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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/P46/002

Note

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

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Submission of information about paediatric studies completed after 26 January 2007 in accordance with Article 46 of Regulation 1901/2006, as amended. GW Pharma (International) B.V. is submitting the following paediatric study which completed on 13th June 2019.

Trial: GWEP15100 - A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol (CBD; GWP42003-P) in infants with infantile spasms following an initial open-label pilot study.

This study is part of a PIP (EMEA-001964-PIP01-16), for which the initial Decision (P/0136/2017) is included in this submission. Also enclosed is a recent PIP modification Opinion (EMEA-001964-PIP01-16-M01, dated 11th December 2019), for which the updated Decision was pending during the procedure.

1.1. Steps taken for the assessment

Submission date:	15 January 2020
Start of procedure:	27 January 2020
Rapporteur's preliminary assessment report	4 March 2020
CHMP comments	N/A
Updated Rapporteur's assessment report	N/A
Request for Supplementary Information (RSI)	26 March 2020
Responses to RSI	28 April 2020
Rapporteur's preliminary assessment report	5 May 2020
CHMP comments	6 May 2020
Updated Rapporteur's assessment report	N/A
CHMP adoption of conclusions	28 May 2020

1.2. Introduction

Epidyolex was approved, via the EU centralised procedure by the Committee for Medicinal Products for Human Use (CHMP), with European Commission (EC) 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 safety and efficacy of Epidyolex (cannabidiol oral solution [CBD-OS]) in infantile spasm (IS) in patients aged 1 month to 24 months. The planned study comprised an open-label pilot phase, with 2 sequential cohorts, followed by a randomised double-blind pivotal phase. All patients could receive GWP42003-P during a subsequent OLE phase, lasting for a maximum of 1 year. The study is part of a paediatric investigational plan (PIP) as approved by the European Medicines Agency's Paediatric Committee (EMA's PDCO).

In the pilot phase, there were no treatment responders after 2 weeks of treatment, as confirmed on video-electroencephalography (EEG) (no patients were both free of clinical spasms and had resolution of hypsarrhythmia). The study met prespecified no-go criteria for the pivotal phase of the study.

As a result, the paediatric study provided individual efficacy and safety data for the 9 enrolled patients with IS. Available safety data are consistent with the known safety profile of CBD in the authorised treatments of Lennox-Gastaut syndrome and Dravet syndrome. No unexpected or clinically significant safety findings were noted.

Therefore, no regulatory consequences were identified by the Marketing Authorisation Holder (MAH).

CHMP comments

The MAH has correctly presented the approved indication for Epidyolex (cannabidiol), namely:

'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 purpose of the present study was to evaluate the efficacy and safety of cannabidiol in the treatment of infantile spasm in patients aged 1 month to 24 months. The study was designed with an initial pilot phase intending to include a total of 10 infants. As the pre-defined No-go criteria were fulfilled after 9 enrolled patients, the study was terminated and therefore the pivotal OLE phase was not carried through.

The study was part of a paediatric investigational plan (PIP) as approved by the European Medicines Agency (EMA)'s Paediatric Committee (PDCO).

Of note, the MAH has not submitted a full clinical study report (CSR) but merely a synoptic CSR and a clinical overview. These two documents are essentially similar. Additional data are presented as summary tables for baseline characteristics, demographics, efficacy and safety data and as patient narratives for Serious Treatment-emergent Adverse Events and Other Significant Events. This is acceptable.

2. Summary of data submitted

2.1. Methodology

2.1.1. Study design

This was a multi-site study evaluating the efficacy and safety of CBD (GWP42003-P) in patients with infantile spasms (IS) who failed to become spasm free following treatment with 1 or more approved IS therapies.

During study planning, discussions were held with multiple paediatric neurology epileptologists from the US and European Union. All were in agreement that in patients who had failed high-dose steroids and/or vigabatrin, the reasonable treatment goal would be the elimination of both hypsarrhythmia and spasms in these patients. Elimination of neither or only 1 feature of IS, i.e., the hypsarrhythmia or the spasms, was considered unlikely to halt the known progressive encephalopathy and development of LGS that occurs over time in most of these patients.

An independent data safety monitoring committee (DSMC) considered the safety of the patients throughout the study and confirmed doses and dose regimens that would have been investigated in the pivotal phase.

To progress from the pilot phase to the pivotal phase, an acceptable safety profile in the pilot phase was required. The Go/No Go criteria developed by the sponsor were as follows:

- If the DSMC determined that data from the pilot phase showed no clinically significant serious adverse events (SAE) (e.g. status epilepticus, hepatic failure, death) occurred, then the study continued (Go criterion), and
- If there were 2 or more responders, the study continued to the pivotal phase (Go criterion).
- If the DSMC determined that data from the pilot phase showed clinically significant SAEs (e.g. status epilepticus, hepatic failure, death) that would likely occur regardless of changes in titration schedule or dose, then the study was halted (No Go criterion), or
- If there were fewer than 2 responders in cohort 1, the study was halted (No Go criterion).
- In order for the study to progress to the pivotal phase, the safety and efficacy Go criteria had to be satisfied.

The planned study comprised an open-label pilot safety phase, with 2 sequential cohorts, followed by a placebo-controlled pivotal phase. The first cohort of the pilot phase enrolled patients aged between 6 and 24 months. The second cohort of the pilot phase enrolled patients aged between 1 and 24 months. All patients received GWP42003-P for 2 weeks. The trial met No-go criteria since none of the 9 patients enrolled during the pilot phase had resolution of spasms and hypsarrhythmia following 2 weeks of open-label treatment. The trial was therefore terminated prior to full enrolment into the pilot phase and the pivotal phase was not initiated.

All patients who completed the pilot phase of the study had the opportunity to receive GWP42003-P during a subsequent OLE phase, lasting for a maximum of 1 year. Following end of treatment, withdrawal, or discontinuation of the study medication, all patients who ended treatment tapered down their study medication over 10 days followed by a safety follow-up.

CHMP comments

The study was designed with an initial pilot phase including a total of 10 infants and with pre-defined Go- and No-go criteria. The approach of having predefined Go- and No-go criteria determining the future of the trial is fully endorsed as this ensured that the study was not unnecessarily prolonged if no clinically relevant effect of the treatment was observed/expected and/or if there were unacceptable safety issues.

2.1.2. Number of Patients (Planned and Analysed)

In total, 10 patients were planned to be enrolled in the pilot phase (5 per cohort). Nine patients were actually enrolled in the pilot phase, 5 in the first cohort and 4 in the second cohort, as No Go criteria were met after the ninth patient completed the 2-week treatment period.

All 9 patients completed the pilot phase and entered the OLE phase.

2.1.3. Diagnosis and Main Criteria for Inclusion and Exclusion

Patients were male or female, who had documented hypsarrhythmia and IS on prolonged video-electroencephalography (EEG) monitoring, aged 6 to 24 months (inclusive) in the first cohort or aged 1 to 24 months (inclusive) in the second cohort, had failed to respond adequately to treatment with 1 or more approved IS therapies, and had been stable for all non-pharmacological interventions for epilepsy for 2 weeks prior to screening.

