with DS or LGS who had completed the double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies). The primary objective of the study was to evaluate the long-term safety and tolerability of Epidyolex, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS. Secondary objectives were to measure the efficacy of the study measured as reduction in seizures and measurement of Quality of life. Overall, the objectives of the study are considered relevant and, the chosen endpoints are considered adequate for the corresponding objectives. Treatment duration was up to a maximum of 6 years, which is considered acceptable for a long-term safety-study.

Eligible patients were patients aged 2 years and above with DS or LGS who had completed the double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies). Treatment was administered as an oral solution and the patients (both DS and LGS) were titrated up to 10 to 20 mg/kg/day (could be increased up to 30 mg/kg/day, if deemed necessary by the Investigator). Recommended dose according to the SmPC is up to 20 mg/kg/day; thus, the overall recommended dose was according to the SmPC. The higher dose may (up to 30 mg/kg/day) may be associated with an increase in (dose-dependent) adverse reactions.

Only descriptive statistical methods were used. Considering the study being an open-labelled safety study, with no formal hypothesis testing, this is considered acceptable. Overall, the statistical methods applied are acceptable.

Conclusion: The overall study design and methodology is considered acceptable. Of note, the study protocol has been approved by the CHMP.

2.2. Results

2.2.1. Disposition of Participants

A total of 681 participants were enrolled into the study. All enrolled participants received at least 1 dose of IMP and thus were included in the safety analysis set.

2.2.1.1. Populations analysed

For this study, the safety analysis set was the only population analysed. The only participants excluded from this safety analysis set were those that had not taken any IMP.

The number of participants that were withdrawn and those that continued to the taper phase are presented below in Table 4-2.

Table 4-2 Participant Disposition (Safety Analysis Set)

		Indication		
Number of participants, n (%)		**Dravet Syndrome (N=315)**	**Lennox-Gastaut Syndrome (N=366)**	**Overall (N=681)**
Treatment phase	Completed	170 (54.0%)	243 (66.4%)	413 (60.6%)
	Withdrawn	145 (46.0%)	123 (33.6%)	268 (39.4%)
Primary reason for withdrawal	AE	26 (8.3%)	38 (10.4%)	64 (9.4%)
Treatment phase	Lost To Follow-Up	2 (0.6%)	1 (0.3%)	3 (0.4%)
	Met Withdrawal Criteria	5 (1.6%)	7 (1.9%)	12 (1.8%)
	Other	27 (8.6%)	18 (4.9%)	45 (6.6%)
	Withdrawal by Subject or Parent/ Guardian	62 (19.7%)	48 (13.1%)	110 (16.2%)
	Withdrawn by the Investigator	23 (7.3%)	11 (3.0%)	34 (5.0%)
Continuing to the taper phase	No	233 (74.0%)	291 (79.5%)	524 (76.9%)
	Yes	82 (26.0%)	75 (20.5%)	157 (23.1%)

Table 4-2 Participant Disposition (Safety Analysis Set)

		Indication		
Number of participants, n (%)		**Dravet Syndrome (N=315)**	**Lennox-Gastaut Syndrome (N=366)**	**Overall (N=681)**
Taper phase	Completed	76 (92.7%)	67 (89.3%)	143 (91.1%)
	Withdrawn	3 (3.7%)	4 (5.3%)	7 (4.5%)
Primary reason for withdrawal - taper phase	AE	1 (1.2%)	1 (1.3%)	2 (1.3%)
	Other	2 (2.4%)	0	2 (1.3%)
	Withdrawal by Participant Or Parent/Guardian	0	3 (4.0%)	3 (1.9%)

AE = adverse event.
Percentages are based on the number of enrolled and treated participants.

2.2.1.2. Demography and Baseline Characteristics

Demographics and baseline characteristics are presented for the safety analysis set.

Demography

The demographic characteristics were similar across the DS and LGS groups (Table 4-3). Overall, there was a similar proportion of male (52.0%) and female (48.0%) participants; the majority were White/Caucasian (87.2%) and from the US (67.5%); the mean (SD) age was 13.05 (8.2) years. Twenty-nine participants had their race recorded as 'other'. Sixteen participants had their race recorded as 'not applicable' as per country specific data protection law.

Table 4-3 Demographics and Baseline Characteristics			
Demographic Characteristic	**Dravet Syndrome (N=315)**	**Lennox-Gastaut Syndrome (N=366)**	**Overall (N=681)**
Age (Years)			
n	315	366	681
Mean (SD)	9.737 (4.4434)	15.906 (9.5392)	13.053 (8.2120)
Median	9.254	13.655	11.017
Min, Max	2.51, 19.25	2.95, 48.33	2.51, 48.33
Age group			
2–5 years	82 (26.0%)	36 (9.8%)	118 (17.3%)
6–11 years	134 (42.5%)	121 (33.1%)	255 (37.4%)
12–17 years	90 (28.6%)	89 (24.3%)	179 (26.3%)
18–55 years	9 (2.9%)	120 (32.8%)	129 (18.9%)

Table 4-3 Demographics and Baseline Characteristics			
Demographic Characteristic	**Dravet Syndrome (N=315)**	**Lennox-Gastaut Syndrome (N=366)**	**Overall (N=681)**
Sex			
Female	159 (50.5%)	168 (45.9%)	327 (48.0%)
Male	156 (49.5%)	198 (54.1%)	354 (52.0%)
Race			
White/Caucasian	269 (85.4%)	325 (88.8%)	594 (87.2%)
Black/African American	10 (3.2%)	15 (4.1%)	25 (3.7%)
American Indian/Alaska Native	1 (0.3%)	0	1 (0.1%)
Asian	6 (1.9%)	10 (2.7%)	16 (2.3%)
Not Applicable^	15 (4.8%)	1 (0.3%)	16 (2.3%)
Other	14 (4.4%)	15 (4.1%)	29 (4.3%)
Country			
Australia	11 (3.5%)	0	11 (1.6%)
France	16 (5.1%)	1 (0.3%)	17 (2.5%)
Israel	3 (1.0%)	0	3 (0.4%)
Netherlands	19 (6.0%)	5 (1.4%)	24 (3.5%)
Poland	36 (11.4%)	34 (9.3%)	70 (10.3%)
Spain	39 (12.4%)	32 (8.7%)	71 (10.4%)
USA	176 (55.9%)	284 (77.6%)	460 (67.5%)
United Kingdom	15 (4.8%)	10 (2.7%)	25 (3.7%)
Region			
Rest of the world	139 (44.1%)	82 (22.4%)	221 (32.5%)
USA	176 (55.9%)	284 (77.6%)	460 (67.5%)
Weight at Baseline (kg)			
n	308	347	655
Mean (SD)	34.01 (17.132)	43.72 (23.231)	39.16 (21.139)
Median	28.00	38.50	33.40
Min, Max	10.5, 133.4	11.2, 142.1	10.5, 142.1
Height at Baseline (cm			
n	307	344	651
Mean (SD)	131.19 (22.271)	142.33 (22.968)	137.08 (23.299)
Median	129.00	146.50	137.00
Min, Max	88.3, 189.0	89.0, 190.5	88.3, 190.5
BMI at Baseline (kg/m^2)			
n	307	344	651
Mean (SD)	18.65 (4.542)	20.18 (6.282)	19.46 (5.578)
Median	17.34	18.52	17.90
Min, Max	11.4, 44.3	10.4, 52.3	10.4, 52.3

BMI = body mass index, Min = minimum, Max = maximum, SD = standard deviation, USA = United States of America

^ Not applicable as per country specific data protection law.

Baseline Characteristics

Baseline Characteristics is summarised in Table 4-4. The data summarised included the number of AEDs that the participants were taking. Overall, the mean (SD) number of AEDs were 3.30 (1.27); 3.19 (1.12)

DS, 3.40 (1.38) LGS. The most commonly used AEDs was CLB (414 participants [60.8%]) followed by VPA (366 participants [53.7%]).

