25 February 2021
EMA/CHMP/168137/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Epidyolex

International non-proprietary name: cannabidiol

Procedure No. EMEA/H/C/004675/II/0005

Note

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

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List of abbreviations

ABBREVIATION	DEFINITION
7-COOH-CBD	7-carboxy-cannabidiol
7-OH-CBD	7-hydroxy-cannabidiol
ACTH	Adrenocorticotrophic hormone
ADR	Adverse drug reaction
AE	Adverse event
AED	Antiepileptic drug
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BUN	Blood urea nitrogen
CAS	Compassionate access scheme
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CBDV	Cannabidivarin
CCGI	Caregiver Global Impression of Change
CI	Confidence interval
CLB	Clobazam
Cmax	Maximum measured plasma concentration
CMC	Chemistry, manufacturing, and controls
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Coefficient of variation
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DRE	Drug-resistant epilepsy
DS	Dravet syndrome
EAP	Expanded access program
EE_{50}	Effective exposure producing 50% maximal effect
EMA	European Medicines Agency
ESC	Epilepsy Study Consortium
EU	European Union
FDA	Food and Drug Administration
G-tube	Gastrostomy tube
GGT	Gamma glutamyltransferase
GW	GW Research Ltd
HV	Healthy volunteer
IMP	Investigational medicinal product
IND	Investigational new drug
ISR	Interim safety report
ISS	Integrated Summary of Safety
ITT	Intention to treat
IVRS	Interactive voice response system
LGS	Lennox-Gastaut syndrome
LEV	Levetiracetam
LSR	Liver safety report
MAA	Marketing Authorisation Application
MADDERS	Misuse, Abuse, and Diversion Drug Event Reporting System
N-CLB	*N*-desmethylclobazam
NDA	New drug application
NOAEL	No observed adverse effect level

ABBREVIATION	DEFINITION
NS	Non-significant
OLE	Open-label extension
OR	Odds ratio
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamic
PK	Pharmacokinetic
POPPK	Population pharmacokinetics
PP	Per protocol
PT	Preferred term
QTc	The QT interval corrected for heart rate
RCT	Randomized controlled trials
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
S/CGIC	Subject/Caregiver Global Impression of Change
SmPC	Summary of product characteristics
SMQ	Standard MedDRA Query
STP	Stiripentol
SUDEP	Sudden unexpected death in epilepsy
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
TIIV-TSC	Type II variation - TSC
TSC	Tuberous sclerosis complex
ULN	Upper limit of normal
USA	United States of America
USPI	United States prescribing information
VFDs	Visual field defects
VGB	Vigabatrin
VNS	Vagus nerve stimulation
VPA	Valproic acid or any prescribed valproate product (valproate semisodium or valproate sodium)
vs.	Against [Latin: *versus*]
w/w	Weight by weight

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GW Pharma (International) B.V. submitted to the European Medicines Agency on 19 March 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 1 year of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. The updated RMP version 1.1 has been submitted.
The MAH also took the opportunity to correct typographic errors and implement editorial updates as well as implement the updated ethanol statement in compliance with the EC Guideline on Excipient.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Epidyolex was designated as an orphan medicinal product EU/3/17/1959 on 17 January 2018. Epidyolex was designated as an orphan medicinal product in the following indication: *Treatment of tuberous sclerosis*.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Epidyolex as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Epidyolex

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision P/0047/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0047/2020 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kirstine Moll Harboe Co-Rapporteur: Ondřej Slanař

Timetable	Actual dates
Submission date	19 March 2020
Start of procedure:	25 April 2020
CHMP Rapporteur Assessment Report	19 June 2020
CHMP Co-Rapporteur Assessment Report	23 June 2020
PRAC Rapporteur Assessment Report	26 June 2020
PRAC Outcome	9 July 2020
CHMP members comments	14 July 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 July 2020
1st Request for supplementary information (RSI)	23 July 2020
MAH's responses to 1st RSI	14 August 2021
CHMP Rapporteur Assessment Report	21 September 2020
PRAC Rapporteur Assessment Report	21 September 2020
Updated PRAC Rapporteur Assessment Report	24 September 2020
PRAC Outcome	1 October 2020
CHMP members comments	5 October 2020
Updated CHMP Rapporteur Assessment Report	8 October 2020

Timetable	Actual dates
2nd Request for supplementary information (RSI)	15 October 2020
MAH's responses to 2nd RSI	27 November 2020
CHMP Rapporteur Assessment Report	22 December 2020
PRAC Rapporteur Assessment Report	22 December 2020
PRAC members comments	6 January 2021
Updated PRAC Rapporteur Assessment Report	7 January 2021
PRAC Outcome	14 January 2021
CHMP members comments	18 January 2021
Updated CHMP Rapporteur Assessment Report	21 January 2021
3rd Request for supplementary information (RSI)	28 January 2021
MAH's responses to 3rd RSI	2 February 2021
CHMP Rapporteur Assessment Report	11 February 2021
CHMP members comments	15 February 2021
Updated CHMP Rapporteur Assessment Report	22 February 2021
Opinion	25 February 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Tuberous Sclerosis Complex (TSC) is a genetic disorder characterised by the formation of non-malignant tumours (tubers) in multiple organ systems. Tumours in TSC patients occur primarily in the brain, eyes, heart, kidney, skin, and lungs. Epileptic seizures are the most common neurological manifestation of TSC, affecting more than 70% of patients.

In this procedure, the MAH is seeking approval to add the new indication for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 1 year of age and older.

Epidemiology

The incidence rate is approximately 1:10000 to 1:5000 live births. Prevalence may be underestimated but in Europe is usually given as 1:25000 to 1:5000. TSC is a chronic, life-long condition. As patients transition into adulthood seizures may persist, and renal and pulmonary issues may become more important, and are associated with increased morbidity and mortality.

Aetiology and pathogenesis

Mutations in the *TSC1* or *TSC2* gene may cause tuberous sclerosis complex. The TSC1 and TSC2 genes code for the proteins hamartin and tuberin, respectively. These proteins normally act as tumour suppressors. The pathogenetic events leading to seizures are not completely understood.

Clinical presentation

Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients. The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms. Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex focal seizures (with or without secondary generalization), generalized tonic-clonic seizures, atonic seizures, and atypical absences. Infantile spasms resolve with time, but the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy. Cognitive impairment (intelligence/developmental quotient < 70) is observed in around 60% of all TSC patients with a history of seizures. Sudden unexpected death in epilepsy is one of the most common causes of death.

Management

Most patients with TSC take between 3 and 5 antiepileptic drugs (AEDs); however, such treatment regimens rarely provide sufficient seizure control and are often accompanied by intolerable side effects.

The only approved therapy for TSC-associated seizures in the EU is the mTOR inhibitor everolimus. Everolimus was originally approved in the EU in 2011 (as Votubia) to treat tumours in patients aged 3 years and older with TSC, and the indication was subsequently extended in 2017 to include adjunctive treatment of adult and paediatric patients aged 2 years and older with TSC-associated partial-onset seizures. The mTOR inhibitors are anti-tumour agents with immunosuppressive properties. In addition to TSC-associated seizures, everolimus is indicated for treatment of advanced or progressive malignancies (breast cancer, neuroendocrine tumours, and renal cell carcinoma), as well as non-cancerous tumours in patients with TSC. Adverse reactions to everolimus include non-infectious pneumonitis, infections, severe hypersensitivity reactions, angioedema, stomatitis, renal failure, impaired wound healing, metabolic disorders, and myelosuppression.

Vigabatrin (VGB) was first licensed as an antiepileptic agent (in the UK and the Republic of Ireland) in 1989 (as Sabril) and was most recently approved in the EU in 2018 (as Kigabeq) to treat infantile spasms, and is often used for treatment of infantile spasms secondary to TSC. Vigabatrin is typically recommended as a first-line treatment for TSC-related spasms or focal seizures in children < 1 year of age in Europe.

Corticotropin (ACTH) or other corticosteroids have been demonstrated as effective in the treatment of infantile spasms. AEs include infections secondary to immunosuppression, hypertension, glucosuria, and metabolic abnormalities. ACTH may contribute to the enlargement of cardiac rhabdomyoma in TSC patients, and close monitoring is required in TSC patients with cardiac rhabdomyoma. Thus, corticosteroid therapy is generally short-term (approximately 2 weeks followed by taper), and close monitoring is required in TSC patients with cardiac rhabdomyoma.

Utilisation of clobazam (CLB) is estimated to be limited to < 20% of the 46,000 patients with TSC in the EU. Benzodiazepines such as CLB are not commonly used for treating seizures associated with TSC, and

guidelines do not support utilisation. Data on effectiveness of CLB on focal seizures are limited, and there are no dosing recommendations to guide initiation, titration, and target dosing of CLB for the treatment of seizures associated with TSC in children aged < 6 years old. While CLB may be a useful add-on medication for some with refractory epilepsy, its clinical utility may be limited by its behavioural side effects (severe aggressive outbursts, hyperactivity, insomnia, and depression with suicidal ideation), which are important comorbidities in some patients with TSC. Additionally, CLB is associated with adverse reactions including somnolence, sedation, cognitive impairment, respiratory depression, tolerance, and dependence.