Patients were not eligible if they had any known or suspected hypersensitivity to cannabinoids or any of the excipients of the investigational medicinal product (IMP), such as sesame oil, had significantly impaired hepatic function at the screening visit, had taken clobazam or any oral mTOR inhibitor within

the 2 weeks prior to the screening visit, and if they had a QTcB interval of >460 msec on 12-lead electrocardiogram (ECG).

For a complete list of inclusion and exclusion criteria, refer to the study protocol (Section 6).

CHMP comments

The study included infants with documented hypsarrhythmia and infantile spasms on prolonged video-electroencephalography (EEG). The initial cohort of the pilot phase included the oldest age-group (6-24 months) and only in the second cohort, children under the age of 6 months were included. Currently, Epidyolex is indicated in children from 2 years however, due to the early debut of the disease (often within the first year from birth) and the progressive nature of the disease, it is considered acceptable to include patients <2 years of age.

By including only patients who had failed to respond on initial therapies approved for infantile spams, the MAH probably aimed for a second-line treatment. Of note, in the interpretation of the results, it should also be considered that only the most severe/treatment-resistant patients were included.

Overall, in- and exclusion criteria are considered appropriate.

2.1.4. Investigational Medicinal Product, Dose, and Mode of Administration

The IMP (GWP42003-P) was 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) and strawberry flavouring.

Mode of administration: Oral. Dosing via a gastrostomy/nasogastric tube (as required) was considered following approval by the GW medical monitor.

Dose (pilot phase): All patients were titrated up to a target dose of 40 mg/kg/day over 4 days (starting at 10 mg/kg/day and increasing by 10 mg/kg/day for the subsequent 3 days) and continued at this dose, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the 2-week treatment phase.

Dose (OLE phase): Patients remained on the same dose reached in the pilot phase, or the highest tolerated dose up to 40 mg/kg/day, for the remainder of the OLE phase.

Dosage: GWP42003-P was taken twice daily (morning and evening), maintaining consistency regarding feeds/meals and other concomitant medications, and could be taken with other concomitant medications as directed by the investigator. If the IMP was poorly tolerated, dosing could be changed to 3 times daily (while keeping the equivalent total daily dose), following approval by the GW medical monitor. The recommended dosing intervals were:

- 12-hourly (8-hourly minimum) for twice daily dosing.
- 6-hourly (minimum) for 3 times daily dosing.

CHMP comments

During the pilot study, infants were titrated up to a target dose of 40 mg/kg/day over 4 days (starting at 10 mg/kg/day and increasing by 10 mg/kg/day for the subsequent 3 days).

For the approved indications (*'as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS)'*), the recommended dose is initially 5 mg/kg per day increased with 5 mg/kg after one week to a maximum recommended dose of 20 mg/kg/day. Thus, despite that the included infants are younger than the licensed indication, the dose is somewhat higher. This may compromise the safety but should ensure

efficacy. Considered that the study included severely ill treatment-refractory patients and that the dose was titrated and the patients were under close supervision, the dose used in the present study is acceptable.

The daily dose was divided in 2-3 dosing intervals which considered the PK value for time to maximum plasma concentration at steady state (being 2.5-5 hours) appears relevant. Further, it is endorsed that the study medication should be given consistently with feeds/meals as co-administration of cannabidiol with high-fat/high-calorie meals increases the absorption rate substantially (approximately a 5-fold increase in Cmax and a 4-fold increase in AUC).

2.1.5. Duration of Treatment and Study period

Study duration

Patients received GWP42003-P for 2 weeks in the pilot phase and up to 1 year in the OLE phase.

Study Period

The date of first informed consent was 24Apr2017.

The initial pilot phase ended on 20May2018, and the open-label extension (OLE) phase continued until 13Jun2019.

The date of last primary endpoint data collection from the last patient was 08May2018.

The date of last observation from the last patient was 13Jun2019.

The date of database lock was 12Aug2019.

CHMP comments

Study dates are presented. As all patients who completed the pilot phase of the study could be enrolled in the subsequent OLE phase. Therefore, the final date for 'last patient last visit' was later than the date for 'last patient last visit' in the pilot phase.

2.1.6. Objectives, Endpoints, Statistical Methods, and Results

Listed below are the objectives, endpoints, statistical analysis and results in the pilot and pivotal phases of the study that are described in this report.

Objective	Endpoint	Statistical Analysis	Results
PILOT PHASE			
Primary			
To determine the maximum safe, tolerable dose and dosing regimen of GWP42003-P in infants with IS, to be utilized in the pivotal phase and OLE.	To assess the safety as determined by AEs, clinical laboratory tests, 12-lead ECG, vital signs and physical examinations during the treatment period.	All safety data were summarized using descriptive statistical methods.	No safety issues of concern were identified by the Data Safety Monitoring Board during the study. The safety Go Criterion was met.
To assess the number and proportion of patients, considered treatment responders, who are free of spasms and having resolution of hypsarrhythmia at the end of the 2-week treatment period.	The number and proportion of patients who were free of spasms and had resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG.	The number and proportion of patients, who were free of spasms and had resolution of hypsarrhythmia at the end of the 2-week treatment period, were summarized.	No patients had resolution of spasms and hypsarrhythmia after 2 weeks of treatment. No Treatment Responders were noted at the 2-week treatment assessment. The efficacy No Go Criterion was met.

Objective	Endpoint	Statistical Analysis	Results
PIVOTAL PHASE			
Primary			
To assess the number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, at the end of the 2-week blinded treatment period versus placebo.	The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia at the end of the 2-week treatment period, as determined by video-EEG.	The pivotal phase was not initiated, as No Go Criteria were met in the pilot phase.	
To assess the safety and tolerability of GWP42003-P.	Safety and tolerability as determined by AEs, clinical laboratory tests, ECG, physical examinations and vital signs.	Although the safety Go Criteria were met, the pivotal phase was not initiated, as efficacy No Go Criteria were met in the pilot phase.	
OPEN-LABEL PHASE			
Primary			
To assess the long-term safety of GWP42003-P in infants with IS.	To assess the long-term safety as determined by AEs, clinical laboratory tests, ECG, vital signs and physical examinations during the treatment period.	All safety data were summarized using descriptive statistical methods.	No new safety issues were identified.
Secondary			
To assess the number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, after 3, 6, 9 and 12 months of treatment.	The number and proportion of patients who are free of spasms and have resolution of hypsarrhythmia, as determined by video-EEG after 3, 6, 9 and 12 months of treatment.	All secondary endpoints were analyzed descriptively and summarized.	Three patients had resolution of spasms and/or hypsarrhythmia at some visits, and 3 patients responded at their last study visit, in 2 patients after the addition of clobazam. However, each of these patients was noted to have other seizure types, and they were each considered to have evolved into an expected type of epilepsy.
To assess changes in spasms and seizure subtypes by caregiver observation during the treatment period.	Proportion of spasms and seizure subtypes by caregiver observation The summary of CGIC score and summary of PGIC score for each study visit.	All secondary endpoints were analyzed descriptively and summarized.	The responses on both the CGIC and PGIC scores were largely favorable at each study visit time point.

AE = adverse event; CGIC = Caregiver Global Impression of Change; ECG = 12-lead electrocardiogram; EEG = electroencephalography; IS = infantile spasms; OLE = open-label extension; PGIC = Physician Global Impression of Change.

CHMP comments

The MAH has clearly presented the primary and secondary endpoint of each part of the study (pilot phase and pivotal phase). All the chosen endpoints are considered relevant or the corresponding objectives.