Table 4-4 Summary Baseline Characteristics (Safety Analysis Set)			
	Dravet Syndrome (N=315)	Lennox-Gastaut Syndrome (N=366)	Overall (N=681)
Number of AEDs Participant Currently Taking (Continuous)			
n	315	366	681
Mean(SD)	3.19 (1.121)	3.40 (1.383)	3.30 (1.272)
Median	3.00	3.00	3.00
Min, Max	1.0, 8.0	1.0, 13.0	1.0, 13.0
Number of AEDs Participant Currently Taking (Categorical)			
1	15 (4.8%)	16 (4.4%)	31 (4.6%)
2	63 (20.0%)	78 (21.3%)	141 (20.7%)
3	127 (40.3%)	111 (30.3%)	238 (34.9%)
4	83 (26.3%)	102 (27.9%)	185 (27.2%)
5	16 (5.1%)	39 (10.7%)	55 (8.1%)
6	7 (2.2%)	15 (4.1%)	22 (3.2%)
7	3 (1.0%)	2 (0.5%)	5 (0.7%)
8	1 (0.3%)	1 (0.3%)	2 (0.3%)
11	0	1 (0.3%)	1 (0.1%)
13	0	1 (0.3%)	1 (0.1%)
Participants taking Clobazam			
No	100 (31.7%)	167 (45.6%)	267 (39.2%)
Yes	215 (68.3%)	199 (54.4%)	414 (60.8%)
Participants taking Valproic Acid			
No	97 (30.8%)	218 (59.6%)	315 (46.3%)
Yes	218 (69.2%)	148 (40.4%)	366 (53.7%)
Participants taking Lamotrigine			
No	307 (97.5%)	232 (63.4%)	539 (79.1%)
Yes	8 (2.5%)	134 (36.6%)	142 (20.9%)
Participants taking Levetiracetam			
No	223 (70.8%)	238 (65.0%)	461 (67.7%)
Yes	92 (29.2%)	128 (35.0%)	220 (32.3%)
Participants taking Rufinamide			
No	300 (95.2%)	257 (70.2%)	557 (81.8%)
Yes	15 (4.8%)	109 (29.8%)	124 (18.2%)
Participants taking Topiramate			
No	232 (73.7%)	305 (83.3%)	537 (78.9%)
Yes	83 (26.3%)	61 (16.7%)	144 (21.1%)
Participants taking Felbamate			
No	301 (95.6%)	310 (84.7%)	611 (89.7%)
Yes	14 (4.4%)	56 (15.3%)	70 (10.3%)

AED = anti-epileptic drug, Min = minimum, Max = maximum, SD = standard deviation.

2.2.1.3. Exposure and Study Intervention Compliance

Exposure

A summary of exposure to GWP42003-P is presented in Table 4-5. The mean [SD] number of dosing days reported during the treatment period was slightly lower in the DS group (638.8 [461.97]) compared with the LGS group (838.0 [464.85] days); the median number of dosing days was also lower in the DS group (444 days) when compared to the LGS group (1090 days).

Table 4-5 Summary of Exposure (Safety Analysis Set)			
Period Statistics	**Dravet Syndrome (N=315)**	**Lennox-Gastaut Syndrome (N=366)**	**Overall (N=681)**
Total Number of Dosing Days in the Treatment Phase (All Participants)			
n	315	365	680
Mean (SD)	638.8 (461.97)	838.0 (464.85)	745.7 (473.72)
Median	444.0	1090.0	852.0
Min, Max	18, 1822	3, 1711	3, 1822
Total Number of Dosing Days in the Treatment Phase (Participants who Completed the Treatment Phase)			
n	170	243	413
Mean (SD)	875.7 (419.36)	1078.3 (313.28)	994.9 (373.84)
Median	928.5	1128.0	1112.0
Min, Max	329, 1822	345, 1711	329, 1822
Maximum dose			
20 mg/kg/day or less	65 (25.0%)	44 (13.8%)	109 (18.9%)
> 20-< 30 mg/kg/day	96 (36.9%)	131 (41.2%)	227 (39.3%)
30 mg/kg/day or more	99 (38.1%)	143 (45.0%)	242 (41.9%)
Missing/Unknown	55	48	103

IVRS = Interactive voice response system, Max = maximum, Min = minimum, SD = standard deviation
*Modal dose, for each participant, was calculated over the same periods associated with IVRS calls for seizure reporting.
Note: Percentages for Maximum Dose categories are out of the number of non-missing Maximum Dose categories.
Note: The maximum duration of the OLE study at the Poland site was a maximum of 6 years (312 weeks after Visit 1)

CHMP comments

The MAH informs that the safety analysis set, defined as all patients who had been treated with at least one dose of IMP was the only population analysed. Considered the primary objective of the study was to evaluate the long-term safety and tolerability of Epidyolex, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS, thus is considered appropriate. A total of 681 participants were enrolled into the study. This is considered sufficient to detect Very common (≥1/10) and Common (≥1/100 to <1/10) adverse events, and thus acceptable. Of the 681 patients, 315 were diagnosed with DS and 366 were diagnosed with LGS.

Overall, 60.6% of all patients completed the treatment phase of the study, with more LGS patients (66.4%) compared to DS patients (54.0%) completing the study. For both patient populations, the most common reason for withdrawal was 'Withdrawn by patient/parent/Guardian (overall 16.2%). The MAH has not provided information regarding the reasons for withdrawal by the patient/parent/Guardian however, this will not be pursued.

Only about ¼ of the patients; totally 23.1%, continued to the taper phase, indicating that the majority of patients continued treatment with epidyolex after finalising the Open-Label Extension (OLE) study.

The demographic characteristics were mostly similar across the DS and LGS groups. 48% were females and the majority (87.2%) were White/Caucasians (Table 4-3). Overall, there was a similar proportion of male (52.0%) and female (48.0%) participants; the majority were White/Caucasian (87.2%). The mean (SD) age was 13.05 (8.2) years with a total of (18.9%) patients being 18-55 years. More patients with LGS (23.8%) compared to patients with DS (2.9%) were >18 years old. This might be coincidental or due to the higher mortality related to DS (reported mortality up to 15%)compared to LGS (reported mortality approximately 5%).

As the primary objective of the study was to investigate safety of epidyolex as adjuctive treatment (underlined by the the Assessor), all patients were treated with at least one other antiepileptic drug (AED); most often clobazam. This is anticipated as clobazam is widely used in patients with DS and LGS. Mean number of AEDs was Overall, the mean (SD) number of AEDs were 3.30 (1.27).

Conclusion: Study participants including demography and baseline characteristics are overall sufficiently described. Approximately half of the 681 patients were diagnosed with LGD and approximately two-thirds of the patients completed the treatment phase of the study. As the most common reason for withdrawal, was 'Withdrawn by patient/parent/Guardian (overall 16.2%). Only one-fourth of the patients continued in the taper phase, indicating that the majority of patients continued treatment with epidyolex after finalising the Open-Label Extension (OLE) study; this is reassuring for the efficacy and safety of Epidyolex (see efficacy and safety assessment later in the present AR).