There remains an unmet medical need for new efficacious pharmaceutical treatments for refractory seizures in TSC. Despite the currently available treatment options, many patients with TSC-associated epilepsy continue to have seizures: more than 60% of patients do not achieve seizure control despite the availability of multiple AEDs and non-pharmacological interventions. Current AEDs are often associated with side effects, which can be worsened by polypharmacy. As with any refractory epilepsy, physicians typically trial several AEDs in order to gain epilepsy control. However, such polypharmacy often leads to a high burden of adverse events (AEs), and thus the appropriate balance of tolerability and efficacy is critical to achieving seizure control. Accordingly, treatment selection is informed by safety and tolerability that may impact quality of life.

2.1.2. About the product

Epidyolex (cannabidiol) oral solution (CBD-OS) was approved in Europe in September 2019 for the 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. Cannabidiol has negligible affinity for the cannabinoid CB1 and CB2 receptors, and the full mode of action is not completely understood.

2.1.3. General comments on compliance with GLP and GCP

Non-clinical

In the initial MAA, several non-clinical studies were not conducted according to GLP due to unreliable bioanalysis. Mitigation measures were undertaken or are ongoing (see Epidyolex EPAR). In this extension of indication procedure, the MAH provided several updated non-clinical study reports (see non-clinical aspects).

Clinical

According to the MAH, the clinical study GWEP1521 was conducted in compliance with the GCP.

2.2. Non-clinical aspects

2.2.1. Introduction

For the TSC indication, the recommended starting dose of cannabidiol is 2.5 mg/kg taken twice daily (5 mg/kg/day) for one week. After one week, the dose should be increased to a dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, the dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) up to a maximum recommended dose of 12.5 mg/kg twice daily (25 mg/kg/day).

In line with new proposed maximal daily dose of 25 mg/kg, the relevant non-clinical sections of SmPC have been updated.

2.2.2. Pharmacology

Primary pharmacodynamic studies

Three new *in vivo* pharmacology studies (GWPP17072, GWPP18020 and GWCRI17024) and a PKPD summary report (GWPP18094) were submitted.

Evaluation of Purified CBD or 7-OH-CBD in the 6 Hz psychomotor seizure test in the mouse (GWPP17072, GWPP18020)

Male Naval Medical Research Institute (NMRI) mice (12/group) were given an i.p. injection of 0 (vehicle; 10% ethanol and 20% Kolliphor HS 15 in physiological saline), 0 (neutral vehicle; 0.2% hydroxypropyl methylcellulose in physiological saline), 2 mg/kg diazepam (positive control), 200 mg/kg Purified CBD, or 150 or 200 mg/kg 7-OH-CBD. Seizures were induced by an electrical shock stimulus via corneal electrodes. The number of tonic convulsions and mortality rate were assessed.

Eleven of the 12 mice in the neutral vehicle group displayed tonic convulsions and there were no differences in effects on seizures for the 2 vehicle substances. Both Purified CBD and 7-OH-CBD markedly decreased the number of mice showing tonic convulsions (-91% and -100% for both doses, respectively).

Male Swiss mice (15/group) were administered (i.p.) physiological saline (neutral vehicle), vehicle (1:2:7 of ethanol/Kolliphor HS15/physiological saline), 300 mg/kg valproate (positive control), 100 or 300 mg/kg CBD, and 25, 50, 100, 200, 250 or 300 mg/kg 7-OH-CBD. Test substances and vehicle were administered 60 minutes before the test, while neutral vehicle and positive control were administered 30 minutes before the test. Rectangular current (44 mA, 3 seconds duration, 6 Hz) via corneal electrodes produced seizures, which were quantified by measuring forelimb clonus.

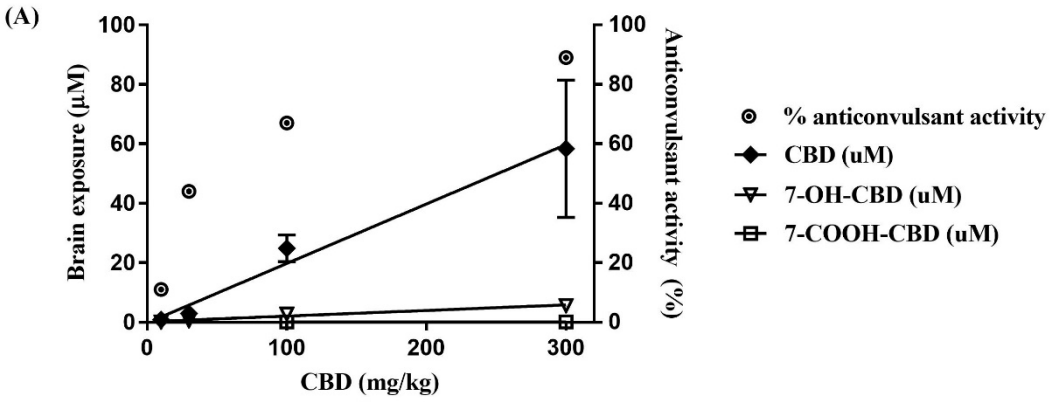
Reductions in the forelimb seizure score compared to vehicle control was seen in mice treated with valproate (300 mg/kg; -88%, p≤0.01), Purified CBD (100 and 300 mg/kg; -67%, p≤0.01; -89%, p≤0.001) and 7-OH-CBD (50, 100, 200, 250 and 300 mg/kg; -67%, ≤0.01; -80%, p≤0.01; -100%, p≤0.01; -80%, p≤0.05, -80%, p≤0.05 and -88%, p≤0.01), but no reductions were seen for 10 and 30 mg/kg Purified CBD (no clear effects; -44%, non-significant [NS]) or 25 mg/kg 7-OH-CBD (-44%, NS).

Data generated from GWPP17072 and GWPP18020 were used to calculate ED_{50} values (effective dose producing 50% maximum effect) for their antiseizure effects, using the log dose versus probits of effects linear regression (7-OH-CBD, 32.1 mg/kg; CBD, 49.6 mg/kg). The brain content of CBD and 7-OH-CBD were measured and EE_{50} values (effective exposure producing 50% maximum effect) were derived using the log brain exposure versus probits of effects of linear regression analysis and were 8.7 µM for 7-OH-CBD and 47.3 µM for CBD (GWPP18094), see Table 1 and Figure 1.

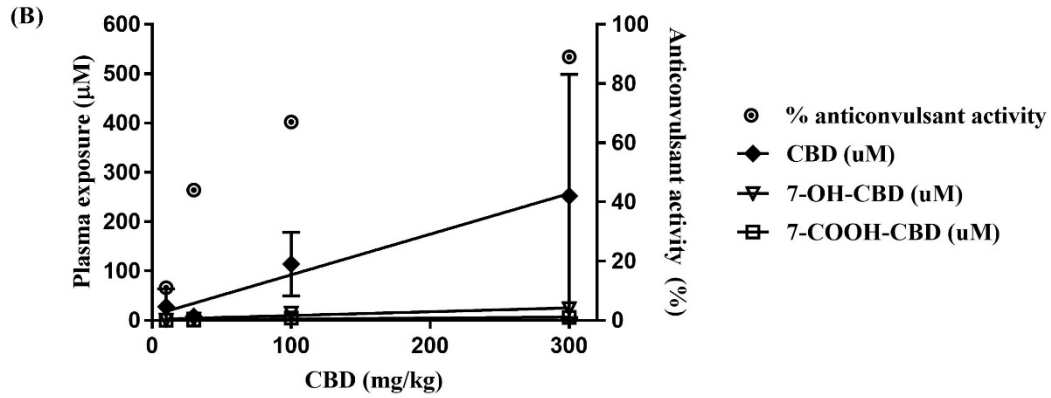
Table 1: Comparisons of ED50 of 7-OH-CBD vs CBD using the 6-Hz mouse model

Analysis	7-OH-CBD ED_{50} (mg/kg)	CBD ED_{50} (mg/kg)	t-test (p value)	7-OH-CBD HED - mg	CBD HED - mg	Diff. in HED (%)
Sigmoidal curve analysis	30.5	46.0	9.7×10^{-6}	397.8	600	40.5
Log-probits analysis	32.1	49.6	2.4×10^{-13}	388.3	600	42.8

Figure 1. Linear relationships of CBD, 7-OH-CBD and 7-COOH-CBD exposures against CBD doses based on bioanalysis on mouse (A) brain and (B) plasma samples. Brain and plasma concentrations are mean values with SEM plotted for n=5 per dose group. Percent anticonvulsant activity is plotted on the right Y-axis.



	CBD	7-OH-CBD	7-COOH-CBD
R square	0.9829	0.9646	1



	CBD	7-OH-CBD	7-COOH-CBD
R square	0.9653	0.907	0.8238

Purified CBD in the Reduced Intensity Status Epilepticus – Spontaneous Recurrent Seizure (RISE-SRS) Model of Temporal Lobe Epilepsy (GWCRI17024)

A reduced intensity, status epilepticus (RISE) form of lithium pilocarpine induced epilepsy was used to model temporal lobe epilepsy. Male Wistar rats of PND 21-28 (two groups of 10/group) were administered 200 mg/kg/day Purified CBD or vehicle (3.5% Kolliphor HS15) p.o. via in drinking water for 6 weeks, at which time before behavioural experiments assessment commenced and treatment continued (weeks 7 and 8 of drug treatment). An additional 10 healthy, age matched, nonepileptic control rats were treated with vehicle.

Compared to healthy vehicle treated rats, epileptic vehicle treated rats experienced seizures and displayed impaired performance on the accelerating rotarod ($p<0.05$), the static beam ($p<0.05$), working memory ($p<0.0001$) and reference memory ($p<0.0001$), with no effect on gait. Purified CBD reduced the seizure index ($p<0.05$) compared to the epileptic vehicle group. Purified CBD treated rats also spent more time on the accelerating rotarod ($p<0.01$) and displayed improved reference memory ($p<0.01$) and working memory ($p<0.0001$; assessed using the hole board test) compared to epileptic vehicle treated rats. Treatment with Purified CBD did not, however, alter performance on the static beam test or gait.