The pilot phase had two primary objectives addressing the efficacy and safety of the product. This is endorsed and also in accordance with the predefined Go- and No-go criteria.

The statistical methods are considered acceptable.

2.2. RESULTS

2.2.1. Summary of Patient Disposition

In total, 10 patients were screened, and 9 patients were enrolled in the pilot phase. All 9 patients completed the 2-week treatment period and entered the OLE phase (Table 1.1).

Table 1.1 Summary of Patient Disposition - All Screened Subjects

Disposition	GWEP42003-P (N=10)
Screen Failure	1
Primary Reason for Screen Failure [1]	
Inclusion/ Exclusion Criteria	1 (10.0)
Patient and/or Parent(s)/Legal Representative Withdrew Consent	0 (0.0)
Investigator Decision	0 (0.0)
Other	0 (0.0)
Enrolled in Pilot Phase	9
Received Treatment	9 (90.0)
Completed Pilot Phase	9 (90.0)
Discontinued Pilot Phase	0 (0.0)
Patient Continued to Open Label Extension	9 (90.0)
Completed	2 (20.0)
Withdrew	7 (70.0)
Primary Reason for Withdrawal	
Adverse Event	0 (0.0)
Sponsor Discontinued Study	0 (0.0)
Patient and/or Parent(s)/Legal Representative Withdrew Consent	3 (30.0)
Protocol Deviation Considered to Potentially Compromise Safety	0 (0.0)
Lost to Follow-Up	0 (0.0)
Patient Met Withdrawal Criteria	0 (0.0)
Patient Withdrawn from Participation by the Investigator	0 (0.0)
Patient has become spasm-free	0 (0.0)
Patient is not perceived to be receiving any benefit from GWP42003-P	3 (30.0)
Other	1 (10.0)

All percentages based on number of subjects screened.

[redacted]

In the OLE phase, 2 patients completed the treatment period and 7 patients withdrew. Four completed 6 months of treatment and 3 completed 12 months of treatment.

Of the 7 patients who withdrew during the OLE phase, 3 withdrew due to lack of perceived benefit, 3 withdrew due to withdrawal of parental consent, and 1 withdrew to begin treatment with commercially available Epidiolex® (Table 1.1).

2.2.2. Exposure

All 9 patients were exposed to GWP42003-P for a median of 15 days during the pilot phase (range: 15 to 17 days) (Table 7.1) and for a median of 9.7 weeks during the OLE phase (range: 2 to 53 weeks) (Table 7.2). All 9 patients reached the target dose (40 mg/kg/day) per the protocol.

Table 7.1 Summary of Exposure and Compliance to Study Treatment - Pilot Phase - Safety

	GWP42003-P (N=9)
Duration of Exposure (days)	
n (missing)	9 (0)
Mean (SD)	15.7 (0.9)
Median	15.0
Min, Max	15, 17
Compliance (%)	
n (missing)	9 (0)
Mean (SD)	100.0 (0.0)
Median	100.0
Min, Max	100, 100
Compliance (%) category	
< 80	0 (0.0)
80 - 120	9 (100.0)
>120	0 (0.0)
[redacted]	

Table 7.2 Summary of Exposure and Compliance to Study Treatment - OLE Phase - Safety

	GWP42003-P (N=9)
Duration of Exposure (weeks)	
n (missing)	9 (0)
Mean (SD)	22.7 (23.0)
Median	9.7
Min, Max	2, 53
Compliance (%)	
n (missing)	9 (0)
Mean (SD)	100.0 (0.0)
Median	100.0
Min, Max	100, 100
Compliance (%) category	
< 80	0 (0.0)
80 - 120	9 (100.0)
>120	0 (0.0)
[redacted]	

CHMP comments

The MAH has sufficiently presented the patient disposition. A total of 9 patients were included in the study as one of the No-go criteria was fulfilled after the 9 patients had completed the 2 weeks' pilot phase. All 9 patients continued in the pivotal OLE study but due to termination of the study (as explained above), only 2 patients completed the entire OLE study period. Three (3) additional patients completed 12 months treatment.

Reasons for withdrawal from the study included withdrawal of consent (3 patients), perceiving that the patient would not benefit from the treatment (3 patients) and one patient withdrew for the reason 'Other'. No patients were withdrawn due to adverse events (AEs).

In accordance with patient disposition and the number of patients completing the pilot phase and the OLE phase of the study, mean and median duration of study treatment in the pilot phase was 15 days (range 15-17 days). Likewise, in accordance with the study protocol, all 9 patients were included in the OLE phase for at least 2 weeks. Mean and median duration of exposure in the OLE phase was 22.7 and 9.7 weeks, respectively. This indicates that the patients were enrolled over a long period which is confirmed by the dates for duration of

treatment and study period (see section 2.1.5. 'Duration of Treatment and Study period' above).

In both of the study phases (pilot phase and OLE phase), all 9 patients had a compliance of 80-120%. Thus, compliance is not considered to have affected neither efficacy nor safety in any significant degree.

2.2.3. Demography and Baseline Characteristics

The mean (standard deviation [SD]) age of the 9 patients at informed consent was 12.2 (5.56) months (range: 6 to 23 months). There were 6 female and 3 male patients; most (8 of 9) were White. The mean (SD) birth weight was 2.9 (0.86) kg (range: 1 to 4 kg) (Table 2.1).

Table 2.1 Summary of Demographic Data - Safety

	GWP42003-P (N=9)
Gestational Age (weeks)	
n (missing)	9 (0)
Mean (SD)	38.3 (3.97)
Median	40.0
Min , Max	28 , 41
Birth weight (kg)	
n (missing)	9 (0)
Mean (SD)	2.9 (0.86)
Median	3.1
Min , Max	1 , 4
Age at Informed Consent (months)	
n (missing)	9 (0)
Mean (SD)	12.2 (5.56)
Median	11.0
Min , Max	6 , 23
Sex	
Male	3 (33.3)
Female	6 (66.7)
Race	
American Indian or Alaskan Native	0
Asian	0
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
White	8 (88.9)
Other	1 (11.1)

[redacted]

CHMP comments

The majority of the included patients were born at time (median gestational age 40 weeks) but one patient was born prematurely at Week 28. Mean and median birth weight was 2.9 and 3.1 kg, respectively. There were 6 females and 3 males thus a small overrepresentation of girls which is not considered to affect the results. The majority (8) of the patients were White. Mean and median age at time of informed consent was 12.2 and 11.0 months, respectively. Overall, the included patients appear to be representative for a European population of infants with infantile spasms.

A total of 8 patients had previously been treated with ACTH, 5 patients had been treated with benzodiazepines derivates, 4 with glucocorticoids and 2 patients with fatty acid derivates and/or barbiturates and derivates. One patient had been treated with carboxamide derivates (data submitted in tabulated form but not presented in the present AR). Thus, all included patients had been treated with at least one initial therapy approved for infantile spams. By including only patients who had failed to respond on initial therapies approved for infantile spams, it may be considered that only the most severe/treatment-resistant patients were included.

2.2.4. Efficacy Results (Safety population)

2.2.4.1. Pilot Phase

Efficacy Endpoint: There were no treatment responders after 2 weeks of treatment, as observed on video-EEG (no patients were both free of clinical spasms and had a resolution of hypsarrhythmia).