2.2.2. Evaluation of Response to Study Intervention, Efficacy

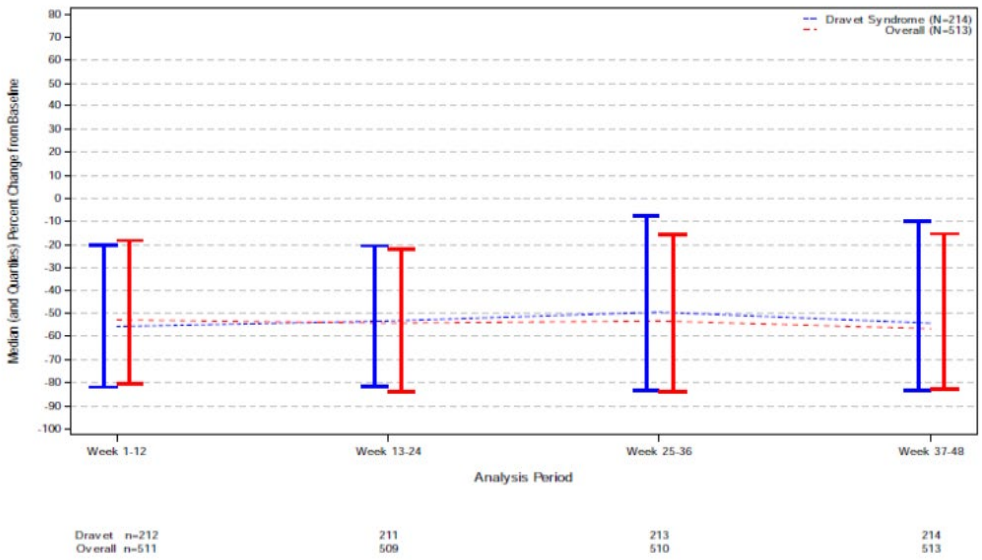
Efficacy data are presented for the safety analysis set defined as all participants who received at least 1 dose of IMP. For the analysis of efficacy, the safety analysis set was split by indication (315 participants DS and 366 participants LGS).

2.2.2.1. Secondary Endpoint, Seizure Frequency

The percentage change from baseline in drop (DS) and convulsive (LGS) seizure frequency in participants with Week 37 to 48 data is presented in Figure 5-1 and Figure 5-2. Reduction in seizure frequency provides an estimate of the effect of CBD on a participant's entire seizure burden.

During Week 37 to 48, participants with DS experienced a median 54.2% reduction from their baseline convulsive seizure frequency (Figure 5-1), and a median 62.6% reduction from their baseline total seizure frequency (Table 5-1).

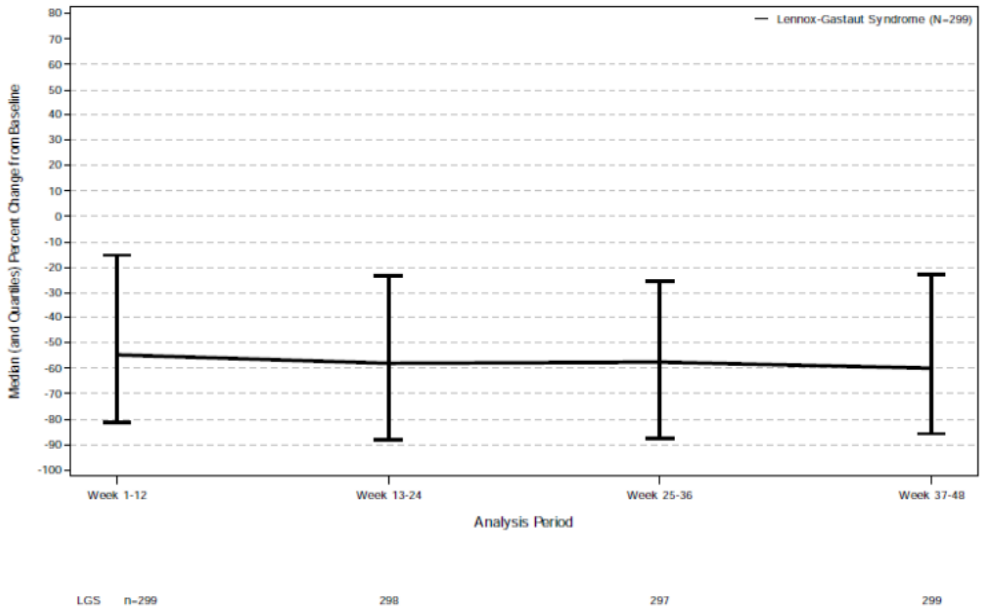
Figure 5-1 Percentage Change in Convulsive Seizure Frequency over Time - Participants with Week 37 to 48 Data (Safety Analysis Set - DS)



DS = Dravet syndrome.

During Week 37 to 48, participants with LGS experienced a median 60.1% reduction from their baseline drop seizure frequency (Figure 5-2), and a median 57.8% reduction from their baseline total seizure frequency (Table 5-1).

Figure 5-2 **Percentage Change in Drop Seizure Frequency over Time - Participants with Week 37 to 48 Data (Safety Analysis Set - LGS)**



LGS = Lennox-Gastaut syndrome

For both participants with DS and LGS, the improvements in seizure frequency emerged during the first 2 weeks of treatment.

Table 5-1 **Percentage Change from Baseline of Convulsive (DS) and Drop (LGS) Seizure Frequency (Safety Analysis Set)**

Variable	Drop Seizures Lennox-Gastaut Syndrome (N=366)	Convulsive Seizure Dravet Syndrome (N=315)	Overall (N=681)
Drop and Convulsive Seizure Frequency (Average per 28 Days) during the Baseline Period			
Baseline Period	366	291	657
Median (Q1, Q3)	80.0 (39.0, 154.0)	12.4 (6.3, 33.4)	50.4 (14.0, 136.3)
Treatment Period (Week 37 to 48)	299	214	513
Median (Q1, Q3)	32.0 (7.3, 74.1)	6.6 (2.0, 20.0)	18.3 (4.8, 56.8)
Percentage Change from Baseline in Drop and Convulsive Frequency (Average per 28 Days) during the Treatment Period			
Treatment Period (Week 1 to 12)	364	287	651
Median (Q1, Q3)	-48.2 (-79.6, -9.8)	-44.9 (-76.7, -9.1)	-45.8 (-76.4,-9.1)
Treatment Period (Week 37 to 48)	299	214	513
Median (Q1, Q3)	-60.1 (-86.0, -23.1)	-54.2 (-83.1, -10.1)	-56.7 (-83.1, -15.3)

Q1 = lower quartile; Q3 = upper quartile.
Note: Total seizures include all seizure types combined.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the day of last dose up to and including the end of treatment visit.

Proportion of Responders

The proportion of ≥50% responders during Weeks 37 to 48 was 52.3% (DS) and 57.9% (LGS).

Number of s*tatus epilepticus* Episodes

There was a reduction in the number of *status epilepticus* episodes in both DS and LGS participants. During the last 12 weeks, only 3.1% of the participants reported convulsive seizures greater than 30 minutes in duration, as compared to 4% during the first 12 weeks. Between Week 193 and Week 264, all participants (100%) had convulsive seizures less than 30 minutes in duration.

Subject/Caregiver Global Impression of Change

The change from baseline in overall condition, assessed using the S/CGIC, was reported during the treatment period and was tested using the safety analysis set. When measured on a numerical scale, a lower score represents an improvement in condition.

At their last visit, more caregivers and participants (combined) reported as having an improvement in overall condition (slightly improved, much improved, or very much improved).

compared to their status before the study; 158 (24.8%), 180 (28.8%), 114 (17.9%) respectively. However, 116 (18.2%) of participants reported no change in their condition. Overall, there was slightly more change reported in participants with LGS as compared to those with DS.

When measured on a continuous scale, the mean S/CGIC scores at last visit was 2.8 (compared to 3.2 at Day 1) which corresponds to "slightly improved.

At their end of treatment visit, more participants had a decrease in average duration of tonic-clonic (190 [54.1%]), tonic (171 [53.1%]), clonic (80 [38.8%]) and atonic (124 [49.8%]) seizures as compared to their Day 1 based on the S/CGIC score.

CHMP comments

Seizure Frequency was a secondary endpoint. The present study found that patients with DS experienced a median 54.2% reduction from their baseline convulsive seizure frequency, and a median 62.6% reduction from their baseline total seizure frequency. These results are in line with the results obtained in the Phase III studies, which found 38.9-56.8% reduction when Epidyolex 20 mg/kg/day was used as adjunct treatment in treatment of patients with DS. Among patients with LGS, the present study found that the patients experienced a median 60.1% reduction from their baseline drop seizure frequency, and a median 57.8% reduction from their baseline total seizure frequency. As for DS, the results for LGS patients are in line with the results obtained in the Phase III studies, which found 39.5-64.3% reduction when Epidyolex 20 mg/kg/day was used as adjunct treatment in treatment of patients withLGS. For both DS and LGS, the highest percentages were obtained in patients treated concomitantly with clobazam. The slightly higher success-rate may (partly) be due to the higher dose, up to 30 mg/kg/day used in the present study and also due to the high rate (60.8%) of patients concomitantly treated with clobazam. Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam.