Secondary pharmacodynamic studies

NA

Safety pharmacology programme

NA

Pharmacodynamic drug interactions

NA

2.2.3. Pharmacokinetics

NA

2.2.4. Toxicology

Single dose toxicity

No new studies were submitted

Repeat dose toxicity

No new studies were submitted; however, several study reports were resubmitted and included an updated bioanalytical reports (see above Methods of Analysis/Toxicokinetics).

Reproduction toxicity

See Methods of Analysis/Toxicokinetics section above.

Toxicokinetic data

Methods of Analysis/Toxicokinetics

The updated bioanalytical reports on studies GWTX1412, 1413, 1503, 1578, 1454, 1408, 1524 and 1551 (initially provided and assessed in the initial MAA procedure, see EPAR) were submitted. In this procedure, only studies conducted with oral administration will be considered for the calculation of safety margins (GWTX1412, 1413, 1503, 1454, 1408 and 1551, see Table 2 below).

Table 2: Overview of studies resubmitted with updated bioanalytical report

Section	Topic	Dose/Active substance	Laboratory	Study number Report issued
Repeat-dose tox	26-weeks oral tox in rat	CBD: 0, 15, 50, 150 mg/kg/day	In life 2014/15	GWTX1412 Amendment 1 19/1/18 and BioA (4/4/18)
Repeat-dose tox	39-weeks oral tox in dog	CBD: 0, 10, 50, 100 mg/kg/day	In life 2014/15	GWTX1413 amendment 1 19/1/18 and BioA (4/4/18)
Repeat-dose tox	13-weeks tox in mouse	CBD: 0, 100, 150, 300 mg/kg/day	In life 2015	GWTX1503 Amendment 1 23/1/18 and (10/5/18)
Embryofetal development	EFD in rat Oral CBD	GD6-17: CBD: 0, 75, 150, 250 mg/kg/day	In life 2015	GWTX1454 3/12/18 and BioA (20/4/18)
Juvenile animal tox	10 weeks s.c. PND 4-6 and p.o. PND 7-77 in juvenile rat	CBD: s.c.: 0, 15, 15, 15 p.o.: 100, 150, 250 mg/kg/day	In life 2015	GWTX1408 17/1/19 and BioA (20/4/18)
Dependence	Potential self-administration in rat	CBD: 0, 5, 25, 75 mg/kg Positive control amphetamine: 0.05 mg/kg	In life 2015	GWTX1551 amendment 2 30/1/18 and BioA (27/3/18)

Safety margins were recalculated using exposure data from the TSC clinical study GWEP1521. Examples of dot plots of patient exposure data are presented in Table 3 and Figure 2.

Table 3: Margin of safety for CBD in a juvenile Population

Species	NOAEL (mg/kg)	$AUC_{(0-t)}$ (at NOAEL) (ng·h/mL)	Margin of Safety[a] calculated using AUC	Study Reference
Juvenile rat (male)	15/150	75500	15.2	GWTX1408 (TK reported from GWTX18001)
Juvenile rat (female)	15/150	61200	12.3	
Mouse (male)	300	44300	8.9	GWTX1503
Mouse (female)	300	46400	9.4	
Rat (male)	150	60000	12.1	GWTX1412
Rat (female)	150	67500	13.6	
Dog (male)	100	20500	4.1	GWTX1413
Dog (female)	100	22400	4.5	
Rat (maternal)	150	149000	30.0	GWTX1454

N.b. all studies describe adult animals except where stated.

[a]From Clinical Study GWEP1521, $AUC_{(0-5)}$ following multiple oral doses (Day 113) of a clinical dose of 25 mg/kg/day CBD. Human AUC (median) was doubled to match the preclinical dosing interval. Adjusted human $AUC_{(0-24h)}$ is 4960 ng.h/mL.

Figure 2: Dot Plot of individual CBD plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (linear scale)

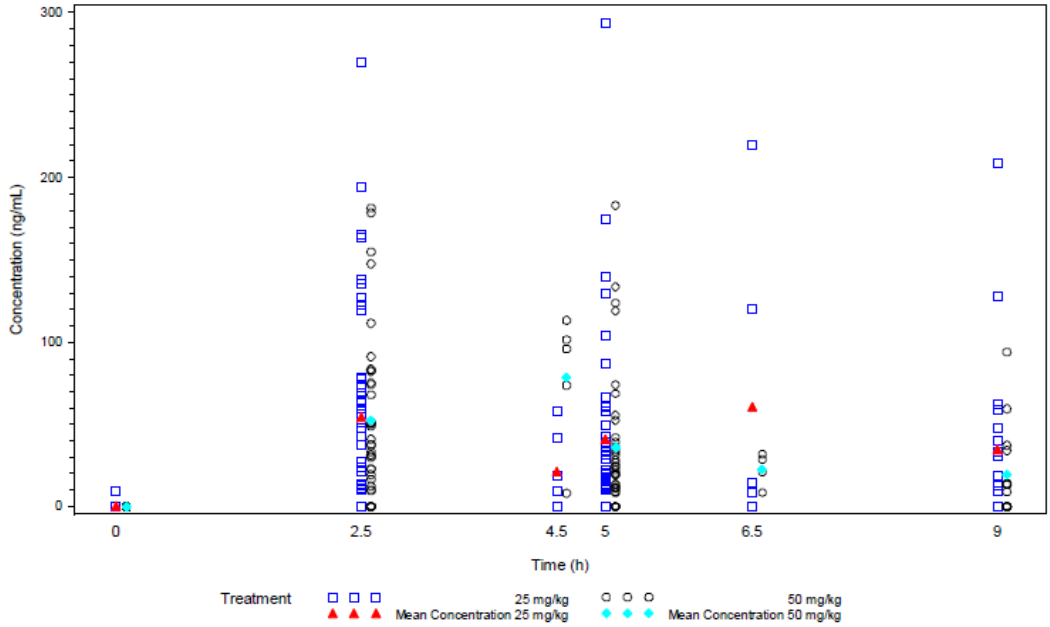
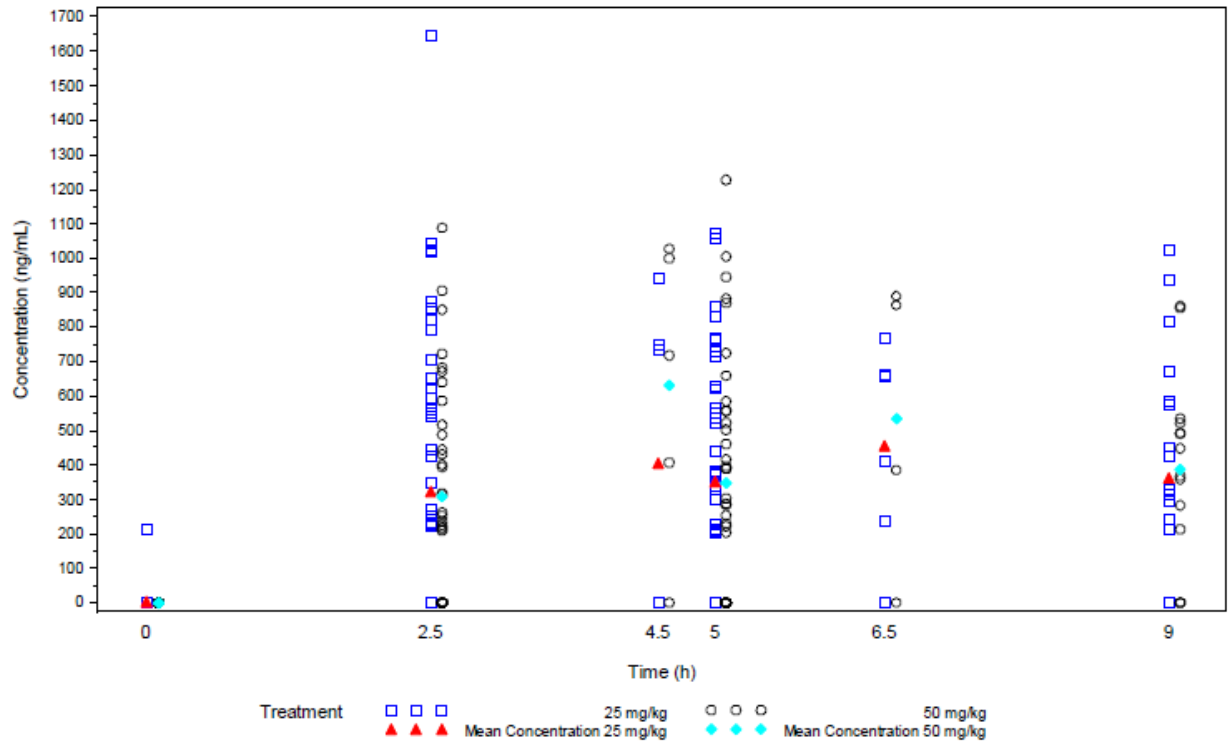


Figure 3: Dot Plot of individual 7-COOH-CBD plasma Concentration vs. Time Profiles, Visit 3, 25 and 50 mg/kg/day (linear scale)



[redacted]

Repeat-dose toxicity GWTX1412, 1413 and 1503

The main reports were updated in order to not refer to any bioanalytical or toxicokinetic results. In the Results section of the main reports, the following statement was found: *Plasma analysis data are listed in*

the Annex, however no claim of GLP compliance is made for this phase. The data confirms a level of exposure was achieved, however due to the issues related to this phase of the study the absolute exposure values cannot be confirmed or reported.