CHMP comment

As stated by the MAH, none of the 9 patients could be considered treatment responders as defined in the pilot phase of the study. None of the 9 patients were free of clinical spasms and all patients had hypsarrhythmia on the EEG. Thus, the study met the No-go criteria and was terminated.

2.2.4.2. OLE Phase

Secondary Efficacy Endpoints:

The proportion of treatment responders at the OLE phase as determined by video-EEG at Days 29, 43, 127, 211, 295, and 379 or End of Treatment is shown in Table 1. Some patients responded at some visits. Three patients were noted to be free of spasms and hypsarrhythmia between Day 29 and Day 379. In 2 of the 3 patients, clobazam had been added prior to the resolution of spasms and hypsarrhythmia. However, in each of these 3 patients, the EEG was not normal, and other seizure types were reported either during the video-EEG or by the caregiver. It is most likely that the IS with hypsarrhythmia was evolving into another type of epilepsy (e.g. LGS) in these patients.

Table 1 Proportion of Treatment Responders (OLE Phase, Safety Analysis Set)

Study Time point/ Number of Patients, n (%)	OLE Phase	
	Responders (N=9)	Non-responders (N=9)
Day 29	1 (11.1%)	7 (77.8%)
Day 43	0	6 (66.7%)
Day 127	0	4 (44.4%)
Day 211	0	3 (33.3%)
Day 295	1 (11.1%)	1 (11.1%)
Day 379 or End of Treatment	3 (33.3%)	4 (44.4%)

EEG = electroencephalography; OLE = Open-label extension.
Note: Treatment responders are patients who are free of spasms and have resolution of hypsarrhythmia at a particular visit, as determined by video-EEG.

[redacted]

Table 2 presents the presence of spasms, hypsarrhythmia, and other seizure types for each patient by visit.

Table 2	Presence of Spasms and Hypsarrhythmia by Patient by Visit			
Patient	Visit	Spasms	Hypsarrhythmia	Other seizure types identified on video-EEG/ Notes
[redacted]	Day 15	Yes	Yes	
	Day 29	Yes	Yes	
	Day 43	Yes	Yes	
[redacted]	Day 15	Yes	Yes	
	Day 29	Yes	Yes	
	Day 43	Yes	Yes	
	Day 127	Yes	Yes	
	Day 211	Yes	Yes	
[redacted]	Day 15	Yes	Yes	
	Day 379*	Yes	Yes	
[redacted]	Day 15	Yes	Yes	
	Day 29	Yes	Yes	
	Day 43	No	No	Myoclonic seizures
[redacted]	Day 15	Yes	Yes	
	Day 29	Yes	Yes	Clobazam added on Day 33
	Day 43	No	Yes	
	Day 127	No	Yes	
	Day 211	No	Yes	Myotonic-tonic/ Slow spike and wave on vEEG
	Day 379*	No	No	
[redacted]	Day 15	Yes	Yes	Myoclonic-tonic
	Day 29	No	No	Myoclonic-tonic and myoclonic, considered transitioning from IS to LGS
	Day 43	No	Yes	Myoclonic noted
	Day 127	Yes	No	
	Day 211	Yes	Yes	Myoclonic-tonic/ Clobazam added on Day 210
	Day 295	No	No	
	Day 379*	No	No	

Table 2	Presence of Spasms and Hypsarrhythmia by Patient by Visit			
[redacted]	Day 15	Yes	Yes	
	Day 29	Yes	Yes	Clobazam added on Day 32
	Day 43	Yes	Yes	
	Day 379*	Yes	Yes	
[redacted]	Day 15	Yes	Yes	Clobazam added on Day 22
	Day 29	Yes	Yes	
	Day 379*	Yes	Yes	
[redacted]	Day 15	Yes	Yes	
	Day 29	Yes	Yes	
	Day 43	Yes	Yes	Myoclonic-tonic/ Clobazam added on Day 43
	Day 127	Yes	Yes	
	Day 211	Yes	Yes	Myoclonic-tonic
	Day 295	Yes	Yes	Myoclonic-tonic

EEG = electroencephalography.
*Day 379 or End of Treatment
[redacted]

The proportion of spasms and seizure subtypes by caregiver observation and by study visit are detailed in the CSR. Caregivers recorded patient's spasms and seizures by category in a daily diary. The seizure subtype, Focal, occurred once in a patient at Day 19, Day 29, and Day 379. The seizure subtype, Tonic-Clonic, occurred once in a patient at Day 127, Day 211, Day 295, and Day 379. The seizure subtype, Absence, occurred once in a patient at Day 127, Day 211, Day 295, and Day 379. The seizure subtype, Myoclonic, occurred once in a patient on Day 127, the seizure subtype, Atonic, occurred once in a patient at Day 295, and the seizure subtype, Clonic, occurred once in a patient at Day 379.

The summary of the Caregiver Global Impression of Change (CGIC) score and summary of the Physician Global Impression of Change (PGIC) score for each study visit are detailed in the CSR. The CGIC is a single question assessment completed by the caregiver, and the PGIC is a single question assessment completed by the investigator. The question assesses the status of the patient's condition since start of treatment rated on a 7-point scale from 1-"very much improved" to 7-"very much worse".

The responses on both the CGIC and PGIC scores were largely favorable at each study visit time point.

- The CGIC scores were either 'very much improved', 'much improved', 'slightly improved', or 'no change' for all responding patients at Days 29, 43, 127, 211, and 295. At End of Treatment (Day 379), 2 (22.2%) patients reported 'very much improved', 1 (11.1%) patient reported 'much improved', 3 (33.3%) patients reported 'slightly improved', whereas 1 (11.1%) patient reported 'slightly worse', and 1 (11.1%) patient reported 'much worse'.
- The PGIC scores were either 'very much improved', 'much improved', 'slightly improved', or 'no change' for all responding patients at Days 29, 43, 71, 127, and 211. At End of Treatment (Day 379), 1 (11.1%) patient reported 'much improved', 3 (33.3%) patients reported 'slightly improved', 2 (22.2%) patients reported 'no change', whereas 1 (11.1%) patient reported 'slightly worse', and 1 (11.1%) patient reported 'much worse'.

The summary of Vineland Adaptive Behaviour Scales Change from baseline by study visit is detailed in the CSR. The Vineland-II scores were assessed by the patient's caregiver and included questions about communication, daily living, skills, physical activity, problem behaviours, social skills and relationships. Scoring generally ranged from "usually" to "never". Higher scores represent greater levels of functioning and lower scores represent lower levels of functioning. The results showed that the overall mean (SD) change from baseline to Day 211 was 6.3 (3.5) and from baseline to End of Treatment (Day 379) was -5.4 (23.4).

The changes from baseline in height, body weight, and head circumference is detailed in the CSR. The average change from baseline to End of Treatment (Day 379) in height was an increase of 5.31 (±4.04) cm, in weight an increase of 1.19 (±0.86) kg, and in head circumference an increase of 1.14 (±1.7) cm.

CHMP comments

In the OLE phase, three patients had temporary resolution of the spasms and hypsarrhythmia in a period of approximately 1 year, though the EEGs were not normal for any of these patients. Furthermore, 2 of these patients had initiated concomitant treatment with clobazam. The MAH states that most likely, the patients' disease was transforming into another type of epilepsy. It is agreed that this is most likely as this is characteristic for the disease of infantile spasms.