Also, the results for the proportion of ≥50% responders during Weeks 37 to 48 were in line (or slightly higher) than observed in the Phase III studies.

Other efficacy parameters including reduction in the number of *status epilepticus*, decrease in average duration of tonic-clonic seizures and effect on 'Subject/Caregiver Global Impression of Change' (slightly improved, much improved, or very much improved) were reported for both DS and LGS.

Effect of the treatment was generally obtained within the first two weeks of treatment for both participants with DS and LGS. This is in line with the expected as steady state obtained within 11-13 days (T½ 56-61 hours).

Conclusion: Overall, addition of Epidyolex to baseline anti-epileptic treatment in patients with DS or LGS, not sufficiently responded on the initial treatment resulted in a reduction in seizures, decreased average duration of seizures, and an improvement in Global Impression of Change. The results are in line with previous studies in a comparable population of patients with DS and LGS.

2.2.3. Safety

The number of participants who experienced TEAEs during the study is summarised in Table 5-2. A total of 659 participants (96.8%) had 1 or more TEAEs during the study: 306 (97.1%) in the DS and 353 (96.4%) in the LGS disease categories.

Table 5-2 Study Summary of Treatment Emergent Adverse Events

Adverse Event Type	Dravet Syndrome (N=315) n (%)	Lennox-Gastaut Syndrome (N=366) n (%)	Overall (N=681) n (%)
All TEAEs	306 (97.1%)	353 (96.4%)	659 (96.8%)
Treatment-related TEAEs	229 (72.7%)	234 (63.9%)	463 (68.0%)
Serious TEAEs	133 (42.2%)	157 (42.9%)	290 (42.6%)
Treatment related serious TEAEs	29 (9.2%)	24 (6.6%)	53 (7.8%)
TEAEs leading to withdrawal from study	28 (8.9%)	43 (11.7%)	71 (10.4%)
Treatment related TEAEs leading to withdrawal from study	23 (7.3%)	30 (8.2%)	53 (7.8%)

TEAE = treatment-emergent adverse event.

Overall, the AE profile was similar between the 2 disease categories although when compared with the LGS group, treatment-related TEAEs for the DS participants were slightly higher.

2.2.3.1. Adverse Events

2.2.3.1.1. Treatment Emergent Adverse Events (TEAEs)

A summary of all-causality TEAEs reported in ≥3% of participants in the All GWP42003-P group is presented in Table 5-3.

Table 5-3 Summary of Treatment-Emergent Adverse Events wiU1 Su bjects with > 3% in Any Group (Safety Ana lysis Set)

System Organ Clas s **Preferred Term**	Dravet Sy nd rom e **{N=315)** n (%)	**Lennox -Gastau t** Syndrome {N=366)n {%)	**Overall {N=681)** 11 (%)
All TEAEs	306 (97.1 %)	353 (96.4%)	659 (96.8%)
Blood and lymphaticsys tem disord ers	21 (6.7%)	41 (11.2%)	62 (9.1%)
Anaem ia	6 (1.9%)	13 (3.6%)	19 (2.8%)
Gastroint estina l **disorders**	192 (61 0%)	227 (62 .0%)	419 (61.5%)
Diarr hea	135 (42.9%)	140 (38 .3%)	275 (40.4%)
Vomi ti ng	63 (2.0.0%)	] 07 (29.2%)	170 (25.0%}
Coll5tipation	20 (6.3%)	43 (11.7%)	63 (9.3%)
Nausea	16 (5.1%)	32 (8.7%}	4 8 (7 . 0 %
Abdo minal pain upper	11 (3.5%)	7 (1.9%)	18 (2.6%)
Gene ra l d isorders and **adminis tration site** cond it ions	162 (514 %)	177 (48 .4%)	339 (49.8 %}
Pvrexia	124 (39.4%)	126 (34 .4%)	250 (36.7%)
Fatigue	39 (12.4%)	38 (10.4%)	77 (11.3%)
Gait dis turba nce	12 (3.8%)	15 (4.1%}	27 (4.0%)
Ast henia	10 (3.2%)	11 (3.0%}	21 (3.1%)
In fect io ns and **infestations**	229 (72.7%)	264 (72.1%)	493 (72.4%}
Upper respiratory tracti nfection	78 {24.8%)	] 04 (28 .4%)	182 (26.7%}
Nasopharyngitis	78 (24.8%)	58 (15.8%)	136 (20.0%)
Sinus itis	38 (12.1%)	49 (13.4%)	87 **(12.8%)**
Pneumo nia	35 {11.1%)	51 (13.9%)	86 (12. 6%)
Ear infection	35 {11.1%)	50 (13.7%)	85 (12 .5%)
Influenza	37 (11.7%)	45 (12.3%)	82 (12. 0%)
Urinary trac t in fection	19 {6.0%)	51 (13.9%)	70 (10.3%)
Pharyng itis s treptococcal	26 {8.3%)	27 (7.4%}	53 (7 8%)
Gas troen terit is vi ral	15 (4.8%)	30 (8.2%)	45 (6.6%)
Otitis media	21 (6.7%)	22 (6.0%}	43 (6.3 %)
Bronchitis	15 (4.8%)	23 (6.3%}	38 (5.6%)
Viral u pper respi ratorytract infectio n	11 (3.5%)	20 (5.5%}	31 (4.6%)
Viral in fection	12 (3.8%)	16 (4.4%)	28 (41 %)

Table 5-3	**Summary of Treatment-Emergent Adverse Events with Subjects with > 3% in Any Group (Safety Analysis Set)**		
System Organ Class Preferred Term	Dravet Syndrome (N=315) n (%)	Lennox-Gastaut Syndrome (N=366) n (%)	Overall (N=681) n (%)
Pharyngitis	15 (4.8%)	12 (3.3%)	27 (4.0%)
Gastroenteritis	16 (5.1%)	7 (1.9%)	23 (3.4%)
Conjunctivitis	5 (1.6%)	17 (4.6%)	22 (3.2%)
Respiratory tract infection	13 (4.1%)	8 (2.2%)	21 (3.1%)
Injury, poisoning and procedural complications	80 (25.4%)	146 (39.9%)	226 (33.2%)
Fall	22 (7.0%)	23 (6.3%)	45 (6.6%)
Laceration	8 (2.5%)	35 (9.6%)	43 (6.3%)
Contusion	15 (4.8%)	25 (6.8%)	40 (5.9%)
Skin abrasion	2 (0.6%)	12 (3.3%)	14 (2.1%)
Investigations	126 (40.0%)	157 (42.9%)	283 (41.6%)
Weight decreased	21 (6.7%)	61 (16.7%)	82 (12.0%)
Alanine aminotransferase increased	37 (11.7%)	30 (8.2%)	67 (9.8%)
Aspartate aminotransferase increased	38 (12.1%)	19 (5.2%)	57 (8.4%)
Gamma-glutamyltransferase increased	32 (10.2%)	20 (5.5%)	52 (7.6%)
Liver function test abnormal	13 **(4.1%)**	**14** (3.8%)	27 (4.0%)
Weight increased	5 (1.6%)	13 (3.6%)	18 (2.6%)
Metabolism and nutrition disorders	127 (40.3%)	139 (38.0%)	266 (39.1%)
Decreased appetite	99 (31.4%)	93 (25.4%)	192 (28.2%)
Dehydration	8 (2.5%)	16 (4.4%)	24 (3.5%)
Increased appetite	8 (2.5%)	12 (3.3%)	20 (2.9%)
Nervous system disorders	214 (67.9%)	251 (68.6%)	465 (68.3%)
Convulsion	79 (25.1%)	141 (38.5%)	220 (32.3%)
Somnolence	87 (27.6%)	107 (29.2%)	194 (28.5%)
Status epilepticus	47 (14.9%)	42 (11.5%)	89 (13.1%)
Lethargy	21 (6.7%)	34 (9.3%)	55 (8.1%)
Headache	18 (5.7%)	26 (7.1%)	44 (6.5%)
Sedation	16 (5.1%)	27 (7.4%)	43 (6.3%)
Drooling	11 (3.5%)	21 (5.7%)	32 (4.7%)
Balance disorder	9 (2.9%)	12 (3.3%)	21 (3.1%)
Tremor	14 (4.4%)	7 (1.9%)	21 (3.1%)
Psychiatric disorders	108 (34.3%)	148 (40.4%)	256 (37.6%)
Abnormal behaviour	34 (10.8%)	23 (6.3%)	57 (8.4%)
Insomnia	16 (5.1%)	40 (10.9%)	56 (8.2%)
Irritability	26 (8.3%)	29 (7.9%)	55 (8.1%)
Aggression	20 (6.3%)	30 (8.2%)	50 (7.3%)