In the new bioanalysis reports, a new appointed principal investigator concluded that bioanalytical data for 7-COOH and 7-OH-CBD was not quantitative/not reliable. Bioanalysis of CBD was deemed in the initial MAA procedure as overall reliable (although not GLP compliant) for all studies and is used for calculation of safety margins.

Toxicokinetics for CBD:

GWTX1412 Rat Week 26

Mean maximum CBD plasma concentrations (C_{max}) of 1400, 5240 and 6160 ng/mL in males, and 2070, 3750 and 7530 ng/mL in females; and mean CBD AUC_{0-t} values of 8700, 36700 and 60000 ng.h/mL in males, and 10800, 39000 and 67500 ng.h/mL in females, were observed at CBD dose levels of 15, 50 and 150 mg/kg/day respectively.

GWTX1413 Dog Week 39

Mean maximum CBD plasma concentrations (C_{max}) of 2150, 3860 and 2570 ng/mL in males, and 2770, 5830 and 2660 ng/mL in females; and mean CBD AUC_{0-t} values of 12500, 26900 and 20500 ng.h/mL in males, and 16500, 35900 and 22400 ng.h/mL in females, were observed at CBD dose levels of 10, 50 and 100 mg/kg/day respectively.

GWTX1503 Mouse Week 13

Mean maximum CBD plasma concentrations (C_{max}) of 3630, 3410 and 5770 ng/mL in females, and 5120, 3700 and 9810 ng/mL in males; and mean CBD AUC0-t values of 22400, 29500 and 46400 ng.h/mL in females, and 21400, 37000 and 44300 ng.h/mL in males, were observed at CBD dose levels of 100, 150 and 300 mg/kg/day respectively.

Embryofetal toxicity in rat GWTX1454

The main report was updated in order to change NOAEL for maternal toxicity from 250 mg/kg/day to 150 mg/kg/day. Hence NOAEL for both maternal toxicity and embryo-lethality is now 150 mg/kg/day. In the main report, toxicokinetics was deemed unreliable in general. The bioanalytical report was updated with a statement of the Principal Investigator that bioanalytical data from 7-OH-CBD is not reliable. The analysis of 7-COOH-CBD, although not GLP-compliant, can be used.

Toxicokinetics for CBD

Following oral administration of CBD to rats, maximum plasma concentrations (C_{max}) with means of 1980, 3120 and 5420 ng/mL on Gestation Day 6 and 9000, 12800 and 13200 ng/mL on Gestation Day 17, and mean AUC_{0-t} values of 25900, 44300 and 83900 h*ng/mL on Gestation Day 6 and 86300, 149000 and 170000 h*ng/mL on Gestation Day 17, were observed at dose levels of 75, 150 and 250 mg/kg/day (Groups 2-4), respectively.

Exposure to CBD (as measured by C_{max} and AUC_{0-t}) increased with increasing dose in a manner that appeared approximately dose proportional on Gestation Day 6, but less than dose-proportional after repeat dosing, with significant accumulation observed on Gestation Day 17 (ratios ranging from 2.03 to 4.54).

Toxicokinetics for 7-COOH-CBD

Following oral administration of CBD to rats, maximum 7-COOH-CBD plasma concentrations (C_{max}) with means of 1170, 1990 and 4120 ng/mL on Gestation Day 6 and 5020, 6140 and 9550 ng/mL on Gestation Day 17, and mean AUC_{0-t} values of 17100, 36300 and 84200 h*ng/mL on Gestation Day 6 and 41500, 100000 and 155000 h*ng/mL on Gestation Day 17, were observed at dose levels of 75, 150 and 250 mg/kg/day (Groups 2-4), respectively.

Exposure to 7-COOH-CBD (as measured by C_{max} and AUC_{0-t}) increased with increasing dose in a manner that appeared approximately dose proportional, with the exception of C_{max} on Gestation Day 17, where the increase in exposure was less than dose proportional. Significant accumulation was observed on Gestation Day 17, with ratios ranging from 1.84 to 4.28.

Juvenile animal toxicity GWTX1408 supported with a new study with toxicokinetics GWTX18001

The main report was updated in order to change the NOAEL from 15/250 mg/kg/day to 15/150 mg/kg/day due to three inconclusive pup-deaths. Similarly to the other toxicity reports, in the main report, toxicokinetics was deemed unreliable in general. To make up for this, a new study of toxicokinetics was conducted (GWTX18001). NOAEL and exposure at NOAEL are marked in **bold** below.

Toxicokinetics for CBD (GWTX18001)

On PND 4, the mean Purified CBD exposure (AUC_{0-t}) in plasma following a single 15 mg/kg subcutaneous dose of Purified CBD to juvenile rats was 14900 h.ng/mL. Following daily subcutaneous doses of Purified CBD (15 mg/kg/day) on PND 4-6 and a single oral dose on PND 7, mean AUC_{0-t} values were 142000, 199000 and 467000 h.ng/mL at 100, 150 and 250 mg/kg/day, respectively.

Following daily subcutaneous doses of Purified CBD (15 mg/kg/day) on PND 4-6 and daily oral doses on PND 7-70, mean $AUC_{(0-t)}$ values after the final dose were 45600, **75500** and 89500 h.ng/mL for males, and 37300, **61200** and 131000 h.ng/mL for females at 100, **150** and 250 mg/kg/day, respectively.

Where calculable (for 5/20 profiles), elimination half-lives for Purified CBD were between 4.67 and 11.6 hours. There was no apparent difference in t½ between males and females, dose routes, dose levels or sampling occasion. Where half-lives could not be calculated, this was because there were less than three quantifiable data points following C_{max}.

Toxicokinetics for 7-OH-CBD (GWTX18001)

On PND 4, the mean AUC(0-t) for 7-OH-CBD following a single 15 mg/kg subcutaneous dose of Purified CBD to juvenile rats was 497 h.ng/mL. Following daily subcutaneous doses of Purified CBD (15 mg/kg/day) on PND 4-6 and a single oral dose on PND 7, mean $AUC_{(0-t)}$ values for 7-OH-CBD were 3870, 4000 and 5160 h.ng/mL at 100, 150 and 250 mg/kg/day, respectively.

Following daily subcutaneous doses of Purified CBD (15 mg/kg/day) on PND 4-6 and daily oral doses on PND 7-70, mean AUC(0-t) values for 7-OH-CBD after the final dose were 2940, 4130 and 3270 h.ng/mL for males, and 3580, **4760** and 6080 h.ng/mL for females at 100, 150 and 250 mg/kg/day, respectively.

Elimination half-lives (and consequently $AUC_{0-\infty}$) for 7-OH-CBD were not calculable on PND 4, PND 7 or PND 70 because there were less than three quantifiable data points following C_{max}.

Toxicokinetics of 7-COOH-CBD (GWTX18001)

On PND 4, the mean $AUC_{(0-t)}$ for 7-COOH-CBD following a single 15 mg/kg subcutaneous dose of Purified CBD to juvenile rats was 1570 h.ng/mL. Following daily subcutaneous doses of Purified CBD (15

mg/kg/day) on PND 4-6 and a single oral dose on PND 7, mean $AUC_{(0-t)}$ values for 7-COOH-CBD were 17700, 18900 and 24000 h.ng/mL at 100, 150 and 250 mg/kg/day, respectively.

Following daily subcutaneous doses of Purified CBD (15 mg/kg/day) on PND 4-6 and daily oral doses on PND 7-70, mean AUC_{0-t} values for 7-COOH-CBD after the final dose were 28900, **86000** and 82600 h.ng/mL for males, and 25100, **45000** and 130000 h.ng/mL for females at 100, **150** and 250 mg/kg/day, respectively.

Elimination half-lives (and consequently $AUC_{0-\infty}$) for 7-COOH-CBD were not calculable on PND 4, PND 7 or PND 70 because there were less than three quantifiable data points following C_{max}.

Table 4: Exposure at steady state (Median AUC_{T1-T2}[#] at end of treatment) of CBD, 7-OH-CBD and 7-COOH-CBD in patients of clinical study GWEP1521 (dose 25 mg/kg/day) and safety margins based on GTX18001.

Patient group	CBD AUC_{0-5h}/*2	Safety margin for CBD	7-OH-CBD AUC_{0-5h}/*2	Safety margin for 7-OH-CBD	7-COOH-CBD AUC_{0-5h}/*2	Safety margin for 7-COOH-CBD
1-6 years	2770/ 5540	13.6	1390/2780	1.5	41200/82400	1.04
7-11 years	1290/ 2580	29	429/858	4.8	62400/124800	1.45
12-17 years	2750/ 5500	13.7	964/1928	2.1	45700/91400	0.94
18-65 years	2350/ 4700	16.0	587/1174	3.5	31200/62400	1.37
Overall	2480/4980	15.2	598/1196	3.4	43300/86600	0.99

[#]: T1-T2 is not specified, however anticipated to be 0-5h as specified in the legends of Table 4. Exposure in rats at PND70 (male used as example, GWTX18001); CBD: 75500, 7-OH-CBD: 4130, 7-COOH-CBD: 86000 h*ng/mL

Note: Safety margins were calculated by the assessor using Applicant's method of doubling human exposure and exposure at NOAEL for male rats from TK report GWTX18001.