2.2.5. Safety Results

Safety data are presented for the Safety Analysis Population defined as all patients who received at least 1 dose of IMP in the pilot phase.

An overall summary of adverse events (AEs) in the pilot phase and OLE phase is provided in Table 3.

Table 3	Overall Summary of Treatment-emergent Adverse Events (Pilot and OLE Phase, Safety Analysis Set)	
	Pilot Phase	OLE Phase
Number of Patients Reporting TEAEs	GWP42003-P (N=9) n (%)	GWP42003-P (N=9) n (%)
At least 1 TEAE	6 (66.7%)	7 (77.8%)
Treatment-related TEAEs	2 (22.2%)	2 (22.2%)
At least 1 serious TEAEs	1 (11.1%)	2 (22.2%)
TEAEs leading to permanent discontinuation of IMP	0	0
Treatment-related TEAEs leading to permanent discontinuation of IMP	0	0
Treatment-related serious TEAEs	0	0
Fatal TEAEs	0	0

IMP = Investigational medicinal product; OLE = Open-label extension; TEAE = Treatment-emergent adverse event.
Note 1: If a patient experienced more than 1 event in a given category, that patient was counted only once in that category.
Note 2: MedDRA Dictionary (Version 19.0) was used for coding adverse events.
[redacted]

2.2.5.1. Treatment-Emergent Adverse Events (TEAEs)

In the pilot phase, 6 (66.7%) patients presented with at least 1 TEAE. The majority of the TEAEs were mild in intensity. One patient experienced a TEAE of moderate intensity (constipation), and 1 patient experienced a TEAE of severe intensity (status epilepticus). Reported TEAEs by SOC and PT are shown in Table 11.2.1.

Table 11.2.1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Pilot Phase - Safety

System Organ Class Preferred Term	GWP42003-P (N = 9)
Patients with any TEAEs	6 (66.7)
Gastrointestinal disorders	4 (44.4)
Diarrhoea	2 (22.2)
Constipation	1 (11.1)
Vomiting	1 (11.1)
Infections and infestations	2 (22.2)
Upper respiratory tract infection	2 (22.2)
Nervous system disorders	2 (22.2)
Somnolence	1 (11.1)
Status epilepticus	1 (11.1)
General disorders and administration site conditions	1 (11.1)
Application site erosion	1 (11.1)
Metabolism and nutrition disorders	1 (11.1)
Increased appetite	1 (11.1)
Psychiatric disorders	1 (11.1)
Irritability	1 (11.1)
Renal and urinary disorders	1 (11.1)
Haematuria	1 (11.1)
Respiratory, thoracic and mediastinal disorders	1 (11.1)
Cough	1 (11.1)

Note 1: A TEAE is defined as any AE occurring or worsening on or after the first dose of study treatment and until 30 days after discontinuation of all study treatment.
Note 2: Patients with one or more adverse events within a MedDRA term is counted only once in that level.
Note 3: System Organ Class terms are sorted in decreasing sequence based on the Total column and preferred terms are sorted in decreasing frequency based on the Total column.
Note 4: MedDRA Dictionary (Version 19.0) was used for coding adverse events.
[redacted]

In the OLE phase, 7 (77.8%) patients presented with at least 1 TEAE. Two patients experienced multiple TEAEs of moderate intensity, and 2 patients experienced multiple TEAEs of severe intensity. Reported TEAEs by SOC and PT are shown in Table 11. 2.2.

Table 11.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - OLE Phase - Safety

System Organ Class Preferred Term	GWP42003-P (N = 9)
Patients with any TEAEs	7 (77.8)
Respiratory, thoracic and mediastinal disorders	5 (55.6)
Upper respiratory tract congestion	3 (33.3)
Acute respiratory failure	1 (11.1)
Adenoidal hypertrophy	1 (11.1)
Hypoxia	1 (11.1)
Pneumonia aspiration	1 (11.1)
Respiratory distress	1 (11.1)
Respiratory failure	1 (11.1)
Infections and infestations	4 (44.4)
Bronchiolitis	2 (22.2)
Enterovirus infection	2 (22.2)
Pneumonia	2 (22.2)
Rhinovirus infection	2 (22.2)
Urinary tract infection	2 (22.2)
Viral upper respiratory tract infection	2 (22.2)
Ear infection	1 (11.1)
Nasopharyngitis	1 (11.1)
Otitis media	1 (11.1)
Pneumonia bacterial	1 (11.1)
Pneumonia klebsiella	1 (11.1)
Sinusitis	1 (11.1)
Urinary tract infection bacterial	1 (11.1)
Viral infection	1 (11.1)
General disorders and administration site conditions	3 (33.3)
Pyrexia	2 (22.2)
Drug tolerance	1 (11.1)

Note 1: A TEAE is defined as any AE occurring or worsening on or after the first dose of study treatment and until 30 days after discontinuation of all study treatment.
Note 2: Patients with one or more adverse events within a MedDRA term is counted only once in that level.
Note 3: System Organ Class terms are sorted in decreasing sequence based on the Total column and preferred terms are sorted in decreasing frequency based on the Total column.
Note 4: MedDRA Dictionary (Version 19.0) was used for coding adverse events.

[redacted]

Table 11.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - OLE Phase - Safety

System Organ Class Preferred Term	GWP42003-P (N = 9)
Metabolism and nutrition disorders	3 (33.3)
Decreased appetite	1 (11.1)
Feeding intolerance	1 (11.1)
Fluid overload	1 (11.1)
Hypokalaemia	1 (11.1)
Hyponatraemia	1 (11.1)
Blood and lymphatic system disorders	2 (22.2)
Anaemia	2 (22.2)
Gastrointestinal disorders	2 (22.2)
Diarrhoea	1 (11.1)
Gingival pain	1 (11.1)
Investigations	2 (22.2)
Blood triglycerides increased	2 (22.2)
Nervous system disorders	2 (22.2)
Myoclonic epilepsy	1 (11.1)
Petit mal epilepsy	1 (11.1)
Somnolence	1 (11.1)
Psychiatric disorders	2 (22.2)
Irritability	2 (22.2)
Sleep disorder	1 (11.1)
Skin and subcutaneous tissue disorders	2 (22.2)

Note 1: A TEAE is defined as any AE occurring or worsening on or after the first dose of study treatment and until 30 days after discontinuation of all study treatment.
Note 2: Patients with one or more adverse events within a MedDRA term is counted only once in that level.
Note 3: System Organ Class terms are sorted in decreasing sequence based on the Total column and preferred terms are sorted in decreasing frequency based on the Total column.
Note 4: MedDRA Dictionary (Version 19.0) was used for coding adverse events.