Table 5-3	Summary of Treatment-Emergent Adverse Events with Subjects with > 3% in Any Group (Safety Analysis Set)		
System Organ Class Preferred Term	**Dravet Syndrome (N=315) n (%)**	**Lennox-Gastaut Syndrome (N=366) n (%)**	**Overall (N=681) n (%)**
Agitation	9 (2.9%)	19 (5.2%)	28 (4.1%)
Sleep disorder	12 (3.8%)	16 (4.4%)	28 (4.1%)
Renal and urinary disorders	17 (5.4%)	51 (13.9%)	68 (10.0%)
Urinary retention	0	17 (4.6%)	17 (2.5%)
Respiratory, thoracic and mediastinal disorders	98 (31.1%)	150 (41.0%)	248 (36.4%)
Cough	42 (13.3%)	63 (17.2%)	105 (15.4%)
Nasal congestion	13 (4.1%)	46 (12.6%)	59 (8.7%)
Rhinorrhoea	20 (6.3%)	19 (5.2%)	39 (5.7%)
Pneumonia aspiration	4 (1.3%)	22 (6.0%)	26 (3.8%)
Hypoxia	2 (0.6%)	21 (5.7%)	23 (3.4%)
Oropharyngeal pain	12 (3.8%)	11 (3.0%)	23 (3.4%)
Epistaxis	13 (4.1%)	9 (2.5%)	22 (3.2%)
Acute respiratory failure	3 (1.0%)	13 (3.6%)	16 (2.3%)
Upper respiratory tract congestion	2 (0.6%)	13 (3.6%)	15 (2.2%)
Skin and subcutaneous tissue disorders	51 (16.2%)	96 (26.2%)	147 (21.6%)
Rash	14 (4.4%)	16 (4.4%)	30 (4.4%)
Alopecia	10 (3.2%)	9 (2.5%)	19 (2.8%)
Erythema	1 (0.3%)	12 (3.3%)	13 (1.9%)

TEAE = Treatment-emergent adverse event.

2.2.3.1.2. Adverse Events by Severity

The number of participants with TEAEs is summarized in Table 5-4. In both DS and LGS groups, majority of participants reported TEAEs of moderate intensity.

Table 5-4	Treatment-Emergent Adverse Events by Maximal Severity			
System Organ Class	**Severity**	**Dravet Syndrome (N=315)**	**Lennox-Gastaut Syndrome (N=366)**	**Overall (N=681)**
Participants Reporting Any TEAEs	Mild	71 (22.5%)	73 (19.9%)	144 (21.1%)
	Moderate	157 (49.8%)	176 (48.1%)	333 (48.9%)
	Severe	78 (24.8%)	104 (28.4%)	182 (26.7%)

TEAE = Treatment-emergent adverse event.

2.2.3.1.3. Treatment-related Adverse Events

Overall, the incidence of treatment related AEs was slightly higher in the DS (229 [72.7%]) group compared to the LGS (234 [63.9%]) group. The most common treatment-related TEAEs by PT reported were diarrhea (149 [21.9%] participants), decreased appetite (106 [15.6%] participants), and somnolence (131 [19.2%] participants).

CHMP comments

The majority (96.8%) of all patients had at least one TEAEs during the study; there were no difference between disease groups (97.1% in the DS and 96.4% in the LGS disease categories). The most commonly reported TEAEs were pyrexia (36.7%) and GI-related TEAEs including diarrhea (40.4%) and decreased appetite (28.2%), vomiting (25.0%) but also neurological TEAEs including somnolence (28.5%) were commonly reported. Convulsions were reported in 32.3% and *status epilepticus* was reported in 13.1%. With regards to severity, approximately 25% of the patients in each disease group experienced severe TEAE(s) and almost 50% of the patients in each disease group experienced moderate TEAE(s).

Overall, the incidence of treatment related AEs was slightly higher in the DS (229 [72.7%]) group compared to the LGS (234 [63.9%]) group; this may (partly) be due to the difference in age-categories as described in the Baseline and demographic section above.

Conclusion: Overall, the reported TEAEs including the frequencies and severity observed in the present study are fully comparable with previous observations from the pivotal trials and as reported in the SmPC for Epidyolex.

2.2.3.2. Serious Adverse Events and Deaths

2.2.3.2.1. Serious adverse events

The number of participants who experienced serious TEAEs regardless of relationship to IMP are presented in Table 5-6. Only PTs experienced by ≥2% of participants in any group are presented. Treatment-related serious TEAEs were reported for 29 (9.2%) participants in the DS group and 24 (6.6%) participants in the LGS group.

Table 5-6 Summary of Serious TEAEs Experienced by ≥ 2% of Participants in Any Group (Safety Analysis Set)

System Organ Class Preferred Term	Dravet Syndrome (N=315) n (%)	Lennox-Gastaut Syndrome (N=366) n (%)	Overall (N=681) n (%)
Participants Reporting Any Serious TEAEs	133 (42.2%)	157 (42.9%)	290 (42.6%)
Gastrointestinal disorders	6 (1.9%)	33 (9.0%)	39 (5.7%)
Vomiting	0	13 (3.6%)	13 (1.9%)
General disorders and administration site conditions	24 (7.6%)	19 (5.2%)	43 (6.3)%
Pyrexia	17 (5.4%)	11 (3.0%)	28 (4.1%)
Infections and infestations	54 (17.1%)	59 (16.1%)	113 (16.6%)
Pneumonia	20 (6.3%)	26 (7.1%)	46 (6.8%)
Influenza	7 (2.2%)	3 (0.8%)	10 (1.5%)
Urinary tract infection	1 (0.3%)	9 (2.5%)	10 (1.5%)
Investigations	18 (5.7%)	28 (7.7%)	46 (6.8%)
Aspartate aminotransferase increased	10 (3.2%)	6 (1.6%)	16 (2.3%)
Alanine aminotransferase increased	7 (2.2%)	7 (1.9%)	14 (2.1%)
Nervous system disorders	82 (26.0%)	76 (20.8%)	158 (23.2%)
Status epilepticus	47 (14.9%)	42 (11.5%)	89 (13.1%)
Convulsion	34 (10.8%)	44 (12.0%)	78 (11.5%)
Respiratory, thoracic and mediastinal disorders	11 (3.5%)	34 (9.3%)	45 (6.6%)
Pneumonia aspiration	4 (1.3%)	16 (4.4%)	20 (2.9%)
Acute respiratory failure	1 (0.3%)	10 (2.7%)	11 (1.6%)
Respiratory failure	2 (0.6%)	8 (2.2%)	10 (1.5%)
Hypoxia	0	9 (2.5%)	9 (1.3%)

TEAE = treatment emergent adverse event

Overall, the most common serious TEAE experienced by the participants were: *Status epilepticus* (89 [13.1%]; 47 and 42 participants in the DS and LGS groups respectively), Convulsion (78 [11.5%]; 34 and 44 participants in the DS and LGS groups respectively), and Pneumonia (46 [6.8%]; 20 and 26

participants in the DS and LGS groups respectively). Five (1.6%) participants from the DS and 3 (0.8%) from the LGS group experienced events of *status epilepticus* related to the study intervention. Two (0.6%) participants from the DS and 3 (0.8%) from the LGS group experienced events of convulsion related to the study intervention. None of the incidences of SAEs of Pneumonia was related to the studyintervention.

