26 January 2023
EMA/CHMP/68212/2023
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/P46/011.1

Note

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

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1. Introduction

On 14 Dec 2021, the MAH submitted a completed paediatric study for Epidyolex, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This study is part of a PIP (EMEA-001964-PIP01-16) for which the recent PIP modification decision is enclosed. (EMEA-001964-PIP01-16-M03, dated 29-January 2021).

Epidyolex (cannabidiol oral solution [CBD-OS]) was approved, via the European Union centralised procedure by the Committee for Medicinal Products for Human Use, with European Commission decision issued on 19 September 2019 for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, in patients 2 years of age and older. Epidyolex was also approved as an adjunctive treatment of seizures associated with tuberous sclerosis complex, for patients 2 years of age and older by the European Commission in April 2021.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that:

"According to Article 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, GW Pharma (International) B.V. is submitting the following paediatric study which was completed on 11th June 2021:

GWEP1521, Phase 3, Long-term Safety and Efficacy

A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately controlled seizures.

As GWEP1521 falls under Article 46, the study report is being provided now to fulfil the 6-month reporting obligation. The GWEP1521 trial results further support the safety profile of the approved Epidyolex SmPC.

No new safety concerns were identified that could result in an update to the current Summary of Product Characteristics as the benefit-risk balance remains unchanged. Therefore, no regulatory consequence is identified."

2.2. Information on the pharmaceutical formulation used in the study

The Investigational Medicinal Product (IMP; GWP42003-P, Epidyolex, CBD-OS) is a clear, colourless to yellow solution containing 100 mg/mL CBD dissolved in the following excipients: sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (sucralose [0.5 mg/mL]) and strawberry flavouring (0.2 mg/mL).

Mode of administration is oral. Dosing via a gastrostomy (G)/nasogastric (NG) tube (as required) was allowed after consultation with the sponsor medical monitor.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- GWEP1521; A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately controlled seizures.

The intent of this paediatric study was to evaluate the long-term safety and efficacy of Epidyolex in 199 patients aged 1 to 65 years who had completed the double-blind treatment (DBT) phase of the study. The study comprised an open-label extension (OLE) study in children and adults as part of a paediatric investigational plan as approved by the European Medicines Agency's Paediatric Committee.

No unexpected or new clinically significant safety findings were noted in this study. Therefore, no regulatory consequences were identified by the Marketing Authorisation Holder.

Assessor's comments

On December 14th 2021, the MAH submitted a clinical study report as well as a critical clinical overview describing the results for the abovementioned Study GWEP1521. A decision for PIP modification was attached: EMEA-001964-PIP01-16-M03, Modification 03 Decision.

Epidyolex, was designated as an orphan medicinal product EU/3/17/1959 on 17 January 2018 in the following indication: Treatment of tuberous sclerosis. Epidyolex was approved as an adjunctive treatment of seizures associated with tuberous sclerosis complex, for patients 2 years of age and older by the European Commission in April 2021. The clinical development program supporting this extension of indication comprises Study GWEP1521; a single, Phase III, randomised, placebo-controlled trial that investigated 25 mg/kg/day and 50 mg/kg/day CBD-OS for the treatment of TSC-associated seizures. The MAH is now submitting the study report for open label extension phase to fulfil 6 months reporting obligation (as part of PIP and fulfils the Art. 46 paediatric study criteria).

The MAH highlights, that no changes to the product information including the SmPC are proposed.

2.3.2. Clinical study

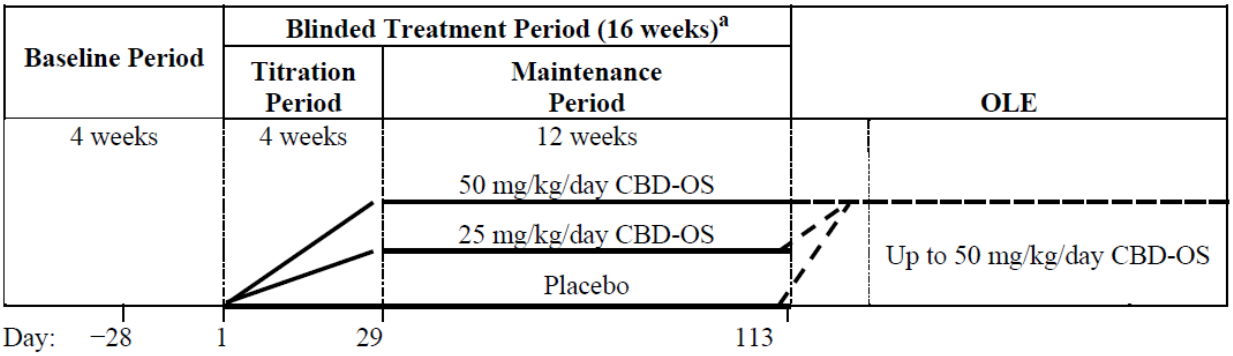
GWEP1521; A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately controlled seizures

Description

The OLE phase of GWEP1521 was a multicenter, open-label trial to investigate the long-term safety and efficacy of GWP42003-P, which was open to patients with TSC who had participated in the randomized, double-blind, placebo-controlled phase of the trial (RCT, GWEP1521) (Figure 1-1).

The OLE trial included a blinded transition period (following completion of double-blind treatment), 3-week titration period; 1-year treatment period (extended to a total of 4 years in the US under Protocol Annex 1, and 3 years in Poland under Protocol Annex 2); 10-day taper period; and a 4-week follow-up period (figure 1-2).

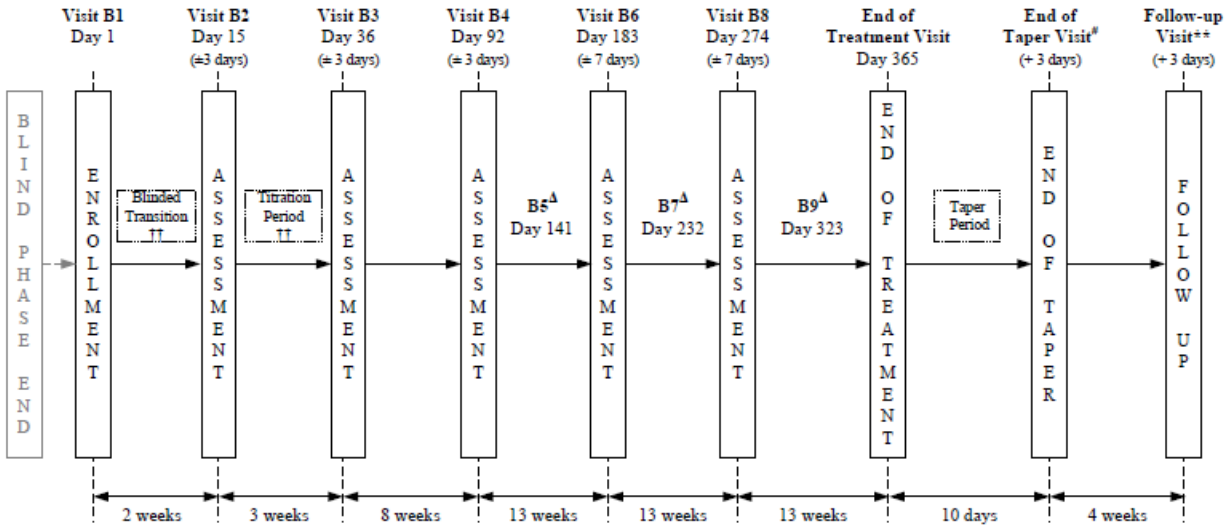
Figure 1-1 GWEP1521 Trial Design Schematic



CBD-OS = cannabidiol oral solution; OLE = open-label extension.

[a] Patients who withdrew during, or on completion of, the pivotal trial were to taper down by 10% per day over 10 days.

Figure 1-2 Study Design and Treatment Schema: Open-label Extension



* To avoid double-dosing of IMP at Visit 1, patients will be instructed to begin titration of IMP the following day, which will be regarded as Day 1. As such, Visit 1 will occur on Day −1 with no clinic visit on Day 1.

Following the 'End of Taper Period' visit, a safety telephone call must be made two weeks later to collect seizure information, and to assess AEs, epilepsy-related hospitalizations, concomitant medications and/or changes to medication.

** Can be conducted by telephone.

Entry to this OLE trial was recommended to be on the same day as Visit 10 of the RCT. Patients who did not enter the OLE had their dose of IMP tapered gradually (10% per day) over a period of 10 days (unless discontinued due to an adverse event [AE]).

Patients entering the OLE first completed a 2-week blinded transition phase. The OLE IMP was titrated up to 25 mg/kg/day whilst blinded IMP was simultaneously tapered down to zero. All patients completed the transition and then entered the OLE taking 25 mg/kg/day of the IMP.

Following completion of the blinded transition period, patients were to complete a 3-week titration up to a maximum dose of 50 mg/kg/day. Beginning at 25 mg/kg/day the dose was increased in increments of 2.5 mg/kg/day every 2 days. Patients then remained on a stable dose of the IMP for the remainder of the OLE with the option for doses to be decreased or increased (maximum of 50 mg/kg/day) based on clinical response and tolerability as deemed necessary by the investigator. Patients whose dose had been decreased could have had their dose increased again if tolerability improved.

At the end of treatment, the dose of IMP was to be reduced over a 10-day taper period, and patients then entered the 4-week follow-up period.

If a patient permanently discontinued treatment at any point during the trial, the patient was to attend a withdrawal visit as soon as possible after the decision was made to permanently discontinue IMP. Unless inadvisable due to an AE, the patient was to taper IMP 10% per day for 10 days and attend the End of Taper visit and then complete the 4-week follow-up period.

Methods

Study participants

Participants aged 1 to 65 years with TSC who had completed the double-blind, placebo-controlled treatment phase of study GWEP1521 were allowed in this study. To be eligible for the double-blind phase, patients had to have experienced at least 8 seizures (including focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral generalized convulsive seizures, and generalized seizures [tonicclonic, tonic, clonic or atonic]) during the first 28 days of the baseline period with at least 1 seizure occurring in at least 3 of the 4 weeks.

Treatments

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

Dosage: Following completion of the blinded transition, patients were to complete a 3-week titration up to a target dose of 50 mg/kg/day. Beginning at 25 mg/kg/day the dose was to increase in increments of 2.5 mg/kg/day every 2 days.

The IMP was to be administered by the patient or their caregiver twice each day (morning and evening) using the syringe(s) provided and could be taken with other concomitant medications, as directed by the investigator.

Patients were not to enter the OLE phase of the study if using a G/NG tube, unless they were still able to take medication orally. Dosing via G/NG tubes was allowed after consultation with the sponsor medical monitor. Alteration in dosing frequency was also considered after consultation with the sponsor medical monitor.

Objective(s)

Primary Objective:

The purpose of this study was to evaluate the long-term safety and tolerability of GWP42003-P as an add-on therapy in patients with TSC with inadequately controlled seizures.

Secondary Objectives:

To evaluate the long-term effects of GWP42003-P:

• As add-on therapy on antiepileptic measures.

• On growth and development in patients < 18 years old.

• On quality of life (QoL).

Exploratory Objective:

• To evaluate the long-term effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioural function and autistic features.

Outcomes/endpoints

Primary Endpoint: The long-term safety profile of GWP42003-P was evaluated by assessment of the incidence, type, and severity of AEs.

Secondary Endpoints: The following endpoints were assessed relative to the pre-randomisation baseline of the blinded phase:

Antiepileptic Efficacy Measures:

Key

- Percentage change in number of TSC-associated seizures* (average per 28 days).
- Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency*
- Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.
- Change in total seizures.

Other

- Number of patients considered treatment responders defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in TSC-associated seizure* frequency.
- Number of patients experiencing a > 25% worsening, − 25 to + 25% no change, 25% to 50% improvement, 50% to 75% improvement, or > 75% improvement in TSC-associated seizure* frequency.
- Change in number of TSC-associated seizure*-free days.
- Change in number of 'other' seizures (absence, myoclonic, focal sensory and infantile/epileptic spasms).

*TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, and focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable.

Growth and Development (patients < 18 years of age)

- Change in serum insulin-like growth factor-1 (IGF-1) levels.
- Change in Tanner Staging score (for patients aged 10–17, inclusive).

Quality of Life

- Changes from baseline in the scores for the Quality of Life in Childhood Epilepsy questionnaire (QOLCE) in patients 2 to 18 years of age or the Quality of Life in Epilepsy inventory (QOLIE-31-P) in patients aged 19+ years.
- Change in the Physician Global Impression of Change (PGIC) score.

Safety and Tolerability

- Clinical laboratory parameters
- Electrocardiogram (ECG)
- Physical examination parameters (including height and weight)
- Vital signs
- Scores for the Columbia-Suicide Severity Rating Scale (C-SSRS) for patients aged 19+ years) or the C-SSRS Children's for patients aged 6 to 18 years, as applicable
- Number of inpatient hospitalisations due to epilepsy
- Abuse liability
- Effects on menstruation cycles (in females)

Exploratory Endpoints:

Antiepileptic Efficacy Measures

- Change in composite focal seizure score (frequency × severity)
- Change in number of seizures by subtype
- Change in use of rescue medication
- Change in the number of episodes of status epilepticus (convulsive and non-convulsive).
- Changes in duration of seizure subtypes as assessed by the SGIC in Seizure Duration (SGIC-SD) or the CGIC in Seizure Duration (CGIC-SD)

TAND

Cognitive and Behavioural Function

- Changes in Vineland Adaptive Behavior Scales, Second Edition (Vineland-II)
- Changes in Wechsler Scales (pre-school, primary, children, adult)
- Changes in Achenbach Child Behavior Checklist (CBCL) and Adult Behavior Checklist (ABCL)

Autistic Features:

- Change in Social Communication Questionnaire (SCQ) score

Statistical Methods

Descriptive presentations of treatment-emergent AEs (TEAEs) were given by preferred term (PT) and system organ class and the number of patients reporting at least 1 TEAE was provided.

Clinical laboratory data at the end of treatment in the OLE and the change from baseline of the RCT to end of treatment were summarized using appropriate summary statistics. Categorical shift tables were also presented, showing the numbers of patients with values outside the normal range.