Table 5: GWEP1521: Exposure to CBD and metabolites over time (Mean of all age groups)

Day - Dose	CBD		7-OH-CBD		7-COOH-CBD	
	n[a]	Arithmetic Mean AUC_{0-t} (h·ng/mL) (CV%)	n[a]	Arithmetic Mean AUC_{0-t} (h·ng/mL) (CV%)	n[a]	Arithmetic Mean AUC_{0-t} (h·ng/mL) (CV%)
Visit 3 (Day 1)-25 mg/kg/day	35	230 (71.6)	35	92.2 (83.4)	30	2120 (54.2)
Visit 3 (Day 1)- 50 mg/kg/day	32	198 (66.0)	31	67.7 (86.0)	27	1820 (51.8)
Visit 10 (Day 113)- 25 mg/kg/day	34	2520 (52.4)	27	723 (52.3)	34	47200 (78.3)
Visit 10 (Day 113)- 50 mg/kg/day	12	2730 (87.2)	11	773 (79.7)	12	62000 (79.8)

7-COOH-CBD = 7-carboxy-cannabidiol, 7-OH-CBD = 7-hydroxy-cannabidiol, AUC_{0-t} = area under the concentration-time curve from administration/time zero to the last time point, CBD = cannabidiol, CV% = coefficient of variation.

[a] n is the number of patients with a numeric result for the given evaluation. Patients excluded from analysis included patients who were withdrawn early or those who had a reduction from their randomized CBD-OS dose during the conduct of the trial.

[redacted]

Metabolism

A report concerning potential induction of CYP2C8, 9 and 19 isoenzymes was submitted. CBD was evaluated in cryopreserved human hepatocytes in concentrations up to 20 µM. The following conclusions could be made:

- CBD was soluble in incubation medium up to 20 µM.
- CBD was not cytotoxic to human hepatocytes at concentrations up to 20 µM during the 48 hours induction assessment.
- CBD is unlikely to be an inducer of CYP2C8 or 2C9 at the concentrations tested in the study.
- There was some evidence for induction of CYP2C19 by CBD in donors 2 and 3. However, a concentration-dependent effect was suggested only in donor 3. The calculated R3 value (based on the effect seen with CBD concentrations of 1 to 20 µM, only) was >0.8 and therefore this is not considered positive for enzyme induction.

Other toxicity studies

A new version of the dependence study report 'Purified CBD: Potential Self-Administration in Male Rats' (GWTX1551) was provided in this procedure.

The main report is updated stating the no GLP compliance for the Pharmacokinetics Phase of the study. and all pharmacokinetics data was removed from main report.

A new version of the bioanalytical report was submitted with a statement from Principal Investigator stating that the quantification of 7-OH-CBD and 7-COOH-CBD is not reliable. It is presumed that the quantification of CBD can be used. Rats were dosed 5, 25 or 75 mg/kg/infusion. Mean AUC_{0-inf} was 195, 978, 2100 h*ng/mL and mean C_{max} was 1390, 6640, 13500 ng/mL. Hence, $AUC_{0-\infty}$ was similar to clinically relevant at the highest dose and C_{max} higher than clinically relevant at all doses in this study.

2.2.5. Ecotoxicity/environmental risk assessment

Within the initial MAA, the CHMP agreed that Phase II assessment was not necessary for the 0.15 mg/L $PEC_{SURFACEWATER}$ based on the following:

1) CBD is already present in the environment as a natural substance in considerable amounts,

2) has shown a low potential for toxicity in a zebrafish pilot assay (high NOEL of 314 µg/L when PECSURFACEWATER for CBD in EU being 0.15 µg/L) and

3) is highly metabolised in humans,

the environmental risk of CBD is considered low and no further studies are required."

In line with the Q&A document for the ERA guideline (EMA/CHMP/SWP/44609/2010 Rev. 1) and the ERA guideline (EMEA/CHMP/SWP/4447/00 corr 2), an updated ERA report was submitted in order to include the new proposed indication of TSC.

The drug substance, cannabidiol (CBD), is a natural component in hemp plants (Cannabis sativa L.) as detailed in various publications including by the European Food Safety Authority/EFSA (2011), Florez-Sanchez and Verpoorte (2008) and Andre et al (2016). The Sponsor uses a process of a chemical transformation of milled botanical raw material from Cannabis sativa to de-carboxylate cannabidiolic acid (CBDA) and a series of subsequent process stages to the isolation of CBD as a purified drug substance ≥ 98% purity. CBD is thus placed as a semi-synthetic drug substance, originating from a herbal source. CBD is naturally found in hemp plants and seeds. The EFSA (2011) provided a Scientific Opinion on the safety of hemp (Cannabis genus) for use as animal feed, and in this report, it is stated that hemp is cultivated in Europe to produce fibre, seeds and derived oil. Between 2002-2010, up to ~15,000 hectares of hemp have been cultivated per year, giving annual amounts of ~25,000 tonnes of fibre, ~40,000 tonnes of hemp hurds and ~6000 tonnes of hemp seed. Apart from the major cannabinoid in the hemp plant, which is delta-9-tetrahydrocannabinol (THC) and its acid precursor (up to 90% of total cannabinoids), other main components are CBD and cannabinol (CBN). As summarized by Andre et al (2016), hemp seed, hemp stem, hemp leaf and hemp flower (each from the fibre-type plant as cultivated throughout Europe, rather than the drug-type plant) contain up to 244, 18090, 20000 and 8590 µg CBD per gram dry weight, respectively.

It can therefore be concluded that much greater overall environmental exposure to CBD will occur as a result of hemp cultivation in Europe, compared to use of CBD in Epidyolex (CBD) Oral Solution, and also taking into account CBD will be metabolised in patients with only a small proportion of the dose excreted as parent CBD.

Nevertheless, based on prevalence of DS, LGS and TSC, the MAH provided an updated $PEC_{SURFACEWATER}$ estimate as 0.2625 µg/L.

In line with the Guideline and the previous ERA conclusion, the CHMP concluded that Epidyolex present a low risk to the environment and is exempt from performing Phase II environmental risk assessment studies.

2.2.6. Discussion on non-clinical aspects

Pharmacology

Three new *in vivo* studies and a PKPD report were submitted to support the understanding of antiepileptic effect of CBD and the new TSC indication.

Two *in vivo* studies of CBD and its active metabolite 7-OH-CBD in the mouse 6 Hz psychomotor model (GWPP17072, GWPP18020), including exposure in plasma and brain around t_{max}, made the basis for a PKPD exercise (GWPP18094). Using data from these two studies, ED_{50} was determined to be 32.1 mg/kg for 7-OH-CBD and 49.6 mg/kg for CBD. When brain exposure was considered using results from the PKPD report, the potency of 7-OH-CBD was even better (the EE_{50} values were determined to be 8.7 µM for 7-OH-CBD and 47.3 µM for CBD). Both compounds appeared highly efficient, however the ED_{50} values should be put into context of human exposure. Although the exposure achieved at ED_{50} in mouse was higher than clinical exposure, analysis using allometric scaling of dose indicated that patients given the scaled equivalent of ED_{50} may exceed exposure observed in mouse. It is noted that brain exposure in humans is not known, and the conversion of ED_{50} in mouse was done by calculating the Human Equivalent Doses (HED). Other *in vivo* seizure studies indicate that mouse may be less sensitive to CBD as compared to rat, hence the quantitative EC_{50} is not of concern even though EC_{50} are higher than human exposure.

In a third study (GWCRI17024), a rat model was used for characterizing the CBD efficacy and the separation to adverse effects in the lithium-pilocarpine model of chronic epilepsy (6 weeks treatment). This model appears to be a valuable supplement to the more acute seizure animal models discussed in the initial Epidyolex MAA and seems relevant as non-clinical proof of concept for the chronic diseases CBD is intended to treat (Dravet and Lennox-Gastaut syndromes and the currently new proposed indication in TSC). In this study, a relatively high dose (200 mg/kg/day) was used. Unfortunately, this study was not supported with plasma or brain exposure.

Overall these new pharmacology studies and data support the understanding of the mechanism of action of CBD. However, a solid PKPD relationship has not been established.

Toxicokinetics

In most of the pivotal toxicity studies provided in the initial MAA, bioanalysis was deemed unreliable or not in compliance with GLP. The reports on most pivotal toxicity studies were therefore resubmitted in this extension of indication variation with a statement from the Study Director that bioanalysis and toxicokinetics was deemed not reliable and not taken into account when concluding on the studies. Similarly, the bioanalytical reports were resubmitted with a statement from Principal Investigator regarding the analytes which were not deemed reliable. After reviewing the bioanalytical reports and validation reports in the iMAA procedure, it was concluded that bioanalysis of CBD was adequately reliable but not of the metabolites. The safety margins were therefore only published for CBD. This also applies for this procedure.

One new GLP compliant toxicokinetics study was submitted in this procedure (juvenile rats, GWTX18001). Considering the new higher maximum dose of 25 mg/kg/day for TSC patients (as compared to 20 mg/kg/day for Dravet and Lennox-Gastaut indications), the safety margins for CBD were recalculated based on the exposures of TSC patients in the study GWEP1521. They are appropriately reflected in section 5.3 in the SmPC.