Ten (3.2%) participants from the DS and 4 (1.1%) from the LGS group experienced events of AST increased, related to the study intervention. Seven (2.2%) participants from the DS and 6 (1.6%) from the LGS group experienced events of ALT increased, related to the study intervention. Also, 4 (1.3%) participants in the DS and 3 (0.8%) in the LGS group experienced events of gamma-glutamyl transferase increased, related to the study intervention.

2.2.3.2.2. Deaths

The number of participants who experienced fatal TEAEs are presented in Table 5-5.

Table 5-5 Summary of Fatal Treatment-Emergent Adverse Events

System Organ Class Preferred Term	Dravet Syndrome (N=315) n (%)	Lennox-Gastaut Syndrome (N=366) n (%)	Overall (N=681) n (%)
Participants Reporting Any Fatal TEAEs	6 (1.9%)	12 (3.3%)	18 (2.6%)
Cardiac disorders	0	2 (0.5%)	2 (0.3%)
Cardiac arrest	0	1 (0.3%)	1 (0.1%)
Cardio-respiratory arrest	0	1 (0.3%)	1 (0.1%)
Gastrointestinal disorders	0	2 (0.5%)	2 (0.3%)
Gastrointestinal necrosis	0	1 (0.3%)	1 (0.1%)
Intestinal ischaemia	0	1 (0.3%)	1 (0.1%)
Intestinal obstruction	0	1 (0.3%)	1 (0.1%)
General disorders and administration site conditions	5 (1.6%)	4 (1.1%)	9 (1.3%)
Sudden unexplained death in epilepsy	4 (1.3%)	4 (1.1%)	8 (1.2%)
Drowning	1 (0.3%)	0	1 (0.1%)
Infections and infestation	0	1 (0.3%)	1 (0.1%)
Peritonitis	0	1 (0.3%)	1 (0.1%)
Septic shock	0	1 (0.3%)	1 (0.1%)
Nervous system disorders	1 (0.3%)	2 (0.5%)	3 (0.4%)
Convulsion	1 (0.3%)	1 (0.3%)	2 (0.3%)
Hypoxic-ischaemic encephalopathy	0	1 (0.3%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	2 (0.5%)	2 (0.3%)
Acute respiratory failure	0	1 (0.3%)	1 (0.1%)
Pneumonia aspiration	0	1 (0.3%)	1 (0.1%)
Respiratory failure	0	1 (0.3%)	1 (0.1%)

TEAE = treatment emergent adverse event.

CHMP comments

A total of 42.6% of all patients experienced at least one Treatment-related serious TEAEs; 29 (9.2%) patients with DS and 24 (6.6%) patients with LGS. Among both disease groups, the most commonly reported serious TEAEs were *status epilepticus* (13.1% in total) and Convulsion (11.5% in total). Considered the multiple convulsions characterizing patients with DS and LGS, and the expectable efficacy of the anti-epileptic treatment (including but not limited to Epidyolex as this was given as adjunct to other anti-epileptic treatment), it is not unexpected that both convulsions and *status epilepticus* was reported in this long-term study where patients were followed for up to 6 years.

With regard to Increase in hepatic enzymes (ALAT and ASAT), please see section below.

A total of 18 (2.6%) patients died during the study period including 6 patients (1.9%) with DS and 12 (3.3%) patients with LGS. The only reason for death which was reported in more than 1 patient in each treatment group was 'Sudden Unexplained Death in Epilepsy', which was reported in 4 patients in each disease group. It is well-known that both DS and LGS has a notably mortality (reported to be up to 15% for DS and approximately 5% for LGS) and therefore the reported deaths during the study period including the number and reasons for death are not unexpected.

Conclusion: A total of 42.6% of all patients experienced at least one Treatment-related serious TEAEs with the most commonly reported serious TEAEs being *status epilepticus* (13.1% in total) and Convulsion (11.5% in total). This is not an unexpected finding in a long-term safety study where patients with DS and LGS were followed in up to 6 years. A total of 18 patients died with the only reason for death which was reported in more than 1 patient in each treatment group was 'Sudden Unexplained Death in Epilepsy'. Overall, the reported serious TEAEs including deaths are within the expected for the study.

2.2.3.3. Discontinuations and/or Dose Modifications Due to Adverse Events

The number of participants who experienced TEAEs that led to permanent discontinuation of IMP and subsequent withdrawal from the study is presented in Table 5-7.

Table 5-7 Summary of Treatment-Emergent Adverse Events by ≥ 1% Leading to Permanent Discontinuation of Study Medication

System Organ Class Preferred Term	Dravet Syndrome (N=315) n (%)	Lennox-Gastaut Syndrome (N=366) n (%)	Overall (N=681) n (%)
Participants Reporting Any TEAEs Leading to Permanent Discontinuation of Study Medication	28 (8.9%)	43 (11.7%)	71 (10.4%)
Gastrointestinal disorders	5 (1.6%)	13 (3.6%)	18 (2.6%)
Diarrhea	0	6 (1.6%)	6 (0.9%)
Vomiting	1 (0.3%)	5 (1.4%)	6 (0.9%)
Investigations	14 (4.4%)	14 (3.8%)	28 (4.1%)
Alanine aminotransferase increased	7 (2.2%)	4 (1.1%)	11 (1.6%)
Aspartate aminotransferase increased	8 (2.5%)	3 (0.8%)	11 (1.6%)
Hepatic enzyme increased	1 (0.3%)	4 (1.1%)	5 (0.7%)
Liver function test abnormal	3 (1.0%)	1 (0.3%)	4 (0.6%)
Nervous system disorders	12 (3.8%)	14 (3.8%)	26 (3.8%)
Convulsion	8 (2.5%)	7 (1.9%)	15 (2.2%)
Somnolence	1 (0.3%)	4 (1.1%)	5 (0.7%)

PT = preferred term; MedDRA; TEAE = treatment-emergent adverse event.
Dictionary Coding: MedDRA Version 19.1.

The most common TEAEs that led to discontinuation of IMP (i.e., PTs reported in >1% of participants in any treatment group) were convulsion (15 [2.2%]; 8 participants in the DS and 7 participants in the LGS group; out of which 9 (1.3%) were treatment related), ALT increased (11 [1.6%]; 7 participants inthe DS and 4 participants in the LGS group; all were treatment related), AST increased (11 [1.6%]; 8 participants in the DS and 3 participants in the LGS group; all were treatment related, diarrhea (6 [0.9%)]); 0 participants in the DS group and 6 participants in the LGS group; out of which 4 (0.6%)

were treatment related, vomiting (6 [0.9%)]) 1 participant in the DS group and 5 participants in the LGS group; out of which 4 (0.6%) were treatment related, hepatic enzyme increased (5 [0.7%]); 1 participant in the DS group and 4 participants in the LGS group; all were treatment related, and somnolence (5 [0.7%]); 1 participant in the DS group and 4 participants in the LGS group; all were treatment related).

CHMP comments

A total of 71 (10.4%) of all patients permanently discontinued treatment with Epidyolex due to TEAE(s). The most commonly reported TEAEs leading to study discontinuation was convulsions (15 [2.2%] patients) and increase in hepatic enzymes (ALAT and ASAT; 11 [1.6%] patients each). Another 4 (0.6%) patients discontinued due to 'Hepatic enzyme increased'. Cannabidiol is known to be able to cause a dose-related increase in hepatic enzymes (ALAT and ASAT) and this increased risk is known to be potentiated by concomitant anti-epileptic treatment with either valproic acid and/or clobazam. Thus, considered that at baseline, 60.8% of the patients were treated with clobazam and 53.7% were treated with valproic acid, it is expectable that increase in hepatic enzymes would be observed as a common (i.e. >10%) adverse reaction. It is reassuring, that only increase in hepatic enzymes were only reported as a serious TEAE in approximately 2%. Importantly, increase in hepatic enzymes is adequately and sufficiently addressed in the Epidyolex SmPC (both in section 4.4 and in section 4.8).