All other endpoints were summarized using appropriate descriptive statistics, with change from baseline and summaries by timepoint provided where necessary. There was no formal hypothesis testing.

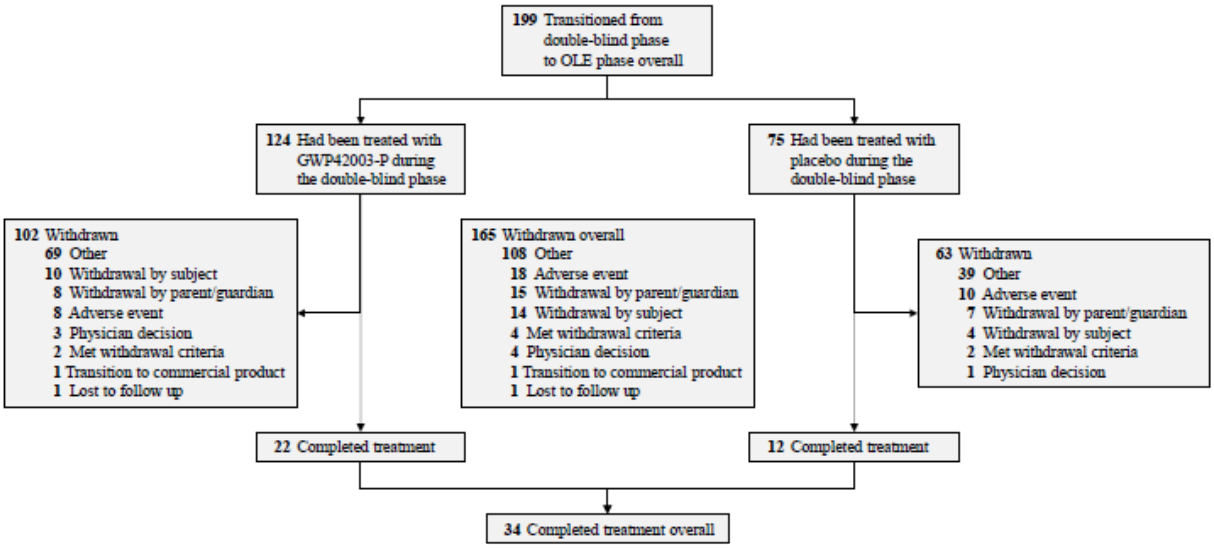
Results

Participant flow

A total of 199 patients were enrolled into the OLE phase of the study; 75 of these patients had received placebo in the RCT. Thirty-four (17.1%) patients completed treatment.

The most frequent reason for withdrawal (108 patients) was transition to commercial product (93 patients) which was categorized as an 'other' reason for withdrawal for 92 patients, and lack of efficacy (11 patients). A total of 18 patients were discontinued due to AEs. Additional reasons for withdrawal were withdrawal by parent or guardian (15 patients), withdrawal by subject (14 patients), physician decision (4 patients), met a withdrawal criterion (4 patients), and lost to follow-up (1 patient).

Figure 4-1 **Disposition of Patients**



OLE = open-label extension.
Note: Withdrawals are shown according to the primary reason reported for each patient. Among the 108 patients who had "other reason" for withdrawal, 92 were withdrawn because they transitioned to commercial product, 11 were withdrawn due to lack of efficacy, 2 were withdrawn due to advice from the medical monitor or their neurologist, 1 withdrew due to difficulties with compliance, 1 withdrew because the study completed, and 1 was due to a parent and investigator decision.
Source: Section 8 OLE Table 1.2; Appendix 2 OLE Listing 1.1.1, OLE Listing 1.1.2.

Assessor's comment

A total of 224 patients were randomized to double-blind phase of the study. Of the 224 randomised patients, 112 (50%) were randomised in the US, 61 (27.2%) in Poland, 24 (10.7%) in Australia, 11 (4.9%) in Spain, 9 (4.0%) in the Netherlands, and 7 (3.1%) in the UK. Overall, 201 patients (89.7%) completed the double-blind phase and 199 patients (88.8%) entered the OLE phase of the trial. At the time of MAA for TSC, 75.4% of OLE patients were still ongoing.

A summary of overall patient disposition is presented in Table 1.

Table 1 Summary of Overall Patient Disposition (OLE Safety Analysis Set)

		DB Phase Treatment Assignment		
		GWP42003-P (N=124)	Placebo (N=75)	Total (N=199)
OLE treatment phase	Ongoing	96 (77.4%)	54 (72.0%)	150 (75.4%)
	Completed	7 (5.6%)	3 (4.0%)	10 (5.0%)
	Withdrawn	21 (16.9%)	18 (24.0%)	39 (19.6%)
Primary reason for withdrawal - OLE treatment phase	AE	2 (1.6%)	9 (12.0%)	11 (5.5%)
	Met withdrawal criteria	0	1 (1.3%)	1 (0.5%)
	Other	8 (6.5%)	3 (4.0%)	11 (5.5%)
	Physician decision	3 (2.4%)	0	3 (1.5%)
	Withdrawal by parent/guardian	3 (2.4%)	2 (2.7%)	5 (2.5%)
	Withdrawal by subject	5 (4.0%)	3 (4.0%)	8 (4.0%)

Currently presented disposition of patients indicate that only 34 patients completed OLE phase. "Other reason" was the most frequent reason for withdrawal. Among the 108 patients who had "other reason" for withdrawal, 92 were withdrawn because they transitioned to commercial product, 11 were withdrawn due to lack of efficacy, 2 were withdrawn due to advice from the medical monitor or their neurologist, 1 withdrew due to difficulties with compliance, 1 withdrew because the study completed, and 1 was due to a parent and investigator decision. 18 patients were withdrawn due to adverse events.

Due to problematic coding of reasons as other despite similar reasons coded individually outside "other" group, the disposition of patients is difficult to evaluate immediately.

For the 34 patients who completed the OLE, the overall median total number of dosing days was 369.5 days. The longest duration of exposure within the OLE trial was 1462 days.

Table 2 Summary of Exposure (Safety Analysis Set)

Parameter Statistics	Double-blind Treatment GWP42003-P (N = 124)	Placebo (N = 75)	Total (N = 199)
Total Number of Dosing Days in the OLE Treatment Phase - All Patients			
n	124	75	199
Mean (SD)	672.02 (402.971)	585.20 (383.159)	639.30 (396.893)
Median	676.50	581.00	631.00
Min, Max	29.0, 1462.0	18.0, 1458.0	18.0, 1462.0
Pooled Maximum OLE Dose - All Patients			
≤ 25 mg/kg/day	71 (57.3%)	35 (46.7%)	106 (53.3%)
> 25 mg/kg/day	53 (42.7%)	40 (53.3%)	93 (46.7%)
Total Number of Dosing Days in the OLE Treatment Phase - Patients who Completed the Treatment Phase			
n	22	12	34
Mean (SD)	502.95 (390.23)	459.67 (314.47)	487.68 (360.98)
Median	368.50	371.00	369.50
Min, Max	95.0, 1462.0	361.0, 1458.0	95.0, 1462.0
Pooled Maximum OLE Dose - Patients who Completed the Treatment Phase (n [%])			
≤ 25 mg/kg/day	13 (59.1%)	4 (33.3%)	17 (50.0%)
> 25 mg/kg/day	9 (40.9%)	8 (66.7%)	17 (50.0%)

OLE = open-label extension; SD = standard deviation.
Source: OLE CSR Table 4-5.

Assessor's comment:

During evaluation of indication extension, long-term safety data for approved dose was not considered adequate in accordance with requirements of ICH E1 guidance (CPMP/ICH/375/95). In RCT, the exposure was 21.11 patient-years (75 patients, 16 weeks) for 25 mg/kg/day group. Overall, 88 patients across the double-blind phase and OLE have been exposed to CBD OS > 1 year. Due to orphan designation, the supportive data from other sources was taken into consideration as support.

Table 1-1 CBD-OS Exposure in TSC Patients in Trial GWEP1521 (Pool TSC, Pool OLE-TSC and Pool LT-TSC)

	Pool TSC			Pool OLE TSC			All CBD-OS Treated Patients
	CBD-OS (mg/kg/day)			CBD-OS Modal Dose (mg/kg/day)			
Statistic	25 (N=75)	50 (N=73)	All CBD-OS (N=148)	≤ 25 (N=156)	> 25 (N= 43)	All CBD-OS (N=199)	(N=223)
n	75	73	148	156	43	199	223
Mean time on treatment, days	102.8	101.8	102.3	258.7	360.5	280.7	317.8
SD	28.8	29.7	29.1	199.8	209.1	205.6	225.2
Median	113	113	113	232	318	267	307.0
Minimum	9	10	9	18	40	18	9.0
Maximum	124	125	125	876	910	910	988.0
Duration of Exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
6 to < 12 months	0	0	0	50 (32.1)	22 (51.2)	72 (36.2)	63 (28.3)
12 to < 24 months	0	0	0	32 (20.5)	10 (23.3)	42 (21.1)	73 (32.7)
≥ 24 months	0	0	0	8 (5.1)	5 (11.6)	13 (6.5)	15 (6.7)

In this study report, the mean time on treatment went up from 317.8 days (n=223) to 631 days (n=199), min-max were 18-1462 days. Overall, more than half of the patients stayed at or below 25 mg/kg/day dose during OLE phase. During evaluation of safety profile in OLE, this should be taken into consideration.

Number of patients who need dose modification and reasons were not summarized by the MAH. This is not pursued due to clear recommendation that 25 mg/kg/day is the maximum recommended dose in this indication.

Demography and Baseline data

Overall, there were more male (59.3%) than female (40.7%) patients (Table 1). Most patients were White/Caucasian (88.9%); 13 patients (6.5%) had their race recorded as 'Other.' Approximately half of all patients were from the USA (51.8%). The mean (standard deviation [SD]) age was 13.15 (10.015) years.

Table 1 Demographics and Baseline Characteristics (OLE Safety Analysis Set)

Demographic Characteristic	Double-blind Treatment		Total
	GWP42003-P (N = 124)	Placebo (N = 75)	(N = 199)
Age (Years)			
n	124	75	199
Mean (SD)	12.69 (9.638)	13.92 (10.632)	13.15 (10.015)
Median	10.03	11.06	10.74
Min, Max	1.1, 56.8	1.2, 55.8	1.1, 56.8
Age group (n [%])			
1 to 6 years	38 (30.6%)	21 (28.0%)	59 (29.6%)
7 to 11 years	32 (25.8%)	18 (24.0%)	50 (25.1%)
12 to 17 years	28 (22.6%)	16 (21.3%)	44 (22.1%)
18 to 65 years	26 (21.0%)	20 (26.7%)	46 (23.1%)
Sex (n [%])			
Female	51 (41.1%)	30 (40.0%)	81 (40.7%)
Male	73 (58.9%)	45 (60.0%)	118 (59.3%)
Race (n [%])			
White/Caucasian	111 (89.5%)	66 (88.0%)	177 (88.9%)
Black/African American	4 (3.2%)	0	4 (2.0%)
American Indian/Alaska Native	1 (0.8%)	0	1 (0.5%)
Asian	1 (0.8%)	3 (4.0%)	4 (2.0%)
Other	7 (5.6%)	6 (8.0%)	13 (6.5%)
Country (n [%])			
Australia	12 (9.7%)	10 (13.3%)	22 (11.1%)
Netherlands	4 (3.2%)	3 (4.0%)	7 (3.5%)
Poland	35 (28.2%)	16 (21.3%)	51 (25.6%)
Spain	8 (6.5%)	2 (2.7%)	10 (5.0%)
United States	62 (50.0%)	41 (54.7%)	103 (51.8%)
United Kingdom	3 (2.4%)	3 (4.0%)	6 (3.0%)
Region (n [%])			
Rest of the World	62 (50.0%)	34 (45.3%)	96 (48.2%)
United States	62 (50.0%)	41 (54.7%)	103 (51.8%)
Weight at Baseline (kg)			
n	124	75	199
Mean (SD)	40.46 (22.529)	44.91 (27.965)	42.14 (24.744)
Median	34.10	36.90	36.30
Min, Max	12.1, 130.0	10.4, 115.7	10.4, 130.0
Height at Baseline (cm)			
n	122	75	197
Mean (SD)	137.23 (28.660)	137.79 (31.358)	137.45 (29.638)
Median	139.55	140.60	140.00
Min, Max	43.0, 196.0	41.5, 182.0	41.5, 196.0
BMI at Baseline (kg/m^2)			
n	122	75	197
Mean (SD)	20.32 (9.593)	22.16 (12.106)	21.02 (10.627)
Media	18.49	19.28	18.71
Min, Max	8.4, 108.7	13.2, 110.3	8.4, 110.3

BMI = body mass index; Min = minimum; Max = maximum; OLE = open-label extension; SD = standard deviation; USA = United States of America.

Note: Two patients (1 from the 50 mg/kg/day GWP42003-P group and 1 from the pooled placebo group) were excluded from the summary of demographic data because their heights at screening were measured in inches but were recorded in cm. This meant that the calculated BMI for each patient at screening was incorrect. These patients have been included in this summary table.

The numbers of patients with tonic-clonic seizures, tonic seizures, clonic, infantile or epileptic spasms were generally higher at baseline in patients treated with GWP43003-P compared with placebo during the double-blind phase (Table 4-4). The numbers of patients with atonic seizures or partial sensory seizures were general lower in patients treated with GWP43003-P compared with patients treated with placebo in the double-blind phase. The numbers of patients with myoclonic seizures or absence seizures were generally similar between the treatment groups.

During the OLE phase, 38 (19.1%) patients reported 1 or more inpatient hospitalizations due to epilepsy: 28 (22.6%) patients treated with GWP42003-P and 10 (13.3%) patients treated with placebo during the double-blind phase.

Overall, the median number of AEDs currently taken was 3.