[redacted]

Table 11.2.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - OLE Phase - Safety

System Organ Class Preferred Term	GWP42003-P (N = 9)
Skin and subcutaneous tissue disorders (Continued)	
Dermatitis diaper	1 (11.1)
Rash	1 (11.1)
Skin irritation	1 (11.1)
Vascular disorders	2 (22.2)
Hypertension	1 (11.1)
Hypotension	1 (11.1)
Ear and labyrinth disorders	1 (11.1)
Deafness	1 (11.1)
Middle ear effusion	1 (11.1)
Eye disorders	1 (11.1)
Pupils unequal	1 (11.1)
Musculoskeletal and connective tissue disorders	1 (11.1)
Scoliosis	1 (11.1)
Renal and urinary disorders	1 (11.1)
Urinary retention	1 (11.1)

Note 1: A TEAE is defined as any AE occurring or worsening on or after the first dose of study treatment and until 30 days after discontinuation of all study treatment.
Note 2: Patients with one or more adverse events within a MedDRA term is counted only once in that level.
Note 3: System Organ Class terms are sorted in decreasing sequence based on the Total column and preferred terms are sorted in decreasing frequency based on the Total column.
Note 4: MedDRA Dictionary (Version 19.0) was used for coding adverse events.

[redacted]

2.2.5.2. Treatment-Related TEAEs

During the pilot phase, 2 patients presented with a total of 5 treatment-related TEAEs (by preferred term [PT]: 2 events of diarrhoea, 1 event of increased appetite, 1 event of somnolence, and 1 event of irritability).

During the OLE phase, 2 patients presented with a total of 2 treatment-related TEAEs (by PT: 1 event of blood triglycerides increase, and 1 event of hypertension).

2.2.5.3. Serious Adverse Events (SAE)

During titration in the pilot phase, 1 patient presented with a SAE of status epilepticus. The event resolved the same day with intravenous fosphenytoin, intramuscular lorazepam, phenobarbital and intravenous levetiracetam. The event was considered severe, but not related to treatment.

During the OLE phase, 2 patients presented with multiple SAEs related to infections (mostly respiratory), diarrhoea, and urinary problems.

Patient 1 presented with the following SAEs considered by the principal investigator (PI) to be of severe intensity: Pneumonia at Days 286-310 (25 days duration), with both Enterovirus infection, Respiratory failure, and Rhinovirus Infection during Days 287-298 (12 days of duration), and with Urinary Retention during Days 309-377 (69 days of duration). This patient had a past medical history of otitis media, dysphagia and gastro-esophageal reflux s/p gastric tube placement. During treatment for pneumonia, the patient was reported to have an AE of deafness, which was mostly likely related to AEs of recurrent otitis media, and subsequent bilateral middle ear effusions, which were also reported as AEs.

Patient 2 presented with 3 SAEs (Acute respiratory failure, Bronchiolitis, and Pneumonia bacterial), considered by the PI to be of severe intensity, all at Days 237-263 (27 days of duration). The patient also experienced narcotic habituation during treatment with morphine while intubated during treatment for pneumonia. The opioid habituation resolved 7 days after discontinuation of morphine. All of the SAEs were resolved and none of the SAEs were considered by the PI to be treatment-related.

2.2.5.4. Fatal TEAEs and TEAEs Leading to Discontinuation

There were no deaths or TEAEs leading to discontinuation of IMP during the pilot phase or the OLE phase.

2.2.5.5. TEAEs of Special Interest

Single events of rash, status epilepticus (severe SAE), urinary retention (severe SAE), drug tolerance, and deafness were reported. None of these were considered by the PI to be treatment related.

Two patients presented multiple episodes of pneumonia, and single episodes of aspiration pneumonia, pneumonia bacterial and pneumonia klebsiella between them, during the OLE phase.

None of these were considered by the PI to be treatment related.

There were 2 TEAEs of anaemia during the OLE phase, reported in individual patients with corresponding low values for haemoglobin and haematocrit. One of the TEAEs was ongoing at the end of the trial.

CHMP comments

As shown in table 3, the majority of the patients experienced at least one TEAE. There was a comparable proportion of patients and a comparable number of AEs in the pilot phase and in the pivotal OLE phase. This indicates that AEs were not only reported in beginning of the treatment.

In the pilot phase, 6 patients reported a total of 13 AEs. The majority of AEs were mild in intensity, 1 was reported as moderate and 1 as severe. There was 1 reported serious AE (SAE) and 2 patients experienced a total of 5 events which were considered treatment related.

In the OLE phase, 7 patients reported a total of 59 AEs. Like the majority of the AEs reported in the pilot phase, the majority of the AEs reported during the OLE phase were mild in intensity, 2 were reported as moderate and 2 as severe. There were 2 reported SAEs and 2 patients experienced a total of 2 events which were considered treatment related.

Reported AEs are presented in Tables 11.2.1 and 11.2.2 above. The majority of the reported AEs were not considered related to study treatment; the only treatment related AEs reported were somnolence, irritability, increased blood pressure, diarrhea, increased appetite and elevated triglycerides. Of these AEs, irritability, somnolence and diarrhea are all included in the tabulated list of adverse reactions, section 4.8 of the SmPC. The severe AE of Status epilepticus reported during the pilot phase is most likely related to the underlying disease, infantile spasms; likewise for the 2 cases of epilepsy (myoclonic epilepsy (1 case) and Petit mal epilepsy (1 case) reported during the OLE phase of the study.

1) A Guideline On Summary Of Product Characteristics (SmPC), September 2009 (page 15).

2.2.5.6. Summary of Clinical Laboratory Findings

Summary results for shifts in haematology and chemistry parameters from baseline to worst post baseline and to last observed treatment value based on both reference ranges and toxicity thresholds for all patients in the pilot phase and OLE phase of the trial are presented.

Notably low values were reported after 295 days of treatment for haemoglobin (2 of 9 [22.2%] patients), haematocrit (2 of 9 [22.2%] patients), erythrocytes (2 of 9 [11.1%] patients), leukocytes (1 of 9 [11.1%] patients) and after 127 days for lymphocytes (1 of 9 [11.1%] patients). The patient repeat values of low hemoglobin, haematocrit, erythrocytes, and leukocytes had been hospitalized twice for pneumonia during the period of these low values. The other patient had transient low values that were within normal limits at end of study. No other markedly abnormal hematology results were observed.

Notably low values were observed for urea nitrogen (2 of 9 [22.2%] patients). Notably high values were observed in triglycerides (2 of 9 [22.2%] patients). No other markedly abnormal clinical chemistry results were observed.

2.2.5.7. Summary of Vital Signs, Physical Examinations and ECG

There were no clinically relevant changes from baseline for vital signs, physical examinations, and ECG in any of the patients in the pilot or OLE phases of the trial. Summary results and changes from baseline for vital signs, physical examinations, and ECG are presented.

The DSMC reviewed the data from the initial 2 weeks of treatment in all 9 patients enrolled, and concluded that none of the AE's raised concerns regarding the safety of the IMP. No additional DSMC meetings were planned or called as study enrolment was halted when No Go criteria were met. Sponsor maintained pharmacovigilance throughout the OLE treatment, as has been done in all other GWP42003-P clinical studies.

CHMP comments

During the study, 2 (22.2%) patients reported low values of haemaglobin, haematocrit and erythrocytes. The MAH has confirmed that the 2 patients were experiencing low values for all parameters Of note there is a mistake in the text above (cited from[1)] and see red text in the following): *"Notably low values were reported after 295 days of treatment for haemoglobin (2 of 9 [22.2%] patients), haematocrit (2 of 9 [22.2%] patients), erythrocytes (2 of 9 [11.1%] patients),…"*. The correct percentage of patients experiencing low values of erythrocytes is 22.2%, thus, the correct sentence is as follows with tracked changes: ", *erythrocytes (2 of 9 [~~11.1~~22.2%] patients),….*" Interestingly, these low values are not mentioned in the tabulated lists of AEs neither is the cases of decreased lymphocytes and low leucocytes nor the 2 cases of low urea nitrogen. This will not be pursued. The 2 cases of increased triglycerides are (correctly) reported in the AEs tables; this is endorsed.