The new GLP compliant toxicokinetics study also allow a preliminary basis for calculation of safety margin to the major metabolite in humans 7-COOH-CBD (>90% of drug related material in plasma of patients) at or below 1. Since the dose of CBD is as high as 1-2 g/day and liver toxicity is a common adverse effect, this is still a concern and will be further investigated in the additional studies regarding the safety evaluation of 7-COOH-CBD (see below)

In a study on human hepatocytes, CBD was shown not to be an inducer of CYP2C8, 9 and 19 isoforms.

Toxicology

No new toxicity studies were submitted with this procedure. During the iMAA procedure, in view of the lack of reliable exposure data for the metabolites and apparent low safety margin for the major human metabolite 7-COOH-CBD, the MAH committed to provide several non-clinical studies post-marketing.

In this procedure, given the concerns regarding the high exposure of 7-COOH-CBD in patients in view of limited safety margins provided by non-clinical studies, the commitments including the associated timelines were further discussed. It was noted that the 2 reproductive toxicity studies of 7-COOH-CBD in rat are expected to be completed in Q1 2023, the 10-week juvenile animal toxicology study in Q4 2023 and the 2-year carcinogenicity study in Q4 2025.

A commitment for submission of studies supporting safety evaluation of the human major metabolite 7-COOH-CBD has been provided.

Assessment of paediatric data on non-clinical aspects

In view of a new indication, a new maximal daily dose (25 mg/kg vs 20 mg/kg) and a new proposed age limit for paediatric patients (1 year of age and older instead of ≤2 years), the applicability of previously submitted data the design of the juvenile animal study (JAS) was discussed by the MAH.

It is agreed that design of conducted Juvenile Animal Study covered the newly paediatric population and that the study conforms with the guideline. The liver as target organ for toxicity undergoes a critical period of structural and functional growth and development in both neonates (< 1 month – 15 years of age) and pup rats (up to PND 35). The juvenile toxicity study (GWTX1408) with dosing commenced from PND 4 via the subcutaneous route changing to oral (gavage) administration from PND 7 to 70 covered this sensitive period. The pathology findings observed in the liver, thyroid, and adrenals on the juvenile study were consistent with those observed in the adult rat study. These findings demonstrated full or partial recovery following a 6-week off-dose period.

No neurological effects or effect on long bone growth were recorded. Isolated increase of bone mineral density in males of high dose group was reversible during recovery. Increase of biochemistry parameters such as cholesterol, calcium and protein did not result in toxicity findings. Underlying cause is therefore unknown (see initial MAA EPAR). In this procedure, a new toxicokinetic study (GWTX18001) supporting the juvenile animal study in rat (oral administration) was provided. This study provides exposure for both CBD and the two major human metabolites after sub-chronic dosing (from PND4 to PND70). The safety margins were recalculated based on these new data.

2.2.7. Conclusion on the non-clinical aspects

The CHMP agrees that the available non-clinical data are acceptable to support the proposed TSC indication.

A commitment for submission of studies supporting safety evaluation of the human major metabolite 7-COOH-CBD has been provided.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical study

The clinical development program supporting the efficacy of CBD-OS in TSC comprises a single, Phase 3, randomized, placebo-controlled trial (GWEP1521) that investigated 25 mg/kg/day and 50 mg/kg/day CBD-OS for the treatment of TSC-associated seizures.

Table 6

Table 7-1 Summary of CBD-OS Pharmacokinetics from the GWEP1521 Patient Trial

Trial Number and Design (Country), Product ID, Batch Number	Trial Objectives	Population No. Subjects (Male/Female) Age Range	Treatments Route, Dose, Dosage Form	PK Parameters
GWEP1521 Phase 3, randomized, DB, placebo-controlled (US, Spain, Poland, Australia, the Netherlands, UK) CBD-OS [redacted]	To evaluate the efficacy of CBD-OS as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with TSC. To determine the PK of CBD and its major metabolites following single and MDs of CBD-OS To investigate the effect of CBD-OS on the plasma concentrations of concomitant AEDs, where available	TSC patients 224 (131/93) 1 to 56.7 years	CBD-OS 25 or 50 mg/kg/day MD	**CBD and Metabolite Plasma Concentrations**

CBD

CBD-OS Dose (mg/kg/day) and PK Day	Cobs (0h)[a]	Cobs (2.5h)[a]	Cobs (4.5h)[a]	Cobs (5h)[a]	Cobs (6.5h)[a]	Cobs (9h)[a]	AUC 0-t[a]
25 Day 1	0.171 (728)[b]	54.3 (113)[f]	21.4 (111)[i]	40.9 (137)[l]	60.5 (150)[i]	34.7 (153)[q]	230 (71.6)[♣]
25 Day 113	195 (56)[c]	611 (56.7)[g]	762 (82.9)[j]	496 (82.7)[m]	451 (52.8)[j]	329 (69.3)[r]	2520 (52.4)[$]
50 Day 1	BLQ (NC)[d]	52.4 (96.2)[h]	78.5 (53.3)[j]	35.7 (117)[n]	22.6 (45.9)[p]	19.6 (142)[s]	198 (66)[£]
50 Day 113	242 (49.6)[e]	726 (90.9)[e]	593 (NC)[k]	604 (83.6)[o]	456 (NC)[k]	547 (88.4)[t]	2730 (87.2)[o]

7-OH-CBD

CBD-OS Dose (mg/kg/day) and PK Day	Cobs (0h)[a]	Cobs (2.5h)[a]	Cobs (4.5h)[a]	Cobs (5h)[a]	Cobs (6.5h)[a]	Cobs (9h)[a]	AUC 0-t[a]
25 Day 1	0.192 (700)[u]	23.3 (114)[d]	3.63 (141)[v]	15.2 (94.7)[d]	20.2 (70.2)[v]	11.8 (82.8)[w]	92.2 (83.4)[£]
25 Day 113	72.8 (57.4)[m]	171 (59.1)[x]	601 (NC)[k]	144 (64.3)[y]	NA	87 (77.2)[z]	723 (52.3)[y]
50 Day 1	BLQ (NC)[u]	19 (108)[g]	3.2 (NC)[k]	13.9 (79.1)[$ £]	3.78 (NC)[k]	7.83 (63.1)[o]	67.7 (86)[#]

2.3.2. Pharmacokinetics

The following PK data were provided to support the new indication in TSC:

- The PK data collected during the Phase 3 pivotal trial in patients with TSC (GWEP1521)
- A pooled Population PK analysis and exposure-response analyses in TSC (GWPP19217) were conducted based on the data collected during the CBD-OS clinical development program

Trial GWEP1521 was a randomized, double-blind (DB), 16-week treatment period efficacy trial, followed by a 10-day taper period (or entry into the open-label extension (OLE) phase of the trial). The PK of CBD and its major metabolites (based on AUC derived from sparse sampling) were investigated following single and multiple doses (MDs) of CBD-OS (or placebo [2:2:1:1 ratio of 25 or 50 mg/kg/day CBD OS versus placebo at 25 or 50 mg/kg/day dose volume equivalents]). In addition, the effects of CBD-OS on clobazam (CLB) (and N-desmethylclobazam (N-CLB)), and other AEDs if taken as concomitant medications, were investigated.

In total, 224 patients (mean age 13.6 years) with a confirmed diagnosis of TSC were randomized, and received at least 1 dose of DB investigational medicinal product (IMP), 201 completed the trial, and the PK of CBD and its major metabolites were investigated in 104 patients randomized to 25 or 50 mg/kg/day CBD-OS.

Absorption

The absolute bioavailability of oral CBD is low (6.49%).

Effect of Food on CBD Pharmacokinetics

In randomized controlled trials, patients were not restricted with regards to timing of dose of CBD-OS. Food intake was shown to impact the relative bioavailability of CBD with a positive 3-fold increase when CBD-OS was taken with a high-fat meal. This increase was moderate when that prandial state was not fully known (2.2-fold increase of the relative bioavailability as seen in the GWPP19217 report). The estimated magnitude of this food-effect is in agreement with a previously reported 2.5-fold increase in CBD bioavailability in healthy subjects (GWPP16110 report).

Distribution

No new data submitted

Elimination

No new data submitted

Dose proportionality and time dependencies

The arithmetic mean CBD and metabolite plasma concentrations and PK parameters for patients included in the analysis for GWEP1521 are presented in the following Table 7:

Table 7

Table 2-1 GWEP1521: Exposure to CBD and Metabolites Over Time						
	CBD		7-OH-CBD		7-COOH-CBD	
Day - Dose	n[a]	Arithmetic Mean AUC_{0-t} (h·ng/mL) (CV%)	n[a]	Arithmetic Mean AUC_{0-t} (h·ng/mL) (CV%)	n[a]	Arithmetic Mean AUC_{0-t} (h·ng/mL) (CV%)
Visit 3 (Day 1)-25 mg/kg/day	35	230 (71.6)	35	92.2 (83.4)	30	2120 (54.2)
Visit 3 (Day 1)-50 mg/kg/day	32	198 (66.0)	31	67.7 (86.0)	27	1820 (51.8)
Visit 10 (Day 113)-25 mg/kg/day	34	2520 (52.4)	27	723 (52.3)	34	47200 (78.3)
Visit 10 (Day 113)-50 mg/kg/day	12	2730 (87.2)	11	773 (79.7)	12	62000 (79.8)

7-COOH-CBD = 7-carboxy-cannabidiol; 7-OH-CBD = 7-hydroxy-cannabidiol; AUC_{0-t} = area under the concentration-time curve from administration/time zero to the last time point; CBD = cannabidiol; CV% = coefficient of variation.

[a] n is the number of patients with a numeric result for the given evaluation included in the analysis.