Five (2.5%) patients were on ketogenic diet and 24 (12.1%) patients were on vagus nerve stimulation. A total of 198 (99.5%) patients took 1 or more concomitant AEDs during the study. The most common classes of AEDs used concomitantly (i.e., reported in > 50% of patients overall) were other antiepileptics (157 [78.9%] patients), fatty acid derivatives (126 [63.3%] patients), and benzodiazepine derivatives (90 [45.2%] patients). The most used AEDs were VPA (86 [43.2%] patients), VGB (73 [36.7%] patients), and clobazam (70 [35.2%] patients).

Overall, 95 (47.7%) patients were recorded as taking rescue medications, with similar proportions of patients between the double-blind phase treatment groups: 58 (46.8%) patients treated with GWP42003-P versus 37 (49.3%) patients treated with placebo during the double-blind phase. The most common class of rescue medication was benzodiazepine derivatives, recorded for 95 (47.7%) patients. The most common rescue medication was diazepam (60 [30.2%] patients).

A total of 178 (89.4%) patients were recorded as taking other concomitant medications. The most common classes of other concomitant medications (i.e., recorded in ≥ 25% of these patients) were anilides (78 [39.2%] patients) and propionic acid derivatives (52 [26.1%] patients). The most common other concomitant medication was paracetamol (74 [37.2%] patients).

Table 4-4 Summary Baseline Characteristics (OLE Safety Analysis Set)			
	Double-blind Phase Treatment		
	GWP42003-P (N = 124)	Placebo (N = 75)	Total (N = 199)
Number of AEDs Patient Currently Taking (Continuous)			
n	124	75	199
Mean	2.62	2.60	2.61
SD	0.993	0.900	0.957
Median	3.00	3.00	3.00
Min, Max	0.0, 5.0	1.0, 5.0	0.0, 5.0
Number of AEDs Patient Currently Taking (Categorical) (n [%])			
0	1 (0.8)	0	1 (0.5)
1	16 (12.9)	8 (10.7)	24 (12.1)
2	36 (29.0)	25 (33.3)	61 (30.7)
3	50 (40.3)	33 (44.0)	83 (41.7)
4	18 (14.5)	7 (9.3)	25 (12.6)
5	3 (2.4)	2 (2.7)	5 (2.5)
Patients Currently Taking Clobazam (n [%])			
No	95 (76.6)	50 (66.7)	145 (72.9)
Yes	29 (23.4)	25 (33.3)	54 (27.1)
Patients Currently Taking Valproic Acid (n [%])			
No	79 (63.7)	40 (53.3)	119 (59.8)
Yes	45 (36.3)	35 (46.7)	80 (40.2)
Patients Currently Taking Vigabatrin (n [%])			
No	72 (58.1)	58 (77.3)	130 (65.3)
Yes	52 (41.9)	17 (22.7)	69 (34.7)
Patients Currently Taking Levetiracetam (n [%])			
No	92 (74.2)	51 (68.0)	143 (71.9)
Yes	32 (25.8)	24 (32.0)	56 (28.1)
Tonic-Clonic Seizures During Baseline (n [%])			
Yes	28 (22.6)	14 (18.7)	42 (21.1)
Tonic Seizures During Baseline (n [%])			
Yes	42 (33.9)	15 (20.0)	57 (28.6)
Clonic Seizures During Baseline (n [%])			
Yes	5 (4.0)	2 (2.7)	7 (3.5)
Atonic Seizures During Baseline (n [%])			
Yes	12 (9.7)	13 (17.3)	25 (12.6)
Absence Seizures During Baseline (n [%])			
Yes	15 (12.1)	7 (9.3)	22 (11.1)
Myoclonic Seizures During Baseline (n [%])			
Yes	8 (6.5)	4 (5.3)	12 (6.0)
Partial Sensory Seizures During Baseline (n [%])			
Yes	2 (1.6)	3 (4.0)	5 (2.5)
Infantile or Epileptic Spasms During Baseline (n [%])			
Yes	10 (8.1)	3 (4.0)	13 (6.5)

AED = antiepileptic drug; OLE = open-label extension; SD = standard deviation.
Note: Current AED use refers to the double-blind phase.
* Percentages are based on the number of patients not currently taking the AED.
Source: Section 8 OLE Table 3.2; Appendix 2 OLE Listing 3.2, OLE Listing 8.1.1, OLE Listing 8.1.2, and OLE Listing 8.2.1.

Assessor's comments

The numbers and percentages of the antiepileptic use in study report section 4.5 do not correspond to the numbers reported in clinical overview and Table 4-4. The MAH is expected to explain. **(OC)**

Number analysed

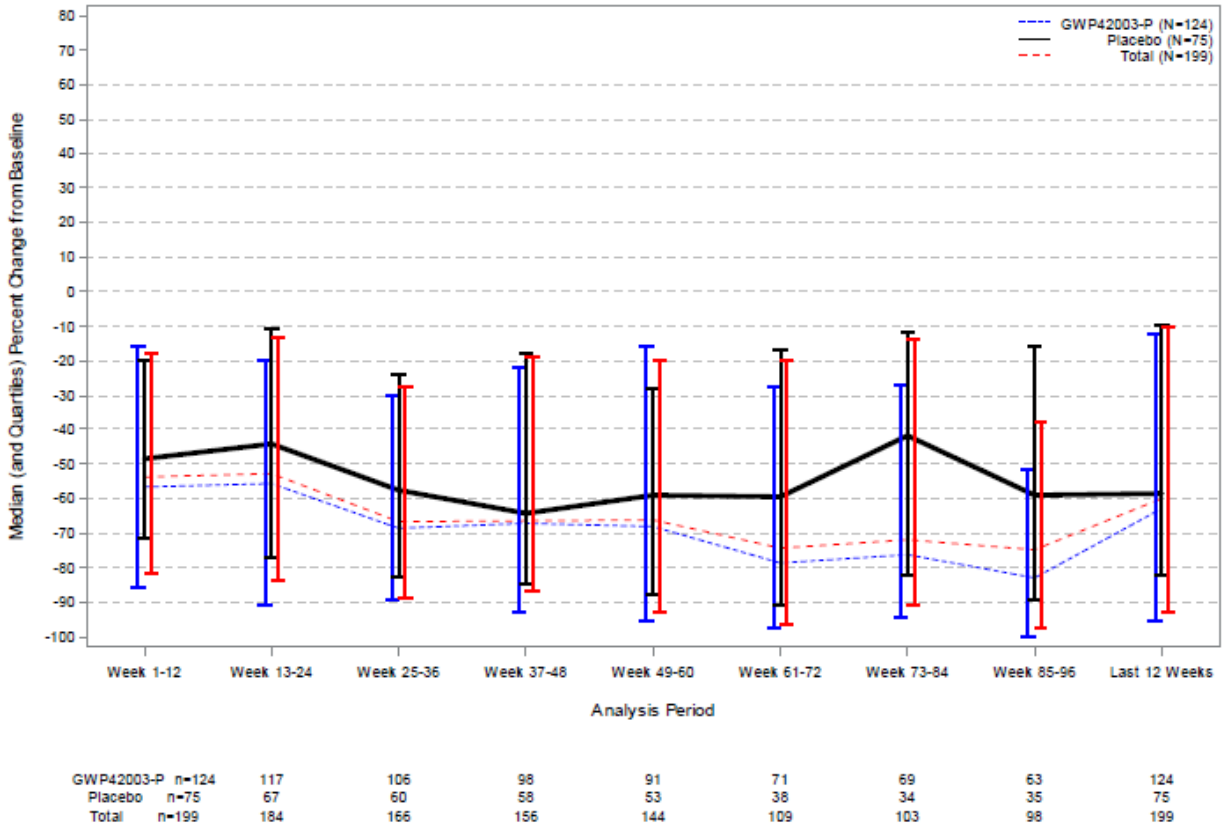
As this was an OLE study, there was no formal sample size calculation. All patients who wished to continue on IMP from the populations included in the double-blind phase of study GWEP1521 were eligible for inclusion. Approximately 210 patients were to be enrolled. Patients were considered enrolled in the study from the time of providing written informed consent/assent. A total of 199 patients from the double-blind phase enrolled in this OLE study and comprised the OLE safety analysis set, defined as all patients who received at least 1 dose of IMP in the OLE.

Efficacy results

Change in TSC-associated seizure frequency:

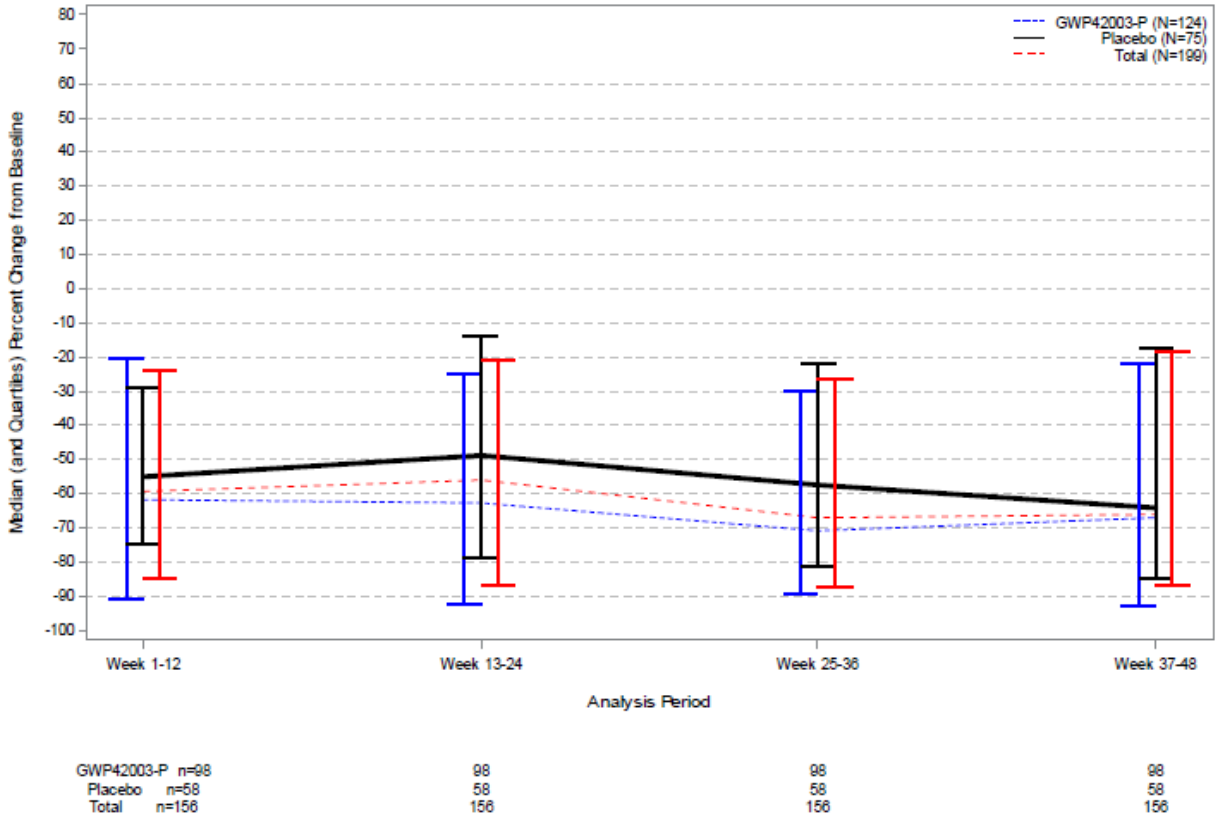
The percentage change in the frequency of TSC-associated seizures by 12-week period is presented in Figure 5-1.

Figure 5-1 Percentage Change in TSC-associated Seizure Frequency Over Time (OLE Safety Analysis Set)



To account for differences in sample size with increasing time, maintenance of efficacy was assessed in 156 patients treated for 37 to 48 weeks. The median percentage reductions in TSC-associated seizure frequency during the first 12 weeks of treatment were similar between patients who had been treated with GWP42003-P versus placebo during DBT and were sustained over time (Figure 5-2).

Figure 5-2 **Percentage Change in TSC-associated Seizure Frequency Over Time (Patients with Data in OLE Week 37 to 48) (OLE Safety Analysis Set)**



Assessor's comments

In double-blind phase, the median percent change from BL in TSC associated seizure frequency was -20 for placebo and -43.4 for 25 mg/kg/day group, meaning primary endpoint was met. During maintenance period, the results were -30% for placebo and -55% for 25 mg/kg/day group. Results were not better with 50 mg/kg/day subgroup.

Looking at all OLE population, the variability of response between placebo-active and active-active subgroups is way above the treatment effect observed in RCT. The MAH analysed 156 patients who were all treated for 37 to 48 weeks, and this analysis resulted in less variability. In this group, the placebo-active patients had an initial reduction in seizures followed by a slight worsening up to week 24 and ended up with similar reduction rate to active-active subgroup.

In SmPC it is stated that:

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was 61% during Week 1–12 (N = 199), which was maintained through to Week 37–48, with a median percentage reduction from baseline in TSC-associated seizure frequency of 68%."

However, the results reflected in Figure 5-1 do not seem to be in line with the reported information in SmPC. The MAH is requested to explain and discuss. **(OC)**

Treatment responders: The number of 50% responders for the 156 patients treated 37 to 48 weeks were similar for patients treated with GWP42003-P (59 [60%] patients) and for those treated with placebo (34 [59%] patients) during DBT and were sustained over time.

Assessor's comments

In double-blind phase, the proportion of patients with a ≥ 50% reduction from baseline in TSC-associated seizure frequency during the treatment period was higher in the 25 mg/kg/day group (36.0%) and 50 mg/kg/day group (39.7%) compared with the placebo group (22.4%). The OR for achieving a ≥ 50% reduction in TSC-associated seizure frequency, which was the first key secondary endpoint, did not reach statistical significance for the 25 mg/kg/day group.

In OLE phase overall, the number of 50% responders for the active-active subgroup was 70 (56%) and for the placebo-active was 36 (48%). These results are better than the double-blind period but with limitation of huge amount of discontinuations over time.