Conclusion: The percentage of patients permanently discontinuing treatment with Epidyolex was 10.4% which is within the expected when compared to other cannabidiol studies. The most common reasons were convulsions and increase in hepatic enzymes. Both are known events to cause treatment discontinuation. It is reassuring that only few patients experienced increase in hepatic enzymes as a serious TEAE.

2.2.3.4. Clinical Laboratory Evaluation

The summary of haematology values by timepoint and treatment group are presented in the listings of the study report. There were no clinically meaningful findings in the hematology in this study. The assessments and observations were comparable across both DS and LGS study groups.

At baseline and EoT, most participants had normal RBC values in both DS (84.1% [n=265/315], and the LGS groups (85.0%, n=311/366 participants. Some small decreases in haemoglobin were observed (across both DS and LGS groups, a mean decrease of 0.21 g/dL from baseline to end of treatment) although clinical implication is unclear. Similarly, at baseline and EoT, haematocrit values were normal for majority of the participants in both DS (86.3, N=272/315) and LGS (86.9%, n=318/366) groups. Similar results were observed for white blood cells and platelets across both DS and LGS groups at baseline and EoT. No other significant cell changes were observed including erythrocyte mean corpuscular volume and erythrocyte mean corpuscular haemoglobin.

When considering individual participant changes, in DS study, increases in ALT or AST >3 × ULN during treatment occurred in 75 participants (23.8%) (Table 5-3). While, in LGS study, elevations in ALT or AST >3 × ULN occurred in 49 participants (13%). Some of the transaminase elevations were reported as AEs and led to discontinuation from the study if they met protocol-defined withdrawal criteria. No participant in the study met laboratory criteria for Hy's Law.

There was a mean change from baseline in creatinine (Enzymatic, µmol/L) at EoT of 3.8 in the DS group and 4.0 in the LGS group.

CHMP comments

Overall only few and minor changes in haematology parameters (haemoglobin, haematocrit, white blood cell count) were reported. There were no reports of serious adverse events related to changes in haematology parameters. Similarly, for changes in creatinine; only few and minor changes were reported.

AS described above, changes in hepatic enzymes (ALAT and ASAT) is a known TEAE to Epidyolex and increase in either ALAT or ASAT was reported for 124 (18.2%) patients. It is reassuring that none of the patients met the laboratory criteria for Hy's Law. Increase in hepatic enzymes leading to permanent treatment discontinuation is described and discussed above.

Conclusion: The most commonly reported changes in laboratory values were increase in hepatic enzymes (ALAT and ASAT), which was reported in a total of 18.2% of the patients. Changes in haematology and creatinine were generally few and minor and does not lead to any concerns.

2.2.3.5. Vital signs, ECG and Physical Examination Findings

2.2.3.5.1. Vital Signs

The changes from baseline in vital sign parameters that met pre-defined criteria for clinical significance over time are presented in the study report.

For each vital sign parameter, including blood pressure, pulse rate, temperature, respiratory rate, mean changes from baseline to end of treatment were similar across both DS and LGS groups. The numbers of participants with a change from baseline in vital signs that met predefined criteria for clinical significance (as per the SAP) were similar across the DS and LGS groups for each parameter, with the following exception:

Potentially clinically significant changes from baseline in sitting systolic blood pressure of >20 mmHg were reported in fewer participants in the DS (19 [6.0%]) compared to LGS (30 [8.2%]) group. Similarly, fewer participants reported changes in sitting diastolic blood pressure of >10 mmHg in DS (41 [13.0%]) compared to LGS (70 [19.1%]).

2.2.3.5.2. ECG

ECG data are summarised by time point and disease groups. No clinically significant ECG parameters were reported. Overall, 8 (2.5%) participants had corrected QT interval with Bazette correction of >450 msec during the DS study compared with 22.0 (6.0%) LGS study.

2.2.3.5.3. Physical Examination Findings

Physical Examination Findings data are summarised by visits up to Week 184.

Body weight remained generally similar/stable during the study for both DS and LGS groups. The mean (SD) change from baseline in weight (kg) in DS group and LGS study at EoT group was 5.84 (8.43), and 4.21 (7.73), respectively. There were fewer number of participants in DS compared to LGS group who reported TEAEs related to decrease in weight i.e., 21 (6.7%) and 61 (16.7%), respectively (Table 5-3). Although 7.3% of participants had lost ≥7% of weight by the end of treatment visit, overall, more participants gained ≥7% of weight (46.0%).

2.2.3.5.4. Inpatient Hospitalisations due to Epilepsy

Six participants in the DS group (1.9%) and 3 participants in the LGS group (0.8%) reported an inpatient hospitalisation due to epilepsy during the baseline period (Day 15). Through study, a total of 33

participants (5.8%) reported 1 or more inpatient hospitalisations due to epilepsy, with similar numbers in each treatment group: 16 participants in the DS group (6.4%), and 17 participants in the LGS group (5.4%).

CHMP comments

A potentially clinically significant changes from baseline in sitting systolic blood pressure of >20 mmHg was reported in a total of 49 (7.2%) patients. Similarly, a total of 30 (4.4%) patients reported corrected QT interval with Bazette correction of >450 msec. Neither increase in blood pressure nor QTC prolongation are mentioned as known adverse reactions to Epidylex however, the few cases reported in the present study are not considered sufficient to justify amendments to the SmPC at this stage.

With regard to physical examination, decrease in weight was the most commonly reported finding. Decrease in weight is a known common (>10%) adverse reaction to treatment with epidyolex. It may be related to the commonly reported GI-related adverse reactions like decreased appetite, nausea and vomiting. As the majority of the study participants were children, it is not surprising that during the study (with up to 6 years of observation), more patients gained weight compared to the proportionwho lost weight.

Conclusion: During the study, increase in systolic/diastolic blood pressure was reported in few patients without a consistent pattern. Likewise, few patients were reported with a corrected QT interval with Bazette correction of >450 msec. As there were no consistent findings and the majority of findings were not repeated at subsequent physical examinations, these findings will not be pursued. The most commonly reported finding during physical examination was weight decreased. This is a known common adverse reaction to Epidyolex.

2.2.3.6. Other Observations Related to Safety

2.2.3.6.1. Children's Columbia-Suicide Severity Rating Scale

No TEAEs relating to suicidality were reported during the study although isolated positive C-SSRS questionnaire scores were received.

One (0.1%) case suicidal ideation and 1 (0.1%) case of suicidal behaviour was reported at Day 1 of the study. Three (0.4%) cases of suicidal ideation and 1 (0.1%) case of suicidal behaviour was reported post dose during the study. Although one case of completed suicide was recorded in the C-SSRS data at Week 104 (Patient X), no AE relating to suicidality was reported, furthermore, this patient had 3 subsequent C-SSRS questionnaire results that were all negative subsequent to Week 104. Thus, the C-SSRS result for completed suicide appears to be a data-entry error for this patient. Overall,in combination with the AE reporting, no signal for a risk of suicidality with CBD was identified.

2.2.3.6.2. Tanner Stages

Details regarding Tanner staging has been presented in the listings.

2.2.3.6.3. Menstrual Detail

The numbers of female participants with any changes in menstrual cycle (since previous visit) at baseline were small 6 (5.7%) and 4 (3.1%) females reported changes at the end of treatment. Two (1.9%) participants reported abnormalities related to menstrual cycle at baseline. No TEAEs relating to menstruation were reported during the study.