[redacted]

- In the 25 mg/kg/day group, the mean plasma concentration at steady state (predose, end of treatment [Day 113]) was 195 ng/mL (range: 73.0 to 452 ng/mL) and mean (CV%) AUC0 t was 2520 h·ng/mL (52.4%) and in the 50 mg/kg/day group, mean plasma concentration at steady state was 242 ng/mL (range: 42 to 462 ng/mL) and mean (CV%) AUC0 t was 2730 h·ng/mL (87.2%).
- On the last day of treatment (Day 113; at steady state), exposures to CBD and its metabolites (based on AUC0–t) were similar between the 25 mg/kg/day and the 50 mg/kg/day CBD-OS groups.
- At steady state, 7-COOH-CBD was the most abundant circulating product followed by CBD and 7-OH-CBD.

The metabolite-to-parent drugs ratios based on AUC0 t (summarized in Table 8) increased for 7 OH CBD between Day 1 (first dose of 2.5 mg/kg in both treatment groups) and Day 113 (steady state 25 and 50 mg/kg/day) whereas for 7 COOH-CBD there was a 122% increase in the 25 mg/kg/day group and 212% increase in the 50 mg/kg/day group between Day 1 and 113.

Table 8

Table 3-2 Comparison of Metabolite-to-parent Ratios for Patients in the GWEP1521 Trial of CBD-OS							
					Metabolite-to-Parent Ratio		
Trial/Type	Day/Dose Freq.	Population	Dose	Parameter	6-OH-CBD	7-OH-CBD	7-COOH-CBD
GWEP1521-MD	Day 1 SD[a]	1 to 6 year old patients with TSC	25 mg/kg/day	AUC_{0-t}	NC	0.38	5.7
			50 mg/kg/day	AUC_{0-t}	NC	0.45	15.9
	Day 113 MD		25 mg/kg/day	AUC_{0-t}	NC	0.40	12.1
			50 mg/kg/day	AUC_{0-t}	NC	0.52	46.8
	Day 1 SD[a]	7 to 11 year old patients with TSC	25 mg/kg/day	AUC_{0-t}	NC	0.48	11.0
			50 mg/kg/day	AUC_{0-t}	NC	0.37	10
	Day 113 MD		25 mg/kg/day	AUC_{0-t}	NC	0.33	50.2
			50 mg/kg/day	AUC_{0-t}	NC	0.31	24.1
	Day 1 SD[a]	12 to 17 year old patients with TSC	25 mg/kg/day	AUC_{0-t}	NC	0.40	12.8
			50 mg/kg/day	AUC_{0-t}	NC	0.65	13.9
	Day 113 MD		25 mg/kg/day	AUC_{0-t}	NC	0.32	18.7
			50 mg/kg/day	AUC_{0-t}	NC	0.32	36.7
	Day 1 SD[a]	18 to 65 year old patients with TSC	25 mg/kg/day	AUC_{0-t}	NC	0.38	11.8
			50 mg/kg/day	AUC_{0-t}	NC	0.30	6.7
	Day 113 MD		25 mg/kg/day	AUC_{0-t}	NC	0.28	18.6
			50 mg/kg/day	AUC_{0-t}	NC	0.28	24.1

6-OH-CBD = 6-hydroxy-cannabidiol, 7-COOH-CBD = 7-carboxy-cannabidiol, 7-OH-CBD = 7-hydroxy-cannabidiol, AUC_{0-t} = area under the concentration-time curve from administration/time zero to the last time point, CBD-OS = cannabidiol oral solution, MD = multiple-dose, NC = not calculable, SD = single-dose, TSC = tuberous sclerosis complex.

[a] Patients were taking 5 mg/kg/day on Day 1 as this was the start of the titration period.

[redacted]

Special populations

There were no effects of intrinsic factors, including age, weight, sex, and race on any PK parameters (GWPP19217).

Total and Inter-subject Variability

Although non-compartmental analysis was conducted for the patient trials, due to the sparse sampling design of these trials, the intersubject variability in patients were better described by the population PK analysis GWPP19217. A comparison of intersubject variability estimates for the clearance and volume parameters from pooled population PK analyses (Healthy Volunteers and patients) is provided in the following Table 9. The estimates of intersubject variability in patients and HV are relatively similar (approximately 2-fold higher in patients), despite the expected larger variation in demographics and concomitant medication use in the patient population.

Table 9

Table 3-1 Population PK Estimates of Interindividual Variability Estimates on Clearance and Volume Parameters from Population PK Analysis		
	Healthy Volunteers	Patients
Parameter	Intersubject Variability (%)	
IIV VP1	27.6	48.8
IIV VP2	91.3	NA
IIV $CL_{F\text{-}7\text{-}OH\text{-}CBD}$	53.4	124.5
IIV $CL_{F\text{-}7\text{-}COOH\text{-}CBD}$	37.8	101
IIV $CL_{E\text{-}7\text{-}COOH\text{-}CBD}$	41.2	97.4

$CL_{E\text{-}7\text{-}COOH\text{-}CBD}$ = apparent elimination clearance of 7-COOH-CBD; $CL_{F\text{-}7\text{-}COOH\text{-}CBD}$ = Apparent formation clearance of 7-COOH-CBD; $CL_{F\text{-}7\text{-}OH\text{-}CBD}$ = apparent formation clearance of 7-OH-CBD; IIV = interindividual variability; NA = not applicable; PK = pharmacokinetics; VP1 = apparent central volume of distribution of CBD; VP2 = apparent peripheral volume of distribution of CBD.

[redacted]

Pharmacokinetic interaction studies

AED Plasma Concentrations

Where available, plasma concentrations of concomitant AEDs were summarized pre-dose on Day 1 in the absence of CBD-OS, and following multiple dosing in combination with CBD-OS or placebo on Day 29, 57, 85, and end of treatment; blood samples for AED analysis were taken prior to IMP administration on each occasion, but no restrictions were placed on when sampling should occur relative to concomitant AED dosing.

Plasma levels of AEDs from Day 1 (pre-IMP) were above the LLOQ for a subset of patients (highest n at any time point in any treatment group per analyte: CLB, 17; N CLB, 17; LEV, 22; TPM, 14; VPA, 35). Due to limited data and because subjects were receiving a variable number of AEDs, interpretation should be made with caution (GWEP1521)

- The majority of patients taking each AED had data at baseline and at least 1 subsequent time point; for 4 ene VPA, there were no patients who took VPA that had 4 ene-VPA > LLOQ and this was likely because of assay sensitivity.
- Mean plasma concentrations of CLB, LEV, TPM, and VPA were similar between the 3 treatment groups and did not change during the conduct of the trial.
- Mean N-CLB plasma concentrations at all visits had increased relative to predose on Day 1 in both the 25 mg/kg/day CBD OS group and the 50 mg/kg/day CBD OS group (Table 10). A total of 72.8% of patients were not receiving CLB.

Table 10

Table 2-2 Mean N-CLB Plasma Concentration					
	Day 1	Day 29	Day 57	Day 85	EOT
Mean N-CLB plasma concentration (ng/mL), 25 mg/kg/day CBD-OS	3350	9100	8740	8750	6890
Mean N-CLB plasma concentration (ng/mL), 50 mg/kg/day CBD-OS	2640	8870	10200	10200	9820

CBD-OS = cannabidiol oral solution; EOT = end of treatment; N-CLB = N-desmethylclobazam.

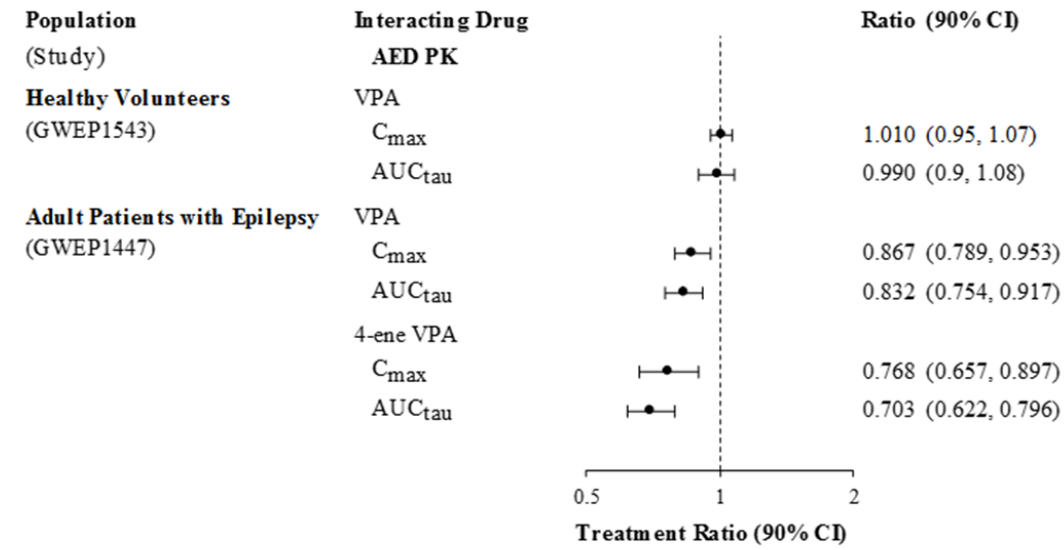
- Mean N-CLB levels in the pooled placebo group were lower than predose Day 1 at all subsequent trial visits. As a result, N-CLB:CLB ratios increased from Day 1 predose values in patients taking CBD-OS whereas in the pooled placebo group, N CLB:CLB ratios were similar throughout the trial.