CGIC or SGIC score: At their last visit, the majority (71.9%) of caregivers and patients (combined) reported an improvement in overall condition (slightly improved, much improved, or very much improved) compared with their status before DBT. Thirty-four (17.9%) patients reported no change in their condition. When measured on a continuous scale, the mean S/CGIC score at the last visit was 2.7, which corresponds to "slightly improved."

Change in total seizure frequency: Reductions were similar between patients treated with GWP42003-P and placebo in DBT and were sustained over time.

Patients experiencing worsening or improvement in seizure frequency: Relative to the pre randomization baseline of the double-blind phase, 139 (70%) patients were considered treatment responders with a ≥ 25% reduction in TSC-associated seizure frequency, 106 (53%) patients were considered treatment responders with a ≥ 50% reduction, 65 (33%) patients were considered treatment responders with a ≥ 75%, and 5 (3%) patients were considered treatment responders with a 100% reduction.

Assessor's comments

Relative to the pre-randomization baseline of the double-blind phase, the following numbers of patients saw a change in TSC-associated seizure frequency: 21 (11%) patients experienced a > 25% worsening, 39 (20%) patients experienced −25% to +25% change ('no change'), 33 (17%) patients experienced 25% to 50% improvement, 41 (21%) patients experienced 50% to 75% improvement, and 65 (33%) patients experienced > 75% improvement.

OLE Table 9.1.2.1: Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom (OLE Safety Analysis Set)

Analysis Visit (N)	Responders		Double-Blind Phase Treatment GWP42003-P (N=124)	Placebo (N=75)	Total (N=199)
Last 12 Weeks	No Baseline Period Seizures		0	0	0
	>25% (Increase)		19 (15%)	11 (15%)	30 (15%)
	>=0% to <=25% (Increase)		5 (4%)	6 (8%)	11 (6%)
	>-25% to <0% (Reduction)		14 (11%)	6 (8%)	20 (10%)
	>-50% to <=-25% (Reduction)		16 (13%)	11 (15%)	27 (14%)
	>-75% to <=-50% (Reduction)		18 (15%)	15 (20%)	33 (17%)
	<=-75% (Reduction)		52 (42%)	26 (35%)	78 (39%)
	>=25%	Yes	86 (69%)	52 (69%)	138 (69%)
		No	38 (31%)	23 (31%)	61 (31%)
	>=50%	Yes	70 (56%)	41 (55%)	111 (56%)
		No	54 (44%)	34 (45%)	88 (44%)
	>=75%	Yes	52 (42%)	26 (35%)	78 (39%)
		No	72 (58%)	49 (65%)	121 (61%)
	100%	Yes	22 (18%)	5 (7%)	27 (14%)
		No	102 (82%)	70 (93%)	172 (86%)

TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and tonic-clonic, tonic, clonic or atonic seizures.
Baseline period includes all data prior to Day 1 of the double-blind phase.
OLE last 12 weeks is defined as all available data from 12 weeks prior to the earliest of the OLE completion date or the last call to IVRS.

Source: OLE Listings 8.1.1 and 8.2.1

OLE Table 9.1.2.1: Summary of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom (OLE Safety Analysis Set)

Analysis Visit (N)	Responders		Double-Blind Phase Treatment GWP42003-P (N=124)	Placebo (N=75)	Total (N=199)
OLE Treatment Period	No Baseline Period Seizures		0	0	0
	>25% (Increase)		14 (11%)	7 (9%)	21 (11%)
	>=0% to <=25% (Increase)		8 (6%)	7 (9%)	15 (8%)
	>-25% to <0% (Reduction)		16 (13%)	8 (11%)	24 (12%)
	>-50% to <=-25% (Reduction)		16 (13%)	17 (23%)	33 (17%)
	>-75% to <=-50% (Reduction)		27 (22%)	14 (19%)	41 (21%)
	<=-75% (Reduction)		43 (35%)	22 (29%)	65 (33%)
	>=25%	Yes	86 (69%)	53 (71%)	139 (70%)
		No	38 (31%)	22 (29%)	60 (30%)
	>=50%	Yes	70 (56%)	36 (48%)	106 (53%)
		No	54 (44%)	39 (52%)	93 (47%)
	>=75%	Yes	43 (35%)	22 (29%)	65 (33%)
		No	81 (65%)	53 (71%)	134 (67%)
	100%	Yes	5 (4%)	0	5 (3%)
		No	119 (96%)	75 (100%)	194 (97%)

TSC-associated seizures include: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and tonic-clonic, tonic, clonic or atonic seizures.
Baseline period includes all data prior to Day 1 of the double-blind phase.
OLE last 12 weeks is defined as all available data from 12 weeks prior to the earliest of the OLE completion date or the last call to IVRS.

Source: OLE Listings 8.1.1 and 8.2.1

During last 12 weeks, 15% of the patients in OLE experienced seizure worsening of more than 25% or 6% experienced seizure increase up to 25%. During overall OLE period, these numbers were 11% and 8%, respectively.

In the SmPC it states that:

"In the controlled trial in TSC patients, an increased frequency of adverse events associated with seizure worsening was seen at doses above 25 mg/kg/day. Although no clear pattern was established, the adverse events reflected increased seizure frequency or intensity, or new seizure types. The frequency of adverse events associated with seizure worsening was 11% for patients taking 25 mg/kg/day cannabidiol and 18% for patients taking cannabidiol doses greater than 25 mg/kg/day, compared to 9% in patients taking placebo."

The MAH is expected to discuss frequency of seizure worsening at doses below and above 25 mg/kg/day during OLE phase and update SmPC with the new information available. **(OC)**

Change in number of 'other' types of seizures: Relative to the pre-randomization baseline of DBT, patients experienced a reduction in the overall frequency of 'other' seizure types with the median (lower quartile, upper quartile) percentage change from baseline during the OLE treatment period of -87.97 (-100.00, -55.56). 'Other' seizure types included absence, myoclonic, focal sensory, and infantile/epileptic spasms.

Assessor's comments

In double-blind phase, 2 patients (2.7%) in the 25 mg/kg/day group and 1 patient (1.3%) in the placebo group had status epilepticus. The number of patients with status epilepticus was 10.1%, much higher in OLE phase.

In SmPC status epilepticus is mentioned in section 4.4: "In the phase 3 clinical trials investigating LGS, DS and TSC, the observed frequency of status epilepticus was similar between the cannabidiol and placebo groups."

The MAH is requested to discuss and update SmPC accordingly. **(OC)**

OLE Table 9.11: Summary of Patients with Status Epilepticus
(OLE Safety Analysis Set)

Parameter	Analysis Period		Double-Blind Phase Treatment GWP42003-P (N=124)	Placebo (N=75)	Total (N=199)
Number of Patients with Status Epilepticus	Baseline Period	Yes	2 (1.6%)	3 (4.0%)	5 (2.5%)
		No	122 (98.4%)	72 (96.0%)	194 (97.5%)
	OLE Last 12 Weeks	Yes	4 (3.2%)	1 (1.3%)	5 (2.5%)
		No	120 (96.8%)	74 (98.7%)	194 (97.5%)
	OLE Treatment Period	Yes	13 (10.5%)	7 (9.3%)	20 (10.1%)
		No	111 (89.5%)	68 (90.7%)	179 (89.9%)

Baseline period includes all data prior to Day 1 of the double-blind phase.
OLE last 12 weeks is defined as all available data from 12 weeks prior to the earliest of the OLE completion date or the last call to IVRS.

Source: OLE Listing 8.2.5

Change in PGIC: Mean (SD) PGIC score at the last visit of the OLE phase was 2.9 (1.21) corresponding to "slightly improved".

Changes in QOLCE Score: Mean (SD) change from baseline in QOLCE score was –4.3 (13.39) for patients aged 2 to 18 years.

Growth and Development (patients < 18 years of age): Relative to the pre-randomization baseline of DBT, the mean (SD) change from baseline in IGF-1 (in nmol/L) was–0.54 (9.069) for patients treated with GWP42003P and –1.00 (9.057) for patients who had received placebo during DBT.

At the end of the OLE, 1 (5.6%) patient was Tanner Stage 1, 2 (11.1%) patients were Stage 2, 5 (27.8%) patients were Stage 3, 1 (5.6%) patient was Stage 4, and 9 (50.0%) patients were Stage 5.

Safety results

Safety data are presented for the Safety Analysis Set, defined as all patients who received at least 1 dose of GWP42003-P in the study.

A total of 192 (96.5%) patients had 1 or more TEAEs during the study: 117 (94.4%) patients treated with GWP42003-P and 75 (100.0%) patients treated with placebo during the double-blind phase. Overall, the adverse-event (AE) profiles were similar between the double-blind treatment groups although, when compared to patients treated with GWP42003-P, the number of treatment-related TEAEs was higher in patients treated with placebo during the double-blind phase.

TEAEs reported in ≥ 3% of patients are summarised by PT in Table 4. Overall, the most frequently reported TEAE PTs were diarrhoea (93 [46.7%] patients), seizure (59 [29.6%] patients), pyrexia (48 [24.1%] patients), decreased appetite (47 [23.6%] patients), vomiting (40 [20.1%] patients), somnolence (39 [19.6%] patients), and nasopharyngitis (35 [(17.6%] patients).

Table 4 **Summary of Treatment-emergent Adverse Events Reported in ≥ 3% of Patients by System Organ Class and Preferred Term (Safety Analysis Set)**

System Organ Class Preferred Term	Double-blind Treatment GWP42003-P (N = 124) n (%)	Double-blind Treatment Placebo (N = 75) n (%)	Total (N=199) n (%)
Patients Reporting Any TEAEs	**117 (94.4%)**	**75 (100.0%)**	**192 (96.5%)**
Blood and lymphatic system disorders	**11 (8.9%)**	**8 (10.7%)**	**19 (9.5%)**
Anaemia	4 (3.2%)	2 (2.7%)	6 (3.0%)
Gastrointestinal disorders	**72 (58.1%)**	**55 (73.3%)**	**127 (63.8%)**
Diarrhoea	50 (40.3%)	43 (57.3%)	93 (46.7%)
Vomiting	27 (21.8%)	13 (17.3%)	40 (20.1%)
Constipation	12 (9.7%)	9 (12.0%)	21 (10.6%)
Abdominal pain	4 (3.2%)	3 (4.0%)	7 (3.5%)
Nausea	3 (2.4%)	4 (5.3%)	7 (3.5%)
Retching	3 (2.4%)	3 (4.0%)	6 (3.0%)
General disorders and administration site conditions	**42 (33.9%)**	**26 (34.7%)**	**68 (34.2%)**
Pyrexia	33 (26.6%)	15 (20.0%)	48 (24.1%)
Fatigue	7 (5.6%)	10 (13.3%)	17 (8.5%)
Infections and infestations	**80 (64.5%)**	**51 (68.0%)**	**131 (65.8%)**
Upper respiratory tract infection	22 (17.7%)	10 (13.3%)	32 (16.1%)
Nasopharyngitis	19 (15.3%)	16 (21.3%)	35 (17.6%)
Influenza	16 (12.9%)	4 (5.3%)	20 (10.1%)
Pharyngitis streptococcal	13 (10.5%)	4 (5.3%)	17 (8.5%)
Otitis media	8 (6.5%)	4 (5.3%)	12 (6.0%)
Conjunctivitis	8 (6.5%)	3 (4.0%)	11 (5.5%)
Pharyngitis	8 (6.5%)	2 (2.7%)	10 (5.0%)
Gastroenteritis viral	7 (5.6%)	3 (4.0%)	10 (5.0%)
Urinary tract infection	7 (5.6%)	3 (4.0%)	10 (5.0%)
Sinusitis	7 (5.6%)	2 (2.7%)	9 (4.5%)
Ear infection	6 (4.8%)	3 (4.0%)	9 (4.5%)
Pneumonia	5 (4.0%)	3 (4.0%)	8 (4.0%)
Gastroenteritis	5 (4.0%)	2 (2.7%)	7 (3.5%)
Viral infection	4 (3.2%)	5 (6.7%)	9 (4.5%)
Viral upper respiratory tract infection	4 (3.2%)	3 (4.0%)	7 (3.5%)
Bronchitis	2 (1.6%)	5 (6.7%)	7 (3.5%)
Injury, poisoning and procedural complications	**34 (27.4%)**	**24 (32.0%)**	**58 (29.1%)**
Fall	13 (10.5%)	8 (10.7%)	21 (10.6%)
Laceration	9 (7.3%)	4 (5.3%)	13 (6.5%)
Contusion	6 (4.8%)	4 (5.3%)	10 (5.0%)
Tooth fracture	5 (4.0%)	1 (1.3%)	6 (3.0%)
Investigations	**38 (30.6%)**	**37 (49.3%)**	**75 (37.7%)**
Alanine aminotransferase increased	8 (6.5%)	6 (8.0%)	14 (7.0%)
Weight decreased	7 (5.6%)	9 (12.0%)	16 (8.0%)
Aspartate aminotransferase increased	6 (4.8%)	4 (5.3%)	10 (5.0%)
Gamma-glutamyltransferase increased	4 (3.2%)	9 (12.0%)	13 (6.5%)
Weight increased	3 (2.4%)	3 (4.0%)	6 (3.0%)
Liver function test increased	2 (1.6%)	6 (8.0%)	8 (4.0%)
Metabolism and nutrition disorders	**28 (22.6%)**	**28 (37.3%)**	**56 (28.1%)**
Decreased appetite	23 (18.5%)	24 (32.0%)	47 (23.6%)
Dehydration	6 (4.8%)	4 (5.3%)	10 (5.0%)
Nervous system disorders	**66 (53.2%)**	**43 (57.3%)**	**109 (54.8%)**
Seizure	40 (32.3%)	19 (25.3%)	59 (29.6%)
Somnolence	15 (12.1%)	24 (32.0%)	39 (19.6%)
Headache	9 (7.3%)	5 (6.7%)	14 (7.0%)
Status epilepticus	9 (7.3%)	1 (1.3%)	10 (5.0%)
Dizziness	5 (4.0%)	4 (5.3%)	9 (4.5%)
Ataxia	4 (3.2%)	5 (6.7%)	9 (4.5%)
Generalised tonic-clonic seizure	4 (3.2%)	2 (2.7%)	6 (3.0%)
Lethargy	3 (2.4%)	5 (6.7%)	8 (4.0%)
Sedation	2 (1.6%)	4 (5.3%)	6 (3.0%)

Psychiatric disorders	**47 (37.9%)**	**32 (42.7%)**	**79 (39.7%)**
Irritability	9 (7.3%)	5 (6.7%)	14 (7.0%)
Agitation	7 (5.6%)	2 (2.7%)	9 (4.5%)
Abnormal behaviour	6 (4.8%)	5 (6.7%)	11 (5.5%)
Sleep disorder	6 (4.8%)	4 (5.3%)	10 (5.0%)
Aggression	5 (4.0%)	9 (12.0%)	14 (7.0%)
Insomnia	5 (4.0%)	6 (8.0%)	11 (5.5%)
Anxiety	4 (3.2%)	3 (4.0%)	7 (3.5%)
Respiratory, thoracic and mediastinal disorders	**34 (27.4%)**	**26 (34.7%)**	**60 (30.2%)**
Cough	13 (10.5%)	13 (17.3%)	26 (13.1%)
Nasal congestion	7 (5.6%)	5 (6.7%)	12 (6.0%)
Oropharyngeal pain	6 (4.8%)	5 (6.7%)	11 (5.5%)
Rhinorrhoea	6 (4.8%)	4 (5.3%)	10 (5.0%)
Skin and subcutaneous tissue disorders	**21 (16.9%)**	**15 (20.0%)**	**36 (18.1%)**
Rash	8 (6.5%)	4 (5.3%)	12 (6.0%)

TEAE = Treatment-emergent adverse event.
Source: OLE CSR Table 5-5.