2.2.3.6.4. Cannabis Withdrawal Scale (CWS)

The CWS (participants aged 18 or over) or PCWS (participants aged 4–17 years) inclusive, CWS/PCWS data were summarised at baseline (Core Studies), the OLE end of taper period, 2 weeks after the OLE end of taper period and at OLE follow-up using appropriate summary statistics. Following end of treatment, a total of 16 participants either completed all questions of at least 1 subcategory of the CWS (5 in the DS group and 11 in the LGS group) or completed all questions of the PCWS (1 in the DS group and 1 in the LGS group). For all other participants with available data, any post-treatment increases from baseline in CWS or PCWS scores were small, with no notable differences across the DS and LGS groups.

2.2.3.6.5. Study Medication Use and Behaviour Survey

Of the 17 questions in the survey, 14 were marked unanimously as 'never', 'no desire', or 'not at all' including all those relating to routes of administration and diversion. For the remaining 3 questions, relating to drug dosage, dose impact, withdrawal syndrome, and desired use, the numbers of responses which were marked as anything other than 'never', 'no', or 'not at all' were small and were similar across the DS and LGS groups.

CHMP comments

Other observations related to safety included Children's Columbia-Suicide Severity Rating Scale, Tanner Stages, Menstrual Detail, Cannabis Withdrawal Scale (CWS) and Study Medication Use and Behaviour Survey. Overall, no significant findings were reported.

It is reassuring that No TEAEs relating to suicidality were reported during the study. It is agreed that the one report of a succeeded suicide in a patient X with no previous events related to suicidality and three subsequent C-SSRS questionnaires without indication of suicidial thoughts most likely is a data-entry error. Additional data cannot be retrieved and the issue will not be pursued. Importantly, sucidial behaviour and suicidial ideation is already included in the Epidyolex SmPC (section 4.4).

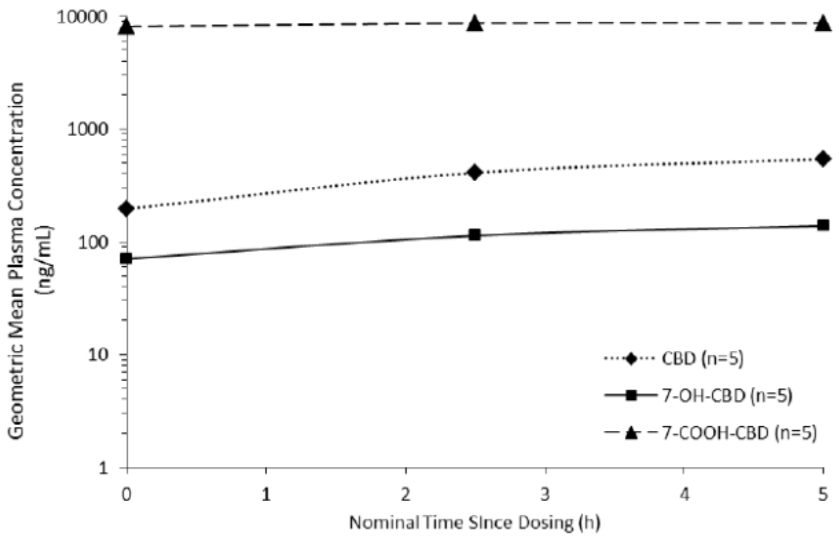
Conclusion: Other observations related to safety included Children's Columbia-Suicide Severity Rating Scale, Tanner Stages, Menstrual Detail, Cannabis Withdrawal Scale (CWS) and Study Medication Use and Behaviour Survey. Overall, no significant findings were reported.

2.2.4. Pharmacokinetics

PK data were collected from 5 participants with DS during this OLE trial; all originating from the GWEP1424 core trial. PK samples were taken no earlier than Visit 4 (Day 85; ±3 days) during the trial, to ensure all participants were on a stable dose of GWP42003-P. The actual doses received ranged from 19-25 mg/kg/day.

All participants had detectable plasma levels of CBD, 7-CBD and 7-COOH-CBD at all 3 nominal time points (see Figure 5-3 for geometric mean plasma concentrations by time; inter-subject variation was low to moderate for CBD and moderate to high for 7-OH-CBD and 7-COOH-CBD).

Figure 5-3 **Geometric Mean Plasma Concentrations of CBD and its Major Metabolites Over Time Following a Single Oral Dose of GWP42003-P at Steady State (Semi-logarithmic Plot)**



Analysis of CBD, 7-OH-CBD and 7-COOH-CBD exposures (AUC0–t) showed that 7-COOH-CBD was the most abundant analyte overall; AUC0–t for 7-COOH-CBD was 21.3-fold higher than parent CBD (Table 5-8).

Table 5-8 **Exposure and Metabolite-to-Parent Ratios**

Analyte	n	Exposure	Metabolite-to-Parent Ratios
		Geometric Mean AUC_{0-t} (h·ng/mL) (%CV)	Geometric Mean Metabolite AUC_{0-t}/CBD AUC_{0-t} (%CV)
CBD	5	1640 (23.3)	-
7-OH-CBD	5	450 (90.7)	0.275 (94.7)
7-COOH-CBD	5	34900 (78.3)	21.3 (83.8)

CHMP comments

Cannabidiol is hepatic metabolised via the CYP450- and UGT-enzymes. The known metabolites of cannabidiol are 7-COOH-CBD, 7-OH-CBD and (to a lesser extend) 6-OH-CBD. The concentration of the 7-OH-CBD metabolite in human plasma has been shown to be ~40% of the CBD-exposure (based on AUC).

Pharmacokinetic (PK) data were collected from 5 participants with DS during this OLE trial thus, the dataset is indeed very limited and no conclusion can be made. Overall, based on these data, the geometric mean AUC_{0-t} of cannabidiol was shown to be 1640 h*ng/mL and the concentration of 7-OH-CBD and 7-COOH-CBD was 450 and 34900 h*ng/mL, respectively. For 7-OH-CBD, this ~27.4% of the CBD-exposure (based on AUC), which is somewhat lower than the previously reported. However, due to the low sample size for PK measurements, no conclusions can be made and the issue will not be pursued.

Conclusion: Pharmacokinetic (PK) data were collected from 5 participants with DS during this OLE trial thus, the dataset is indeed very limited and no conclusion can be made. There were no unexpected findings.

3. Scientific discussion

Please see section Assessor's comments in section 2 above for at critical review of the data provided.

4. Overall conclusion

The present study was designed as a multi-center, open-label extension (OLE) study for patients with DS or LGS who had completed the double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies). The primary objective of the study was to evaluate the long-term safety and tolerability of Epidyolex, as adjunctive treatment, in children and adults with inadequately controlled DS or LGS. Secondary objectives were to measure the efficacy of the study measured as reduction in seizures and measurement of Quality of life. The overall study design and methodology is considered acceptable. The most commonly concomitantly used AED was clobazam (60%). Of note, the study protocol has been approved by the CHMP.

With regard to the efficacy of Epidyolex, the present study showed that addition of Epidyolex to baseline anti-epileptic treatment in patients with DS or LGS, not sufficiently responded on the initial treatment, resulted in a reduction in seizures, decreased average duration of seizures, and an improvement in Global Impression of Change. The results are in line with previous studies in a comparable population of patients with DS and LGS.

With regard to the safety profile of Epidyolex, the present study confirmed previous safety findings. The far majority of the patients experienced at least one TEAE with the most commonly reported TEAEs being pyrexia and GI-related AEs including diarrhoea, vomiting and decreased appetite. Increase in hepatic enzymes were also commonly reported and was one of the most commonly reported TEAEs leading to permanent treatment discontinuation. The most commonly reported serious TEAEs were convulsions and status epilepticus. Overall, the safety profile of Epidyolex reported in this OLE safety study with a safety observation up to 6 years was fully in accordance with the known safety profile for Epidyolex (cannabidiol) and no new safety findings have been identified.

Conclusively, the results from the present long-term safety study are fully in line with findings in previous studies with Epidyolex, including the pivotal studies. Further, the present study does not lead to any need for update of the SmPC.

The Benefit-risk assessment for Epidyolex (cannabidiol) in the following indication: *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* remains positive.

☒ **Fulfilled:**

No further action required.