The MAH informs that during the study, there were no clinically relevant changes in baseline for vital signs, physical examinations and ECGs. This is agreed when reviewing the submitted tables (not included in this assessment report) for absolute values of and changes in diastolic blood pressure, systolic blood pressure, pulse, ECGs and BMI.

1) Synoptic Report Body for Study GWEP15100, Title: A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol (CBD; GWP42003-P) in infants with infantile spasms following an initial open-label pilot study. Page 17.

3. Scientific discussion

Epidyolex (cannabidiol) 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 purpose of the present study was to evaluate the efficacy and safety of cannabidiol in the treatment of infantile spasm in patients aged 1 month to 24 months. The study was designed with an initial pilot phase intending to include a total of 10 infants. The study was part of a paediatric investigational plan (PIP) as approved by the European Medicines Agency (EMA)'s Paediatric Committee (PDCO). The study design including the study objective, endpoints and planned duration is endorsed. Especially, the approach of having predefined Go- and No-go criteria determining the future of the trial is fully endorsed as this ensured that the study was not unnecessarily prolonged if no clinically relevant effect of the treatment was observed/expected and/or if there were unacceptable safety issues. Only patients failing on approved therapies for Infantile spasms were included thus, only the most severe and/or treatment refractory patients were included.

After evaluation of 9 patients included in the pilot phase, the study was prematurely terminated as none of the 9 patients responded to the treatment as both IS and hypsarrhythmia persisted after 2 weeks of treatment. Thereby the efficacy-related No-go criteria was met. It may be considered that as only severe/treatment refractory patients were included, the result cannot be extrapolated to the milder forms of infantile spasms and it remains unclear if cannabidiol can have effect in these patients. Of note, the patients were treated with a high dose of cannabidiol (according to the study protocol, patients were titrated to a maximum daily dose of 40 mg/kg/day. During the OLE phase, three patients had temporary resolution of the spasms and hypsarrhythmia in a period of approximately 1 year, though the EEGs were not normal for any of these patients. Furthermore, 2 of these patients had initiated concomitant treatment with clobazam. It is considered most likely, that the patients' disease was transforming into another type of epilepsy, which is characteristic for the disease of infantile spasms.

The majority of patients experienced at least one AE both during the pilot phase and during the OLE phase. The majority of the AEs were mild in intensity and temporary. Further, only few AEs were considered related to the study drug. Most of the serious (and severe) AEs were well-known AEs reported for Epidyolex or related to lack of treatment (status epilepticus).

Conclusively, the MAH for Epidyolex has submitted a synoptic CSR and a clinical overview for the Study GWEP15100: A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol (CBD; GWP42003 P) in infants with infantile spasms following an initial open label pilot study.

Of the 9 patients treated in the pilot phase with open label GWP42003-P, both IS and hypsarrhythmia persisted after 2 weeks of treatment. Thus, the study met the predefined No Go efficacy criteria and the study was halted.

The benefit-risk for Epidyolex (cannabidiol) in the licensed 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.

4. List of questions

4.1. Major objections

No Major objections have been identified.

4.2. Other concerns

Question 1:

Considered the known effects of cannabidiol and a total of 3 reports of 'Irritability' (1 during the pilot phase and 2 during the OLE phase), the MAH is asked to provide more data regarding these cases including the temporary relationship, dose and concomitant AEs under the SOC 'Nervous system disorders'. The MAH should also inform if Irritability (or any other mood disorders) has been reported among other patients treated with Epidyolex (registration studies and post-approval studies), discuss potential biological causality, provide a literature review and lastly based on this discussion, consider if 'Irritability' should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC. In this context the SmPC Guideline[1)] stating *"This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable*

possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports." should be kept in mind.

Question 2:

During the study, 2 (22.2%) patients reported low values of haemagobin, haematocrit and erythrocytes. It is expected that this is 2 patients experiencing low values for all parameters; please confirm.

Question 3:

On page 17 in the Synoptic Report Body for Study GWEP15100, Title: A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol (CBD; GWP42003-P) in infants with infantile spasms following an initial open-label pilot study, it is stated that (red text marked by the medical assessor): *"Notably low values were reported after 295 days of treatment for haemoglobin (2 of 9 [22.2%] patients), haematocrit (2 of 9 [22.2%] patients), erythrocytes (2 of 9 [11.1%] patients),…"*. It is expected that the actual number of patients ("2") is correct percentage ("11.1%") is wrong; please confirm.

5. Assessment of responses (May 2020)

5.1. Major objections

No Major objections were identified.

5.2. Other concerns

Question 1:

Considered the known effects of cannabidiol and a total of 3 reports of 'Irritability' (1 during the pilot phase and 2 during the OLE phase), the MAH is asked to provide more data regarding these cases including the temporary relationship, dose and concomitant AEs under the SOC 'Nervous system disorders'. The MAH should also inform if Irritability (or any other mood disorders) has been reported among other patients treated with Epidyolex (registration studies and post-approval studies), discuss potential biological causality, provide a literature review and lastly based on this discussion, consider if 'Irritability' should be included in the tabulated list of adverse reactions in section 4.8 of the SmPC. In this context the SmPC Guideline[1)] stating *"This section should include all adverse reactions from clinical trials, post-authorisation safety studies and spontaneous reporting for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports."* should be kept in mind.

MAH's response: The Marketing Authorisations Holder (MAH) confirms events of irritability are a common psychiatric event with cannabidiol oral solution (CBD-OS) use and acknowledges the 3 reports of irritability observed during the pilot phase and open-label extension (OLE) phase of GWEP15100.

In the pivotal trials for the indications of Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS), an imbalance of irritability was noted with CBD-OS use in comparison to placebo. As such the MAH has listed irritability as a common psychiatric undesirable effect in section 4.8 of the summary of product characteristics (SmPC) (see SmPC Table 2 below).

Of note, across the development programme, irritability events were generally non-serious in nature and did not lead to discontinuation of CBD-OS.

Table 2: Tabulated list of adverse reactions

System Organ Class	Frequency	Adverse reactions from clinical trials
Infections and infestations	Common	Pneumonia[a], Bronchitis, Nasopharyngitis, Urinary tract infection
Metabolism and nutrition disorders	Very common	Decreased appetite
	Common	Increased appetite
Psychiatric disorders	Common	Irritability, Insomnia, Aggression, Abnormal behaviour, Agitation
Nervous system disorders	Very common	Somnolence[a]
	Common	Lethargy, Drooling, Tremor
Respiratory, thoracic and mediastinal disorders	Common	Cough
Gastrointestinal disorders	Very common	Diarrhoea, Vomiting
Hepatobiliary disorders	Common	AST increased, ALT increased, GGT increased, Liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Rash
General disorders and administration site conditions	Very common	Pyrexia, Fatigue
Investigations	Common	Weight decreased

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase.