Assessor's comments

Specifically, for somnolence, sedation, weight decrease, decreased appetite and liver function test abnormalities, there are much more frequent events in placebo-active group. This is assumed to be due to titration of cannabidiol and confirms the relationship to treatment for these events which are already included in 4.8.

In SmPC section 4.8 it states that:

"Somnolence and sedation

Somnolence and sedation (including lethargy) events have been observed in controlled trials (see section 4.4) with cannabidiol in LGS, DS and TSC, including 29% of cannabidiol-treated patients (30% of patients taking cannabidiol 20 or 25 mg/kg/day and 27% of patients taking cannabidiol 10 mg/kg/day). These adverse reactions were observed at higher incidences at dosages above 25 mg/kg/day in the controlled study in TSC. The rate of somnolence and sedation (including lethargy) was higher in patients on concomitant clobazam (43% in cannabidiol-treated patients taking clobazam, compared with 14% in cannabidiol-treated patients not on clobazam)."

In OLE phase, Clobazam use seems to be higher than double-blind phase but somnolence is same, 19.6 versus 19.6%, respectively. The Applicant is requested to discuss sedation, somnolence and their relationship to other antiepileptics versus cannabidiol dose or titration phase. **(OC)**

Of the patients with TEAEs, most experienced events of moderate intensity (55.8%) when assessed by maximal severity.

One patient died 2 months after starting the open-label GWP42003 P treatment. This fatal TEAE of cardiopulmonary failure due to TSC was considered by the investigator to be unrelated to the IMP. The patient died in their sleep with no immediate cause of death (the sudden, unexpected death of someone with epilepsy was not noted). Confounding factors in the patient history included idiopathic dilated cardiomyopathy, congestive heart failure/left ventricular hypertrophy, hypertension, and TSC with renal and cardiac involvement.

SAEs reported for ≥ 1% of patients regardless of relationship to IMP are summarised in Table 5. The most frequently reported treatment-emergent SAEs were seizure (16 [8.0%] patients), status epilepticus (10 [5.0%] patients), dehydration (6 [3.0%] patients), influenza (5 [2.5%] patients), and pneumonia (5 [2.5%] patients). Treatment-related serious TEAEs were reported for 15 (7.5%) patients; the most common was transaminases increased (2 [1.0%] patients).

Table 5 Summary of Serious Treatment-emergent Adverse Events Experienced by ≥ 1% of Patients Overall (OLE Safety Analysis Set)			
	Double-blind Treatment		
System Organ Class Preferred Term	GWP42003-P (N = 124) n (%)	Placebo (N = 75) n (%)	Total (N = 199) n (%)
Patients Reporting Any Serious TEAEs	**38 (30.6%)**	**18 (24.0%)**	**56 (28.1%)**
Infections and infestations	**15 (12.1%)**	**5 (6.7%)**	**20 (10.1%)**
Pneumonia	4 (3.2%)	1 (1.3%)	5 (2.5%)
Influenza	5 (4.0%)	0	5 (2.5%)
Adenovirus infection	2 (1.6%)	0	2 (1.0%)
Injury, poisoning and procedural complications	**4 (3.2%)**	**1 (1.3%)**	**5 (2.5%)**
Toxicity to various agents	1 (0.8%)	1 (1.3%)	2 (1.0%)
Investigations	**7 (5.6%)**	**7 (9.3%)**	**14 (7.0%)**
Transaminases increased	0	2 (2.7%)	2 (1.0%)
Alanine aminotransferase increased	1 (0.8%)	1 (1.3%)	2 (1.0%)
Aspartate aminotransferase increased	1 (0.8%)	1 (1.3%)	2 (1.0%)
Liver function test increased	1 (0.8%)	1 (1.3%)	2 (1.0%)
Platelet count decreased	1 (0.8%)	1 (1.3%)	2 (1.0%)
Metabolism and nutrition disorders	**5 (4.0%)**	**3 (4.0%)**	**8 (4.0%)**
Dehydration	4 (3.2%)	2 (2.7%)	6 (3.0%)
Decreased appetite	1 (0.8%)	1 (1.3%)	2 (1.0%)
Nervous system disorders	**22 (17.7%)**	**7 (9.3%)**	**29 (14.6%)**
Seizure	12 (9.7%)	4 (5.3%)	16 (8.0%)
Status epilepticus	9 (7.3%)	1 (1.3%)	10 (5.0%)
Lethargy	1 (0.8%)	1 (1.3%)	2 (1.0%)
Psychiatric disorders	**2 (1.6%)**	**0**	**2 (1.0%)**
Mental status changes	2 (1.6%)	0	2 (1.0%)
Respiratory, thoracic and mediastinal disorders	**5 (4.0%)**	**2 (2.7%)**	**7 (3.5%)**
Pneumonitis	1 (0.8%)	1 (1.3%)	2 (1.0%)

OLE = Open-label extension; TEAE = treatment-emergent adverse event.
Source: OLE CSR Table 5-7.

The most common TEAEs that led to discontinuation of IMP were diarrhoea (4 [2.0%] patients), seizure (4 [2.0%] patients), liver function test increased (2 [1.0%] patients), and decreased appetite (2 [1.0%] patients).

The mean changes in clinical laboratory values and vital signs were similar between the patients, regardless of their double-blind phase treatment. When considering changes in transaminases, increases in ALT or AST > 3 × ULN occurred in 6 (4.8%) patients who had been treated with GWP42003-P during the double-blind phase and 14 (18.7%) patients who had been treated with placebo during the double-blind phase, while increases in ALT or AST > 5 × ULN occurred in no patients who had been treated with GWP42003-P during the double-blind phase and in 4 (5.3%) patients who had been treated with placebo during the double-blind phase. Some of the transaminase elevations were reported as AEs and led to discontinuation from the study if they met protocol-defined withdrawal criteria. No patient in the study met laboratory criteria for Hy's Law. There was a mean increase from baseline in creatinine (Enzymatic) at EoT of 2.8 µmol/L for patients who had been treated with GWP42003-P during the double-blind phase (n = 22) and 1.5 µmol/L for patients who had been treated with placebo during the double-blind phase (n = 16). Using the Jaffe method, the mean (SD) increase from baseline in creatinine at EoT was 2.3 (8.36) µmol/L for patients who had been treated with GWP42003-P during the double-blind phase (n = 19) and 8.3 (5.12) µmol/L for patients who had been treated with placebo during the double-blind phase (n = 12).

ECG data are summarized by time point and double-blind phase treatment groups. The QTcB results did not show any important increases. Of the 5 patients that had clinically significant ECG parameters

indicative of an AE, 2 patients had ECG-related TEAEs reported. One TEAE each of right atrial enlargement and left ventricular hypertrophy were reported in 1 patient treated with GWP42003-P during the double blind phase on OLE Day 183 and 1 TEAE of ECG QTc interval prolonged was reported in 1 patient treated with GWP42003-P during the doubleblind phase on OLE Day 190. One patient treated with GWP42003-P during the double-blind phase had a clinically significant ECG parameter that was not reported as an AE. Overall, there was no clear signal for a QTc prolongation during the OLE phase of the study.

Assessor's comments

The signals observed with TEAEs leading to discontinuation and laboratory-vital values were in line with the safety profile reflected in SMPC.

There were 5 patients who had clinically significant ECG parameters indicative of an AE and 1 patient who was not reported as AE. A further thorough QTc trial in the fed state is scheduled to provide robust additional data on any CBD-OS effect on QTc at therapeutic and supra-therapeutic exposures. The applicant will submit the trial results to the EMA upon completion of the trial. This was estimated to be September 2021. The MAH is requested to give updates on this trial. **(OC)**

2.3.3. Discussion on clinical aspects

The MAH concludes that the results from the open-label phase of study GWEP1521 confirmed that GWP42003-P had a positive effect on seizure control when used as a long-term adjunctive therapy and displayed a safety profile similar to that established in other short- and long-term pivotal studies in the clinical development program with GWP42003-P in patients with refractory epilepsies. No new safety concerns were identified that could result in an update to the current Summary of Product Characteristics as the benefit-risk balance remains unchanged. Therefore, no regulatory consequence is identified.

Assessor's comments

On December 14th 2021, the MAH submitted a clinical study report as well as a critical clinical overview describing the results for the Study GWEP1521. A decision for PIP modification was attached: EMEA-001964-PIP01-16-M03, Modification 03 Decision.

Epidyolex, was designated as an orphan medicinal product EU/3/17/1959 on 17 January 2018 in treatment of tuberous sclerosis. Epidyolex was approved as an adjunctive treatment of seizures associated with tuberous sclerosis complex, for patients 2 years of age and older by the European Commission in April 2021. The clinical development program supporting this extension of indication comprises Study GWEP1521; a single, Phase III, randomised, placebo-controlled trial that investigated 25 mg/kg/day and 50 mg/kg/day CBD-OS for the treatment of TSC-associated seizures. The type II variation included data from:

- GWEP1521 trial in TSC, "Pool TSC" (double-blind period, cutoff date 15 Feb 2019)

- Trial GWEP1521 OLE, "OLE TSC" (ongoing open-label period, cutoff date 26 Feb 2019).

The MAH is now submitting the study report for open label extension phase to fulfil 6 months reporting obligation (as part of PIP and fulfils the Art. 46 paediatric study criteria).

A total of 224 patients were randomized to double-blind phase of the study. Overall, 201 patients (89.7%) completed the double-blind phase and 199 patients (88.8%) entered the OLE phase of the trial, and only 34 patients completed OLE phase. At the time of MAA for TSC, 75.4% of OLE patients

were still ongoing. Approximately half of all patients were from the USA (51.8%), and the rest were from EU and Australia.

"Other reason" was the most frequent reason for withdrawal. Among the 108 patients who had "other reason" for withdrawal, 92 were withdrawn because they transitioned to commercial product. 18 patients were withdrawn due to adverse events.

During evaluation of indication extension, long-term safety data for approved dose was not considered adequate in accordance with requirements of ICH E1 guidance (CPMP/ICH/375/95). In RCT, the exposure was 21.11 patient-years (75 patients, 16 weeks) for 25 mg/kg/day group. Overall, 88 patients across the double-blind phase and OLE have been exposed to CBD OS > 1 year. Due to orphan designation, the supportive data from other sources was taken into consideration as support. In the current study report, the mean time on treatment went up from 317.8 days (n=223) to 631 days (n=199), min-max were 18-1462 days. Overall, more than half of the patients stayed at or below 25 mg/kg/day dose during OLE phase. During evaluation of safety profile in OLE, this should be taken into consideration.

Number of patients who need dose modification and reasons were not summarized by the MAH. This is not pursued due to clear recommendation that 25 mg/kg/day is the maximum recommended dose in this indication.

The MAH highlights, that no changes to the product information including the SmPC are proposed. This is not agreed and is subject to further discussion and evaluation of answers to other concerns raised in section 4 and presented below.

Baseline data:

The numbers and percentages of the antiepileptic use in study report section 4.5 do not correspond to the numbers reported in clinical overview and Table 4-4. The MAH is expected to explain. (OC)

Efficacy:

In double-blind phase, the median percent change from BL in TSC associated seizure frequency was -20 for placebo and -43.4 for 25 mg/kg/day group, meaning primary endpoint was met. During double-blind maintenance period, the results were -30% for placebo and -55% for 25 mg/kg/day group. Results were not better with 50 mg/kg/day subgroup. Looking at all OLE population, the variability of response between placebo-active and active-active subgroups is way above the treatment effect observed in RCT. To decrease impact of time, the MAH analysed 156 patients who were all treated for 37 to 48 weeks, and this analysis resulted in less variability. In this group, the placebo-active patients had an initial reduction in seizures followed by a slight worsening up to week 24 and ended up with similar reduction rate to active-active subgroup. In SmPC it is stated that: "Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was 61% during Week 1–12 (N = 199), which was maintained through to Week 37–48, with a median percentage reduction from baseline in TSC-associated seizure frequency of 68%." However, the results reflected in Figure 5-1 do not seem to be in line with the reported information in SmPC. The MAH is requested to explain and discuss. (OC)

In double-blind phase, the proportion of patients with a ≥ 50% reduction from baseline in TSC-associated seizure frequency during the treatment period was higher in the 25 mg/kg/day group (36.0%) and 50 mg/kg/day group (39.7%) compared with the placebo group (22.4%). The OR for achieving a ≥ 50% reduction in TSC-associated seizure frequency, which was the first key secondary endpoint, did not reach statistical significance for the 25 mg/kg/day group. In OLE phase overall, the number of 50% responders for the active-active subgroup was 70 (56%) and for the placebo-active

was 36 (48%). These results are better than the double-blind period but with limitation of the huge amount of discontinuations over time.

Relative to the pre-randomization baseline of the double-blind phase, 21 (11%) patients experienced a > 25% worsening and 39 (20%) patients experienced −25% to +25% change ('no change'). Meanwhile for OLE phase, during last 12 weeks 15% of the patients experienced seizure worsening of more than 25% or 6% experienced seizure increase up to 25%. During all OLE period, these numbers were 11% and 8%, respectively. In the SmPC it states that: "In the controlled trial in TSC patients, an increased frequency of adverse events associated with seizure worsening was seen at doses above 25 mg/kg/day. Although no clear pattern was established, the adverse events reflected increased seizure frequency or intensity, or new seizure types. The frequency of adverse events associated with seizure worsening was 11% for patients taking 25 mg/kg/day cannabidiol and 18% for patients taking cannabidiol doses greater than 25 mg/kg/day, compared to 9% in patients taking placebo." The MAH is expected to discuss frequency of seizure worsening at doses below and above 25 mg/kg/day during OLE phase and update SmPC with the new information available. (OC)

Safety:

In double-blind phase, 2 patients (2.7%) in the 25 mg/kg/day group and 1 patient (1.3%) in the placebo group had status epilepticus. The number of patients with status epilepticus was 10.1%, much higher in OLE phase. In SmPC status epilepticus is mentioned in section 4.4: "In the phase 3 clinical trials investigating LGS, DS and TSC, the observed frequency of status epilepticus was similar between the cannabidiol and placebo groups." The MAH is requested to discuss and update SmPC with information from OLE phase. (OC)

Somnolence, sedation, weight decrease, decreased appetite and liver function test abnormalities were more frequently observed in placebo-active group. This is assumed to be due to titration of cannabidiol and confirms the relationship to treatment for these events which are already included in 4.8. In SmPC section 4.8 it states that: "Somnolence and sedation (including lethargy) events have been observed in controlled trials (see section 4.4) with cannabidiol in LGS, DS and TSC, including 29% of cannabidiol-treated patients (30% of patients taking cannabidiol 20 or 25 mg/kg/day and 27% of patients taking cannabidiol 10 mg/kg/day). These adverse reactions were observed at higher incidences at dosages above 25 mg/kg/day in the controlled study in TSC. The rate of somnolence and sedation (including lethargy) was higher in patients on concomitant clobazam (43% in cannabidiol-treated patients taking clobazam, compared with 14% in cannabidiol-treated patients not on clobazam)." In OLE phase, Clobazam use seems to be higher than double-blind phase but somnolence is same, 19.6 versus 19.6%, respectively. The Applicant is requested to discuss sedation, somnolence and their relationship to other antiepileptics versus cannabidiol dose or titration phase. (OC)

There were 5 patients who had clinically significant ECG parameters indicative of an AE and 1 patient who was not reported as AE. A further thorough QTc trial in the fed state is scheduled to provide robust additional data on any CBD-OS effect on QTc at therapeutic and supra-therapeutic exposures. The applicant will submit the trial results to the EMA upon completion of the trial. This was estimated to be September 2021. The MAH is requested to give updates on this trial. (OC)

3. Rapporteur's overall conclusion and recommendation

In general, the benefit-risk assessment for Epidyolex (cannabidiol) currently remains positive.

Based on the data submitted (see Requests for supplementary informations/Assessments of responses hereafter), section 5.1 of the SmPC should be updated as follows:

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. *The median modal dosage was 25 mg/kg/day and median treatment period was 90 weeks (range: 2.6-209 weeks).* In the OLE, the median percentage reduction from baseline in TSC associated seizure frequency was *54%* during Week 1–12 (N = 199), which was maintained through to *Week 85-96 (N = 98)*, with a median percentage reduction from baseline in TSC associated seizure frequency of *75%*. ~~*Additional seizure frequency data collected for up to 3 years demonstrated seizure reduction and safety outcomes consistent with the results from the other pivotal studies*~~".

The MAH should submit a variation in accordance without any delay and ***no later than 60 days after the receipt*** of these conclusions.

4. Request for supplementary information

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

Other Concerns

1. The numbers and percentages of the antiepileptic use in study report section 4.5 do not correspond to the numbers reported in clinical overview and Table 4-4. The MAH is expected to explain.
2. In SmPC it is stated that: "Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was 61% during Week 1–12 (N = 199), which was maintained through to Week 37–48, with a median percentage reduction from baseline in TSC-associated seizure frequency of 68%." However, the results reflected in Figure 5-1 do not seem to be in line with the reported information in SmPC. The MAH is requested to explain and discuss.
3. Relative to the pre-randomization baseline of the double-blind phase, 21 (11%) patients experienced a > 25% worsening and 39 (20%) patients experienced −25% to +25% change ('no change'). Meanwhile for OLE phase, during last 12 weeks 15% of the patients experienced seizure worsening of more than 25% or 6% experienced seizure increase up to 25%. During all OLE period, these numbers were 11% and 8%, respectively. In the SmPC it states that: "In the controlled trial in TSC patients, an increased frequency of adverse events associated with seizure worsening was seen at doses above 25 mg/kg/day. Although no clear pattern was established, the adverse events reflected increased seizure frequency or intensity, or new seizure types. The frequency of adverse events associated with seizure worsening was 11% for patients taking 25 mg/kg/day cannabidiol and 18% for patients taking cannabidiol doses greater than 25 mg/kg/day, compared to 9% in patients taking placebo." The MAH is expected to discuss frequency of seizure worsening at doses below and above 25 mg/kg/day during OLE phase and update SmPC with the new information available.
4. In double-blind phase, 2 patients (2.7%) in the 25 mg/kg/day group and 1 patient (1.3%) in the placebo group had status epilepticus. The number of patients with status epilepticus was 10.1%, much higher in OLE phase. In SmPC status epilepticus is mentioned in section 4.4: "In

the phase 3 clinical trials investigating LGS, DS and TSC, the observed frequency of status epilepticus was similar between the cannabidiol and placebo groups." The MAH is requested to discuss and update SmPC with information from OLE phase.

5. Somnolence and sedation were more frequently observed in placebo-active group. In SmPC section 4.8 it states that: "Somnolence and sedation (including lethargy) events have been observed in controlled trials (see section 4.4) with cannabidiol in LGS, DS and TSC, including 29% of cannabidiol-treated patients (30% of patients taking cannabidiol 20 or 25 mg/kg/day and 27% of patients taking cannabidiol 10 mg/kg/day). These adverse reactions were observed at higher incidences at dosages above 25 mg/kg/day in the controlled study in TSC. The rate of somnolence and sedation (including lethargy) was higher in patients on concomitant clobazam (43% in cannabidiol-treated patients taking clobazam, compared with 14% in cannabidiol-treated patients not on clobazam)." In OLE phase, Clobazam use seems to be higher than double-blind phase but somnolence is same, 19.6 versus 19.6%, respectively. The Applicant is requested to discuss sedation, somnolence and their relationship to other antiepileptics versus cannabidiol dose or titration phase.

6. There were 5 patients who had clinically significant ECG parameters indicative of an AE and 1 patient who was not reported as AE. A further thorough QTc trial in the fed state is scheduled to provide robust additional data on any CBD-OS effect on QTc at therapeutic and supra-therapeutic exposures. The applicant will submit the trial results to the EMA upon completion of the trial. This was estimated to be September 2021. The MAH is requested to give updates on this trial.

5. Assessment of MAH responses to Request for supplementary information

Question 1

The numbers and percentages of the antiepileptic use in study report section 4.5 do not correspond to the numbers reported in clinical overview and Table 4-4. The MAH is expected to explain.

Summary of the MAH Response

The MAH would like to clarify that Table 4-4 in the GWEP1521 OLE CSR describes the baseline characteristics prior to subjects starting the OLE phase of the study. CSR Section 4.5 is referring to the OLE data that includes any concomitant AEDs that started on or after the first dose of OLE IMP or any concomitant AEDs continued from the double-blind phase of GWEP1521. For example, 40.2% of patients were taking VPA at baseline (Table 4-4 OLE Table 3.2;) whereas 43.2% of patients took VPA concomitantly during the OLE phase (OLE Table 6.2).

Assessment of the MAH Response

The explanation is acknowledged.

Conclusion

Issue resolved.

Question 2

In SmPC it is stated that: "Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was 61% during Week 1–12 (N = 199), which was maintained through to Week 37–48, with a median percentage reduction from baseline in TSC-associated seizure frequency of 68%." However, the results reflected in Figure 5-1 do not seem to be in line with the reported information in SmPC. The MAH is requested to explain and discuss.

Summary of the MAH Response

The current EU-SmPC reflects the interim GWEP1521 CSR results submitted with the type II variation to add TSC as an indication for Epidyolex (EMA procedure EMEA/H/C/004675/II/0005, CHMP Opinion dated 25 February 2021).

On 09 March 2022, the MAH submitted a type II variation (procedure no: EMEA/H/C/004675/II/0020) which included a proposed update to the EU-SmPC to reflect the final GWEP1521 OLE results as follows:

Open-label data

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was ~~61~~54% during Weeks 1-12 (N = 199), which was maintained through to Weeks 37–48 (N = 156), with a median percentage reduction from baseline in TSC-associated seizure frequency of ~~68~~66%. In the TSC patients who reached at least Weeks 145-156 (N = 45), the median percentage

reduction from baseline in TSC-associated seizure frequency was 87%. The open-label data showed that cannabidiol had a sustained effect on seizure control when used as a long-term adjunctive therapy and displayed a safety profile similar to that established in other pivotal studies".

The above wording aligns with the results reflected in Figure 5-1 (GWEP1521 OLE CSR Table 9.1.1.1) and is pending review by the CHMP.

Assessment of the MAH Response

The proposed change is assessed.

Trial Code: GWEP1521 Open Label Extension
27 Oct 2021

GW pharmaceuticals

OLE Table 9.1.1.1: Summary of TSC-associated Seizure Frequency (OLE Safety Analysis Set)

Percent Change from Baseline

Analysis Period	Double-Blind Phase Treatment	n	Seizure Free	Mean	Standard Deviation	Lower Quartile	Median	Upper Quartile	Min	Max
Week 1-12	GWP42003-P (N=124)	124	8	-40.33	60.77	-85.94	-56.43	-15.76	-100.0	295.8
	Placebo (N=75)	75	3	-41.94	43.44	-71.43	-48.56	-19.61	-100.0	126.8
	Total (N=199)	199	11	-40.93	54.77	-81.69	-53.76	-17.69	-100.0	295.8
Week 13-24	GWP42003-P (N=124)	117	12	-31.98	108.69	-91.11	-55.36	-20.16	-100.0	850.0
	Placebo (N=75)	67	2	-36.80	50.81	-77.06	-44.06	-10.46	-100.0	100.8
	Total (N=199)	184	14	-33.73	91.79	-83.73	-52.75	-13.23	-100.0	850.0
Week 25-36	GWP42003-P (N=124)	106	11	-48.68	64.31	-88.98	-68.58	-30.30	-100.0	316.7
	Placebo (N=75)	60	4	-47.13	48.00	-82.33	-57.39	-23.75	-100.0	100.6
	Total (N=199)	166	15	-48.12	58.79	-88.44	-66.44	-27.40	-100.0	316.7
Week 37-48	GWP42003-P (N=124)	98	14	-42.27	75.97	-92.94	-67.19	-21.97	-100.0	372.7
	Placebo (N=75)	58	3	-47.80	50.07	-84.63	-64.21	-17.95	-100.0	112.7
	Total (N=199)	156	17	-44.32	67.38	-86.70	-66.27	-18.64	-100.0	372.7
Week 49-60	GWP42003-P (N=124)	91	16	-35.65	97.05	-95.11	-68.13	-15.97	-100.0	533.3
	Placebo (N=75)	53	5	-40.86	84.25	-87.78	-58.73	-28.15	-100.0	452.4
	Total (N=199)	144	21	-37.57	92.27	-92.80	-66.29	-20.29	-100.0	533.3
Week 61-72	GWP42003-P (N=124)	71	14	-25.18	221.22	-97.10	-78.80	-27.71	-100.0	1700.0
	Placebo (N=75)	38	7	-48.42	46.58	-91.11	-59.61	-16.98	-100.0	89.2
	Total (N=199)	109	21	-33.28	180.52	-96.11	-74.20	-19.63	-100.0	1700.0

Percent Change from Baseline

Analysis Period	Double-Blind Phase Treatment	n	Seizure Free	Mean	Standard Deviation	Lower Quartile	Median	Upper Quartile	Min	Max
Week 145-156	GWP42003-P (N=124)	34	11	-71.26	61.68	-100.00	-91.46	-78.71	-100.0	232.5
	Placebo (N=75)	11	3	-50.27	53.19	-100.00	-56.67	-10.33	-100.0	59.4
	Total (N=199)	45	14	-66.13	59.83	-100.00	-87.39	-56.67	-100.0	232.5
Week 157-168	GWP42003-P (N=124)	27	9	-83.06	20.66	-100.00	-93.16	-72.27	-100.0	-28.1
	Placebo (N=75)	5	0	-44.45	58.48	-82.70	-59.76	-35.39	-96.1	51.7
	Total (N=199)	32	9	-77.03	31.66	-100.00	-85.87	-61.90	-100.0	51.7
Week 169-180	GWP42003-P (N=124)	12	5	-86.25	19.32	-100.00	-94.61	-77.87	-100.0	-41.6
	Placebo (N=75)	3	0	-64.66	25.77	-94.40	-50.48	-49.10	-94.4	-49.1
	Total (N=199)	15	5	-81.93	21.63	-100.00	-91.30	-59.25	-100.0	-41.6
Week 181-192	GWP42003-P (N=124)	4	1	-73.47	25.71	-93.91	-75.89	-53.03	-100.0	-42.1
	Placebo (N=75)	1	0	-27.20		-27.20	-27.20	-27.20	-27.2	-27.2
	Total (N=199)	5	1	-64.22	30.40	-87.82	-63.96	-42.11	-100.0	-27.2
Week 193-204	GWP42003-P (N=124)	3	0	-64.18	19.18	-75.87	-74.62	-42.04	-75.9	-42.0
	Total (N=199)	3	0	-64.18	19.18	-75.87	-74.62	-42.04	-75.9	-42.0
Last 12 Weeks	GWP42003-P (N=124)	124	22	-24.82	135.95	-95.26	-62.95	-12.44	-100.0	868.5
	Placebo (N=75)	75	5	-35.07	67.11	-82.01	-58.53	-9.58	-100.0	205.1
	Total (N=199)	199	27	-28.68	114.85	-92.74	-60.00	-10.24	-100.0	868.5

Below update is considered acceptable. Instead of values for weeks 145-156 (when there are only 45 patients), the MAH should include information on dosing, duration of exposure and additional information on OLE phase. The mean time on treatment was 631 days (n=199) (min-max were 18-1462 days). More than half of the patients stayed at or below 25 mg/kg/day dose during OLE phase.