[a] Grouped Terms: **Pneumonia:** Pneumonia, Pneumonia RSV, Pneumonia mycoplasmal, Pneumonia adenoviral, Pneumonia viral, Aspiration pneumonia; **Somnolence:** Somnolence, Sedation.

An important consideration regarding events of irritability is the behavioural and psychiatric comorbidities often seen in patients with DS and LGS. The patient population often has an overlap of comorbidities related to cognition and behavioural disturbances including attention deficit/hyperactivity disorder, anxiety, aggressive behaviour, psychosis and depression (Arzimanoglou 2009; Camfield 2011, Dravet 2011).

The MAH provided the details of the 3 subjects in GWEP15100 who had an adverse event (AE) of irritability.

Subject 1 enrolled in GWEP15100 with a medical history consistent with gene mutation, lissencephaly, dysphagia, gastroesophageal reflux, developmental delay, ventriculomegaly, and laparoscopic gastrostomy (G-tube). At baseline the subject was concomitantly receiving levetiracetam, topiramate, and vigabatrin as well as a ketogenic diet. On Day 26 of the OLE phase, the subject experienced irritability that was mild in severity and did not warrant a dose change and was considered not related to CBD-OS by the investigator. Clobazam was added on Day 210. The event of irritability had not resolved at the point of data cut.

Subject 2 enrolled in GWEP15100 with a medical history consistent of second degree AV block, patent foramen ovale, bilateral cryptorchidism, hip dysplasia, syndactyly, abnormal eye movements, intermittent constipation, developmental delay, left axis deviation, hypotonia, nephrocalcinosis, intermittent hiccups, hair loss, diaper rash, increased sweating, and gastrojejunostomy button. At baseline the subject was concomitantly receiving vigabatrin and levetiracetam. On Day 24 the subject commenced concomitant treatment with clobazam. On Day 57, during the OLE phase, the subject experienced irritability that was mild in nature and resolved on Day 91. There was no change in CBD-OS dose, and the event was considered not related to CBD-OS by the investigator. Of note, during the AE of irritability the subject also experienced AEs of pyrexia from Day 59 to Day 66 and gingival pain from Day 60 to Day 67.

Subject 3 enrolled in GWEP15100 with a medical history consistent with Aicardi syndrome, bilateral polymicrogyria, bilateral retinal coloboma, gastroesophageal reflux, intracranial arachnoid cysts, and hypotonia. The subject was not receiving concomitant medications at baseline. On Day 1 of the pilot phase of GWEP15100, the subject experienced irritability that was mild in nature and considered related to CBD-OS by the investigator. The subject

recovered on Day 3 without a dose change and continued CBD-OS.It is important to note that in trial GWEP15100 these subjects were titrated up to 40 mg/kg/day CBD-OS over 4 days, while hospitalised. Prior to treatment, the subjects underwent 24 hours of video electroencephalography monitoring. Thus, the occurrence of 3 cases of irritability, given the high dose of CBD-OS and the hospitalisation, does not impact the current information provided in the SmPC regarding irritability in LGS and DS subjects titrated more slowly, over 1 week to 10 mg/kg/day, and to a maximum dose of 20 mg/kg/day.

CHMP comment

As requested, the MAH has presented short narratives of the three patients who reported 'Irritability' as a (potential) adverse reaction to Epidyolex. This is endorsed. The MAH has also, correctly, drawn the attention to the commonly reported comorbidities of behavioural and psychiatric disorders in patients with Dravet syndrome and Lennox-Gastaut syndrome; it is indeed agreed that this may be confounding factors. Lastly, it is endorsed that 'Irritability' is included as a common adverse reaction in the tabulated list of adverse reactions in section 4.8 of the Epidyolex SmPC.

Conclusion: Issue resolved.

Question 2:

During the study, 2 (22.2%) patients reported low values of haemagobin, haematocrit and erythrocytes. It is expected that this is 2 patients experiencing low values for all parameters; please confirm.

MAH's response: The MAH confirms that the 2 (22.2%) subjects reporting low values of haemoglobin, haematocrit, and erythrocytes are the same subjects, respectively. Details of the events of the subject are provided below.

Subject 1 enrolled in GWEP15100 with a medical history of trisomy 21-down syndrome, esotropia, occasional constipation, dysphagia, developmental delay, seasonal allergies, and laparoscopic gastrostomy. The subject was concomitantly taking vigabatrin, clobazam, and zonisamide while maintaining a ketogenic diet. Baseline lab values were within normal range for haemoglobin (120 g/L), haematocrit (0.355 fraction of 1), and erythrocytes (4.05 10/L). On Day 295, of the OLE phase the subject experienced an AE of anaemia with lower lab values than baseline of hemoglobin (84 g/L), haematocrit (0.257 fraction of 1), and erythrocytes (2.71 10/L). The AE of anaemia was mild in nature and considered not related to CBD-OS. Of note, there was no change in CBD-OS. The event resolved on Day 379 with lab values within normal range of haemoglobin (128 g/L), haematocrit (0.381 fraction of 1), and erythrocytes (3.86 10/L).

Subject 2 enrolled in GWEP15100 with a medical history of neutropenia LIS1 mutation, lissencephaly, dysphagia, gastroesophageal reflux, developmental delay, ventriculomegaly, and laparoscopic gastrostomy (G-tube). The subject was concomitantly taking levetiracetam, topiramate, vigabatrin, clobazam, diazepam, and lorazepam while maintaining a ketogenic diet. Baseline lab values were within normal range for haemoglobin (119 g/L), haematocrit (0.358 fraction of 1), and erythrocytes (4.2 10/L). On Day 237 of the OLE phase the subject experienced anaemia that was mild in nature and considered not related to CBD-OS by the investigator. Lab values were unavailable for this date. At the point of data cut off, the event had not resolved and the subject did not have any changes to CBD-OS dose.

CHMP comments

The MAH has confirmed that the 2 (22.2%) patients reporting low values of haemoglobin, haematocrit, and erythrocytes are the same patients. Presentation of the 2 patients' narratives is endorsed.

Conclusion: Issue resolved.

Question 3:

On page 17 in the Synoptic Report Body for Study GWEP15100, Title: A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of cannabidiol (CBD; GWP42003-P) in infants with infantile spasms following an initial open-label pilot study, it is stated that (red text marked by the medical assessor): *"Notably low values were reported after 295 days of treatment for haemoglobin (2 of 9 [22.2%] patients), haematocrit (2 of 9 [22.2%] patients), erythrocytes (2 of 9 [11.1%] patients),…"*. It is expected that the actual number of patients ("2") is correct and the percentage ("11.1%") is wrong; please confirm.

MAH's response: The MAH confirms the sentence "Notably low values were reported after 295 days of treatment for haemoglobin (2 of 9 [22.2%] patients), haematocrit (2 of 9 [22.2%] patients), erythrocytes (2 of 9 [11.1%] patients),…" did have a typing error. It is confirmed that the 2 subjects experienced low values of haemoglobin, haematocrit, and erythrocytes with a correct frequency of 22.2% for all the values.

CHMP comments

The MAH has confirmed that the correct percentage for the 2 patients who experienced low values of haemoglobin, haematocrit, and erythrocytes was 22.2%.

Conclusion: Issue resolved.

6. Overall conclusion (May 2020)

☒ **PAM fulfilled (all commitments fulfilled) - No further action required**