Open-label data

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. 34 patients completed OLE phase and median treatment period was 631 days (range:

18-1462). Following completion of the blinded transition, patients were to complete a 3-week titration up to a target dose of 50 mg/kg/day (Xx% of patients stayed at or below 25 mg/kg/day dose during OLE phase). In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was ~~61~~54% during Weeks 1-12 (N = 199), which was maintained through to Weeks 37–48 (N = 156)~~,~~ with a median percentage reduction from baseline in TSC-associated seizure frequency of ~~68~~66%. ~~In the TSC patients who reached at least Weeks 145-156 (N = 45), the median percentage reduction from baseline in TSC-associated seizure frequency was 87%. The open-label data showed that cannabidiol had a sustained effect on seizure control when used as a long-term adjunctive therapy and displayed a safety profile similar to that established in other pivotal studies~~".

The MAH is requested to update accordingly **(OC)**.

Conclusion

Issue partially resolved.

Question 3

Relative to the pre-randomization baseline of the double-blind phase, 21 (11%) patients experienced a > 25% worsening and 39 (20%) patients experienced −25% to +25% change ('no change'). Meanwhile for OLE phase, during last 12 weeks 15% of the patients experienced seizure worsening of more than 25% or 6% experienced seizure increase up to 25%. During all OLE period, these numbers were 11% and 8%, respectively. In the SmPC it states that: "In the controlled trial in TSC patients, an increased frequency of adverse events associated with seizure worsening was seen at doses above 25 mg/kg/day. Although no clear pattern was established, the adverse events reflected increased seizure frequency or intensity, or new seizure types. The frequency of adverse events associated with seizure worsening was 11% for patients taking 25 mg/kg/day cannabidiol and 18% for patients taking cannabidiol doses greater than 25 mg/kg/day, compared to 9% in patients taking placebo." The MAH is expected to discuss frequency of seizure worsening at doses below and above 25 mg/kg/day during OLE phase and update SmPC with the new information available.

Summary of the MAH Response

The MAH would like to confirm that the Epidyolex EU-SmPC wording in Section 4.8, cited in the question with respect to seizure worsening in the GWEP1521 RCT, was based on AE reporting rather than seizure count data captured as part of the efficacy endpoints in both phases of the study and referenced in the first part of the question; therefore, these frequencies cannot be directly compared. Given the nature of the disease in the patients in this study, with refractory epilepsy uncontrolled by the use of multiple AEDs, with the variation in seizure frequency, and exacerbation of seizures that can occur as part of the natural course of the disease, the focus of this response is based on the reporting of AEs that may be indicative of seizure worsening, as these are more likely to be clinically significant.

With respect to the final GWEP1521 OLE data relating to seizure worsening AEs, the MAH has applied the same analysis approach (of utilising a predefined group of AE PTs relating to seizure worsening to create an AESI) as that used in the RCT phase and described in the EU-SmPC Section 4.8 – and cited above in the question.

Table 1 below shows that the frequency of patients with at least one AE relating to the grouped AESI term for 'seizure worsening' was higher in patients with a median dose in the OLE of > 25 mg/kg/day. This matches the trend seen in the RCT and described in EU-SmPC Section 4.8. Although it is noted

that seizure worsening AEs in the OLE phase were more frequent than the RCT phase, to some degree this is not unexpected given the much longer duration of observation in the OLE phase compared to the RCT phase, which means the commonly observed natural variation in seizure frequency in these patients is more likely to be observed.

Table 1 Frequency of Treatment-Emergent Adverse Events Contained Within the Adverse Event of Special Interest: Seizure Worsening, in the GWEP1521 OLE Phase

	Number of Patients (%)		
	CBD-OS		
Preferred Term	≤ 25 mg/kg/day (N=140) n (%)	> 25 mg/kg/day (N=59) n (%)	All CBD-OS (N=199) n (%)
Number of patients with at least one Seizure Worsening AESI	42 (30.0)	25 (42.4)	67 (33.7)
Seizure	41 (29.3)	18 (30.5)	59 (29.6)
Status epilepticus	6 (4.3)	4 (6.8)	10 (5.0)
Generalised tonic-clonic seizure	2 (1.4)	4 (6.8)	6 (3.0)
Postictal state	0	1 (1.7)	1 (0.5)
Seizure cluster	0	1 (1.7)	1 (0.5)

AESI = Adverse event of special interest; CBD-OS = cannabidiol oral solution; OLE = open-label extension.
Source: Ad-hoc output as Appendix 1.

Given the lack of placebo control in the OLE, and the similar trend for a higher frequency of AEs relating to seizure worsening at doses > 25 mg/kg/day in both the RCT and OLE, the MAH believes the existing wording in EU-SmPC Section 4.8, describing the RCT data, is the most appropriate for prescribers to be provided with. Along with an existing warning to prescribers in Section 4.4 about increased seizure frequency, as well as 'seizure' being listed as an ADR in Section 4.8, the existing wording in EU-SmPC Section 4.8 is deemed most effective to convey the message that there is an increased frequency of AEs associated with seizure worsening in patients receiving doses higher than that approved for the TSC indication (25 mg/kg/day).

Assessment of the MAH Response

The MAH explained the source of data used to report in SmPC and considers that warning in 4.4 and seizure ADR and description in 4.8 is sufficient. This could be agreed.

It is noted that despite the "seizure" ADR and description in 4.8 and existing warning to prescribers in Section 4.4 about increased seizure frequency, the "seizure worsening" is still listed as important potential risk in RMP. The MAH should update it as important identified risk **(OC)**.

Conclusion

Issue partially resolved.

Question 4

In double-blind phase, 2 patients (2.7%) in the 25 mg/kg/day group and 1 patient (1.3%) in the placebo group had status epilepticus. The number of patients with status epilepticus was 10.1%, much higher in OLE phase. In SmPC status epilepticus is mentioned in section 4.4: "In the phase 3 clinical trials investigating LGS, DS and TSC, the observed frequency of status epilepticus was similar between the cannabidiol and placebo groups." The MAH is requested to discuss and update SmPC with information from OLE phase.

Summary of the MAH Response

The MAH would like to clarify that in the question, the quoted frequency of status epilepticus in study GWEP1521 OLE of 10.1% is based on the efficacy endpoint IVRS, whereas the quoted frequencies of status epilepticus in the double-blind phase in the question is based on the safety endpoint of AE reporting, so cannot be directly compared.

In the GWEP1521 OLE, the frequency of status epilepticus, based on AE reporting, was 10/199 patients or 5.0% in all patients in the OLE. This is slightly higher than the frequency of status epilepticus (based on AE reporting) in the RCT phase, where 2 patients (2.7%) in the 25 mg/kg/day group and 1 patient (1.3%) in the placebo group had status epilepticus AEs (no patient in the 50 mg/kg/day group had treatment-emergent status epilepticus). However, given the longer duration of observation in the OLE phase (median number of dosing days was 631 days) compared to 113 days in the RCT, this would be to some degree expected in the patient population with inadequately controlled seizures associated with TSC. The low absolute number of patients with status epilepticus AEs in both the RCT and OLE phase also creates some uncertainty when trying to draw any conclusions. Based on AE reporting, the frequency of status epilepticus in the RCT was very low and similar between the CBD-OS treatment groups and placebo, and no clear increased frequency was seen in the OLE when treatment duration is accounted for.

Based on the efficacy endpoint of the IVRS capturing status epilepticus occurrences, 10.1% of patients had a status epilepticus event in the OLE. This is similar to the frequencies of status epilepticus recorded via IVRS in the RCT phase (6.7% in the 25 mg/kg/day group and 2.7% in the 50 mg/kg/day group, compared to 9.2% in the placebo group), despite the longer duration of observation and exposure to CBD-OS in the OLE phase, compared to the RCT phase. Again, the low absolute number of patients with status epilepticus reported via IVRS in both the RCT and OLE phase also creates some uncertainty when trying to draw any conclusions – particularly given that the frequency of status epilepticus was greatest in the placebo treatment group in the RCT. Furthermore, when looking at the last 12 weeks of treatment in the OLE, the frequency of status epilepticus was 2.5%, lower than overall frequency of status epilepticus in the OLE as measured by the IVRS of 10.1%. This implies a lack of any increased risk of status epilepticus with longer-term CBD-OS exposure.

Overall, when comparing frequencies of status epilepticus between the RCT and OLE phases in GWEP1521, using both efficacy endpoint IVRS reporting and safety endpoint AE reporting, no important increase in frequency is observed that would suggest an association between longer-term CBD-OS exposure and the risk of status epilepticus. No updates to the EU-SmPC Section 4.4 are required as the RCTs remain the best source of evidence for a description of any association between CBD-OS and status epilepticus.

Assessment of the MAH Response

Based on the efficacy endpoint of the IVRS capturing status epilepticus occurrences, 10.1% of patients had a status epilepticus event in the OLE. The frequencies of status epilepticus recorded via IVRS in the RCT phase were 6.7% in the 25 mg/kg/day group and 2.7% in the 50 mg/kg/day group, compared to 9.2% in the placebo group. Due to refractory nature of the disease in enrolled population and longer follow up in OLE, the change is not considered significant. No update to 4.4 is acceptable.

Conclusion

Issue solved.

Question 5

Somnolence and sedation were more frequently observed in placebo-active group. In SmPC section 4.8 it states that: "Somnolence and sedation (including lethargy) events have been observed in controlled trials (see section 4.4) with cannabidiol in LGS, DS and TSC, including 29% of cannabidiol-treated patients (30% of patients taking cannabidiol 20 or 25 mg/kg/day and 27% of patients taking cannabidiol 10 mg/kg/day). These adverse reactions were observed at higher incidences at dosages above 25 mg/kg/day in the controlled study in TSC. The rate of somnolence and sedation (including lethargy) was higher in patients on concomitant clobazam (43% in cannabidiol-treated patients taking clobazam, compared with 14% in cannabidiol-treated patients not on clobazam)." In OLE phase, Clobazam use seems to be higher than double-blind phase but somnolence is same, 19.6 versus 19.6%, respectively. The Applicant is requested to discuss sedation, somnolence and their relationship to other antiepileptics versus cannabidiol dose or titration phase.

Summary of the MAH Response

The MAH agrees that the frequency of the PT 'somnolence' in the OLE is the same as that seen in the CBD-OS treatment arms of the RCT phase of study GWEP1521. The MAH also agrees that the use of clobazam was more frequent in the OLE than the RCT. However, when the safety data from the RCT was reviewed by dose, whereas the data from the OLE phase is reviewed by treatment group in the preceding RCT phase, important differences arise. These differences are presented below, and taken together, do not reveal any important new characteristics of the important identified risk of somnolence that require a change to the EU-SmPC.

Table 2 below shows the frequency of the PTs somnolence, sedation, and lethargy in the RCT phase of GWEP1521, and Table 3 below shows the frequency of the PTs somnolence, sedation, and lethargy in the OLE phase of GWEP1521.

Table 2 Frequency of Treatment-Emergent Adverse Events of Somnolence, Lethargy and Sedation in GWEP1521 RCT Phase

	Number of Patients (%)			
	CBD-OS			
Preferred Term	25 mg/kg/day (N=75) n (%)	50 mg/kg/day (N=73) n (%)	All CBD-OS (N=148) n (%)	Placebo (N=76) n (%)
Somnolence	10 (13.3)	19 (26.0)	29 (19.6)	7 (9.2)
Lethargy	4 (5.3)	3 (4.1)	7 (4.7)	5 (6.6)
Sedation	1 (1.3)	0	1 (0.7)	1 (1.3)

Abbreviations: CBD-OS = cannabidiol oral solution; RCT = randomised controlled trial.
Source: ISS Table TSC.41.1.1.

In the RCT phase, although frequency of somnolence in the CBD-OS treatment groups was 19.6%, a clear dose relationship can be seen between the 25 and 50 mg/kg/day doses. Only doses up to 25 mg/kg/day are approved for the treatment of seizures associated with TSC in the EU-SmPC. In the RCT phase, clobazam was used by ~25% of patients across the CBD-OS treatment arms. Per the Epidyolex EU-SmPC, somnolence events generally occur more commonly early in treatment with CBD-OS. This was the case in the GWEP1521 RCT phase, with 27/29 patients in the CBD-OS treatment groups with the PT somnolence experiencing the first event in first 6 weeks of starting CBD-OS. Sedation and lethargy were reported much less frequently than somnolence.

In the OLE phase, although the frequency of somnolence in all patients in the OLE was 19.6%, given that it is known from the RCT phase of GWEP1521 (as well as pivotal studies in similar refractory epilepsies LGS and DS) that somnolence tends to occur during the first 6 weeks of CBD-OS treatment,

it is useful to review the OLE data by the patient's double-blind treatment. Table 3 shows that somnolence was almost 3 times as frequent in patients starting CBD-OS for the first time in the OLE. As approximately two-thirds of patients in the OLE had already received CBD-OS treatment in the RCT phase, this results in an *overall* frequency of somnolence in all patients in the OLE (19.6%) that may be less than that expected given the greater use of clobazam in the OLE. Clobazam was used by 35.2% of patients in the GWEP1521 OLE. Sedation and lethargy events were again much less frequent than events of somnolence.

Table 3 Frequency of Treatment-Emergent Adverse Events of Somnolence, Lethargy and Sedation in GWEP1521 OLE Phase

	Number of Patients (%)		
	Double-blind Phase Treatment		
Preferred Term	CBD-OS (N=124) n (%)	Placebo (N=75) n (%)	Total (N=199) n (%)
Somnolence	15 (12.1)	24 (32.0)	39 (19.6)
Lethargy	3 (2.4)	5 (6.7)	8 (4.0)
Sedation	2 (1.6)	4 (5.3)	6 (3.0)

Abbreviations: CBD-OS = cannabidiol oral solution; OLE = open-label extension.
Source: GWEP1521 OLE CSR, Section 8 OLE Table 11.2.

Overall, somnolence (along with similar terms sedation, and lethargy) are ADRs for CBD-OS and are important identified risks in the CBD-OS RMP. The frequency of these ADRs occurring is increased by concomitant use of clobazam, likely due to the known PK interaction that results in increased plasma levels of the active metabolite N-desmethylclobazam. No important increase in the frequency of these events was seen in the GWEP1521 OLE phase compared to the RCT phase. The characteristics of the risk of somnolence, as well as lethargy and sedation, are appropriately described in the Sections 4.4, 4.5 and 4.8 of the Epidyolex EU-SmPC. No new characteristics of these risks were identified in the data from the GWEP1521 OLE study and therefore an update to the EU-SmPC is not required.

Assessment of the MAH Response

The MAH did not directly analyse the somnolence, lethargy, sedation events in CLB using subgroup of OLE and did not provide any discussion if new CLB start in OLE while using CBD-OS for more than 6 weeks had an impact on less frequent events observed in OLE phase. The issue is not pursued as it is expected that the treating physician would avoid starting CLB and CBD-OS simultaneously due to management of epilepsy in these children and warning in 4.4. should be informative on the risk of increased incidence.

Conclusion

Issue not further pursued.

Question 6

There were 5 patients who had clinically significant ECG parameters indicative of an AE and 1 patient who was not reported as AE. A further thorough QTc trial in the fed state is scheduled to provide robust additional data on any CBD-OS effect on QTc at therapeutic and supra-therapeutic exposures. The applicant will submit the trial results to the EMA upon completion of the trial. This was estimated to be September 2021. The MAH is requested to give updates on this trial.

Summary of the MAH Response

The study start was delayed due to COVID-19 and protocol review by the FDA. The study conduct has now completed. The final CSR is expected by Q4 2022 and will be provided to the EMA on finalisation.

Assessment of the MAH Response

The requested information is provided. The MAH is expected to report the results.

Conclusion

Issue solved.

6. 2nd Request for supplementary information

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

Other Concerns

1. From Q2: Below update is considered acceptable. Instead of values for weeks 145-156 (when there are only 45 patients), the MAH should include information on dosing, duration of exposure and additional information on OLE phase. The mean time on treatment was 631 days (n=199) (min-max were 18-1462 days). More than half of the patients stayed at or below 25 mg/kg/day dose during OLE phase.

   Open-label data

   "Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. 34 patients completed OLE phase and median treatment period was 631 days (range: 18-1462). Following completion of the blinded transition, patients were to complete a 3-week titration up to a target dose of 50 mg/kg/day (Xx% of patients stayed at or below 25 mg/kg/day dose during OLE phase). In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was ~~61~~54% during Weeks 1-12 (N = 199), which was maintained through to Weeks 37–48 (N = 156)~~,~~ with a median percentage reduction from baseline in TSC-associated seizure frequency of ~~68~~66%. ~~In the TSC patients who reached at least Weeks 145-156 (N = 45), the median percentage reduction from baseline in TSC-associated seizure frequency was 87%. The open-label data showed that cannabidiol had a sustained effect on seizure control when used as a long-term adjunctive therapy and displayed a safety profile similar to that established in other pivotal studies~~".

   The MAH is requested to update accordingly.

2. From Q3: It is noted that despite the "seizure" ADR and description in 4.8 and existing warning to prescribers in Section 4.4 about increased seizure frequency, the "seizure worsening" is still listed as important potential risk in RMP. The MAH is requested to update it as important identified risk through a variation.

7. Assessment of MAH responses to Request for supplementary information

Question 1

1. From Q2 (initial list of questions): Below update is considered acceptable. Instead of values for weeks 145-156 (when there are only 45 patients), the MAH should include information on dosing, duration of exposure and additional information on OLE phase. The mean time on treatment was 631 days (n=199) (min-max were 18-1462 days). More than half of the patients stayed at or below 25 mg/kg/day dose during OLE phase.

   Open-label data

   "Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. 34 patients completed OLE phase and median treatment period was 631 days (range: 18-1462). Following completion of the blinded transition, patients were to complete a 3-week titration up to a target dose of 50 mg/kg/day (Xx% of patients stayed at or

below 25 mg/kg/day dose during OLE phase). In the OLE the median percentage reduction from baseline in TSC-associated seizure frequency was ~~61~~54% during Weeks 1-12 (N = 199), which was maintained through to Weeks 37–48 (N = 156)~~,~~ with a median percentage reduction from baseline in TSC-associated seizure frequency of ~~68~~66%. ~~In the TSC patients who reached at least Weeks 145-156 (N = 45), the median percentage reduction from baseline in TSC-associated seizure frequency was 87%. The open-label data showed that cannabidiol had a sustained effect on seizure control when used as a long-term adjunctive therapy and displayed a safety profile similar to that established in other pivotal studies~~".

The MAH is requested to update accordingly.

Summary of the MAH Response

The Applicant would like to clarify the number of patients who completed the open-label part of GWEP1521, Table 1 below summarizes the overall patient disposition. While only 34 patients were defined as completers, of 108 patients withdrawn for "other reasons," 92 (85%) were withdrawn because they transitioned to commercial Epidyolex, 11 (9%) were withdrawn due to lack of efficacy, 2 (2%) were withdrawn due to advice from the medical monitor or their neurologist, 1 (<1%) withdrew due to difficulties with compliance, 1 (<1%) withdrew because the study completed, and 1 (<1%) was due to a parent and investigator decision. Thus, 126 (63%) of 199 patients who enrolled in the open-label portion of the trial continued treatment with Epidyolex, in some cases for as long as 209 weeks. The majority of patients (53.3%) reached a maximum dosage of ≤ 25 mg/kg/day, with the median modal dosage across the trial of 25 mg/kg/day.

Table1: Summary of Overall Patient Disposition

Treatment phase		CBD-OS (n-124)	Placebo (n-75)	Total (n-199)
OLE treatment phase	Completed	22	12	34
	Withdrawn	102	63	165
Primary reason for withdrawal	Adverse event	8	10	18
	Lost to follow-up	1	0	1
	Met withdrawal criteria	2	2	4
	Other	69	39	108
	Physician decision	3	1	4
	Transition to commercial product	1	0	1
	Withdrawal by parent/guardian	8	7	15
	Withdrawal by subjects	10	4	14

Source: CSR: OLE listings 1.1.1 and 1.1.2

The Applicant acknowledges the CMHP comments and request for additional information regarding study GWEP1521 in the SmPC. Based on the information provided above, the Applicant proposes the following amended language be included in Section 5.1 of the SmPC:

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. **The median modal dosage was 25 and median treatment period was 90 weeks (range: 2.6-209 weeks). In the OLE, the median percentage reduction from baseline in TSC associated seizure frequency was 54% during Week 1–12 (N = 199), which was maintained through to Week 85-96 (N = 98), with a median percentage reduction from baseline in TSC associated seizure frequency of 75%. Additional seizure frequency data collected for up to 3**

years demonstrated seizure reduction and safety outcomes consistent with the results from the other pivotal studies".

Note: Upon the CHMP endorsement of open-label changes in the SmPC, the Applicant will include the agreed updates as part of ongoing major Type II variation (EMEA/H/C/004675/II/0020) under assessment by the CHMP. As the changes are minor in nature which does not impact the benefit-risk ratio of the product, the Applicant proposes that this timing is adequate to implement the proposed wording in the label, with no separate variation required.

Assessment of the MAH Response

The MAH proposes below update:

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. *The median modal dosage was 25 and median treatment period was 90 weeks (range: 2.6-209 weeks).* In the OLE, the median percentage reduction from baseline in TSC associated seizure frequency was *54%* during Week 1–12 (N = 199), which was maintained through to *Week 85-96 (N = 98)*, with a median percentage reduction from baseline in TSC associated seizure frequency of *75%*. *Additional seizure frequency data collected for up to 3 years demonstrated seizure reduction and safety outcomes consistent with the results from the other pivotal studies*".

The proposed text is considered acceptable except for the last sentence and the dosage text. So the SmPC text should as below:

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. *The median modal dosage was 25 mg/kg/day and median treatment period was 90 weeks (range: 2.6-209 weeks).* In the OLE, the median percentage reduction from baseline in TSC associated seizure frequency was *54%* during Week 1–12 (N = 199), which was maintained through to *Week 85-96 (N = 98)*, with a median percentage reduction from baseline in TSC associated seizure frequency of *75%*. ~~*Additional seizure frequency data collected for up to 3 years demonstrated seizure reduction and safety outcomes consistent with the results from the other pivotal studies*~~".

Conclusion

Issue partially solved. The MAH should delete the marked sentence and the dose details.

Question 2

From Q3 (initial list of questions): It is noted that despite the "seizure" ADR and description in 4.8 and existing warning to prescribers in Section 4.4 about increased seizure frequency, the "seizure worsening" is still listed as important potential risk in RMP. The MAH is requested to update it as important identified risk through a variation.

Summary of the MAH Response

The MAH acknowledges that, as with other ASMs, a clinically relevant increase in seizure frequency may occur during treatment with CBD-OS, which may require adjustment in dose of CBD-OS and/or concomitant AEDs or discontinuation of CBD-OS. There is currently insufficient evidence to conclude that this association is causal, which is a prerequisite for a risk to be categorised as 'identified' rather than 'potential'. The current Epidyolex EU-SmPC informs prescribers of this potential risk.

There is currently no evidence to suggest that CBD-OS leads to seizure worsening when administered as per the approved SmPC. The incidence of TEAEs of Seizure in pooled data from 5 Phase III studies across 3 indications (LGS/DS/TSC) shows seizure was reported in 7.5% of patients administered CBD-OS vs 7.3% of the patients administered PBO in these studies. A comprehensive analysis of all PTs reported that could suggest 'seizure worsening' showed an incidence of 14.9% in subjects taking CBD-OS vs 13.3 % in PBO-administered patients. Analysis of the same data excluding the TSC study (where doses up to 50 mg/kg/day were administered) shows AEs of seizure worsening occurred in 15.1% in the LGS/ DS population administered CBD-OS vs 14.4% in the LGS/ DS patients administered PBO.

Upon CHMP request during the assessment of Type II variation to add TSC as a new indication, the MAH had previously agreed to add PT 'seizure' to the ADR table and included a description of seizure worsening in Section 4.8 of the EU-SmPC. The SmPC states 'In the controlled trial in TSC patients, an increased frequency of adverse events associated with seizure worsening was seen at doses above 25 mg/kg/day'. The incidence of adverse events associated with seizure worsening in the TSC trial is similar between CBD 25 mg/kg/day (8/75 subjects, 10.7%) and placebo groups (7/76 subjects, 9.2%). It is also to be noted that no clear pattern was noted for these AE terms suggesting 'seizure worsening'. The frequency of AE terms suggestive of seizure worsening was higher with doses above 25 mg/kg/day (17.8%). Of note, doses >25 mg/kg/day are not approved doses as per SmPC.

The Special Warning and precaution section in the SmPC states that 'As with other AEDs, a clinically relevant increase in seizure frequency may occur during treatment with cannabidiol…'. This statement was primarily introduced in the initial MAA based on efficacy data analysis suggesting an increase in seizure frequency in a subgroup of the LGS patient population (without clobazam). This finding was not observed in the efficacy analysis of the off-clobazam subgroups in the trials of DS and TSC. Analysis of AEs suggestive of seizure worsening reported in the off-clobazam subgroups in the LGS phase 3 studies shows a similar incidence between CBD-OS and PBO (14.9% vs 16%). There was also a similar incidence of AEs suggesting seizure worsening in the off-clobazam subgroups in the DS Phase 3 studies between CBD-OS and PBO (18.2% vs 17.0%).

Assessment of postmarketing data to date has not shown any new characteristics of the risk for seizure worsening beyond that already described in the EU-RMP v2.0 and which was agreed with the EMA during the Type II TSC indication extension procedure.

Overall, the assessments performed by the MAH do not show any clear evidence of a causal association of CBD-OS with seizure worsening in the approved indications. This lack of evidence leads the MAH to continue to list 'Seizure worsening' as an important potential risk in the EU-RMP v2.0. The MAH believes this is aligned with GVP Module V, which requires the RMP to address the important risks for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal, as an important potential risk. Therefore, the MAH maintains this is the appropriate categorisation for 'seizure worsening' based on current data.

Assessment of the MAH Response

The MAH explained the reason underlying the current categorisation as "important potential risk" for seizure worsening.

Conclusion

Issue solved.

8. Conclusion

The proposed text for section 5.1 of the SmPC is considered acceptable except for the last sentence and the dosage text. The modified SmPC text should read as follow:

"Of the 201 patients who completed the GWPCARE6 study, 99.0% (199 patients) were enrolled into the OLE study. *The median modal dosage was 25 mg/kg/day and median treatment period was 90 weeks (range: 2.6-209 weeks).* In the OLE, the median percentage reduction from baseline in TSC associated seizure frequency was *54%* during Week 1–12 (N = 199), which was maintained through to *Week 85-96 (N = 98)*, with a median percentage reduction from baseline in TSC associated seizure frequency of *75%*. ~~*Additional seizure frequency data collected for up to 3 years demonstrated seizure reduction and safety outcomes consistent with the results from the other pivotal studies*~~".

The MAH should submit a variation in accordance without any delay and ***no later than 60 days after the receipt*** of these conclusions.