Co-administration of CBD and valproate:

Decreases in plasma Cmax and AUCtau of VPA (Cmax: 17%; AUCtau: 21%) and 4 ene-VPA (Cmax: 28%; AUCtau: 33%) has been demonstrated in patients with epilepsy in GWEP1447, see Figure 4 below:

Figure 4

Figure 2-13 Effect (Geometric Mean Ratio and 90% CIs) of CBD-OS on Steady-state Valproate PK Parameters in Healthy Volunteers and Patients



4-ene VPA = 2-propyl-4-pentenoic acid; AED = antiepileptic drug; AUC_{tau} = area under the plasma concentration- time curve over a dosing interval, where tau is the dosing interval; CBD-OS = cannabidiol oral solution; CI = confidence interval; C_{max} = maximum measured plasma concentration; PK = pharmacokinetic; VPA = valproic acid.

[redacted]

2.3.3. Pharmacodynamics

Mechanism of action

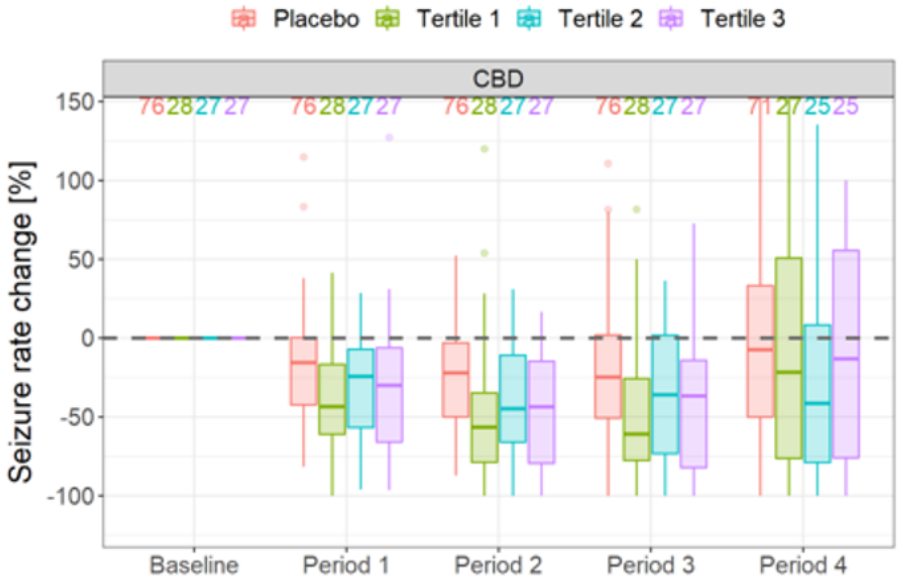
CBD showed anticonvulsant effect in several relevant animal seizure models. The proposed targets are as an antagonist on the GPR55 receptor, a TRPV1 agonist inducing desensitization and a reuptake inhibitor of adenosine.

Pharmacokinetic-efficacy Relationships

A logistic regression was carried out to analyse the probability of a subject being a treatment responder, i.e., having at least 50% reduction from baseline in the frequency of TSC-related seizures over 28-day periods, in relation to AUC0-12, Day 71 of the 3 analytes. Placebo patients were excluded from this analysis.

Figure 5

Figure 3.5-1 Plot of the Relative Change from Baseline in 28-day Period Seizure Frequency Split by Treatment Group or by Tertiles of $AUC_{0\text{-}12,\ Day\ 71}$ for CBD



AUC = area under the concentration-time curve; CBD = cannabidiol.
Note: Periods denote 28-day periods.

[redacted]

The plot of relative change from baseline for CBD is presented in Figure 5 above. None of the tested relationships was statistically significant at a significance level of 0.05.

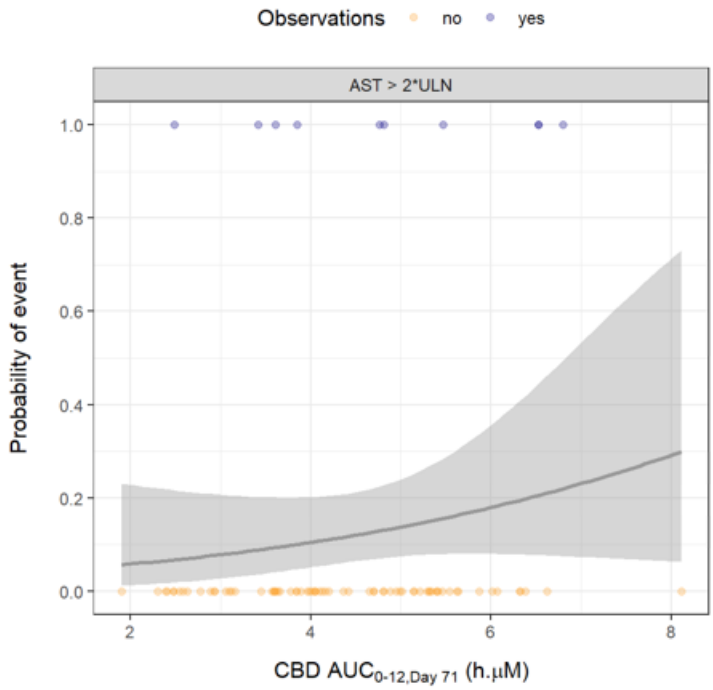
In order to investigate the off-CLB exposure-response relationship, a similar logistic regression analysis was carried out for the subset of patients who did not receive concomitant CLB therapy. As for the overall treated population (i.e. including patients with concomitant CLB) none of the tested relationships was statistically significant at a significance level of 0.05.

Pharmacokinetic-safety Relationships

No exposure-response analysis could be performed for severe non-laboratory AEs owing to the very limited number of patients within the PK population experiencing events (one patient with severe diarrhoea and one patient with severe nausea). No statistically significant relationship ($p < 0.05$) was identified between AUCss of any of the analytes and the AEs included in the logistic regression analysis (diarrhoea, loss of appetite, somnolence of any severity). When analysing exposure-response relationships for the laboratory AEs, a statistically significant relationship was identified between the probability of AST increase above 2 times the ULN and AUCss of 7-OH-CBD. The estimated odds ratio of 2.53 (95% confidence interval, 1.14 to 5.99) for a unit increase in AUCss of 7-OH-CBD denoted a relatively shallow exposure-response relationship.

Figure 6

Figure 3.6-1 Logistic Regression for the Probability of Laboratory Adverse Event of AST Elevation in Relation to $AUC_{0\text{-}12,\ Day\ 71}$ of CBD



AST = aspartate aminotransferase; $AUC_{0\text{-}12,\ Day\ 71}$ = area under the concentration-time curve during a 12-hour interval on Day 71; CBD = cannabidiol; ULN = upper limit of normal.
Symbols: observations; line (shaded area), logistic regression curve (95% confidence interval).

[redacted]

Effect of CBD OS on QT Interval

The results of the TQT trial demonstrated that CBD-OS did not significantly affect ECG parameters.

2.3.4. PK/PD modelling

GWPP19217: Population Pharmacokinetic Analysis and Exposure Response Analysis in Patients with Tuberous Sclerosis Complex

A POPPK model was built to derive individual exposure metrics of CBD, 7-OH-CBD and 7-COOH-CBD in patients with TSC from trial GWEP1521, using a joint population PK model previously developed in healthy adults (GWPP16110), and further refined using sparse data from trials (GWEP1332A, GWEP1414, GWEP1423, GWEP1424, and GWEP1521), and to explore (and possibly model) relationships between exposure metrics, seizure frequency, and selected AEs (GWPP19217).

Method

The population PK model previously developed in LGS patients (GWPP17004) was transposed to the current pooled patient population (including information from TSC, DS, and LGS patients).

The first step was to apply the POPPK Model to the pooled population of patients fixing parameter estimates to the values previously obtained. The second step consisted of re-evaluation of the absorption model based on the available data. The IIV was estimated to account for the between-subject-variability in the patient population. Then, a covariate modelling was performed to integrate the potential significant covariates explaining part of the variability. Finally, individual simulation-based exposure metrics were derived.

The POPPK Model structure comprises two compartments for CBD with a linear disposition parameterized as CLF-7-OH-CBD, CL10, Q12, VP1, and VP2. CBD was assumed to be sequentially converted into 7-OH-CBD and 7-COOH-CBD.

A one-compartment structure was sufficient to describe the disposition of 7-OH-CBD and 7-COOH-CBD. The estimated parameters were apparent formation and elimination clearances. Apparent central volumes of distribution were set to 1 L for both metabolites to prevent structural identifiability issues.

CBD absorption followed zero-order absorption kinetics (duration: D1).

For the PK/PD analyses, correlations were assessed graphically and if sufficient data was available for a quantitative test, then a regression analysis was performed, and statistical significance explored on the slope estimate.

Results

The population PK analysis was performed on the basis of a population that had measurable observations of CBD, 7-OH-CBD and 7-COOH-CBD (408 patients) - who received the CBD-OS at nominal doses of 5, 10, 20, 25, or 50 mg/kg/day. The model is overall presented, developed and validated in accordance with regulatory requirements.

The apparent multiphasic concentration-time profiles of 7-OH-CBD were adequately described by a 1-compartment disposition model branched to the 2-compartment disposition model of CBD through a slow formation clearance (CLF-7-OH-CBD: 0.012 L/h). The apparent volume of distribution had to be set to 1 L. Under this assumption, its apparent clearance was 14.44 L/h, all of which formed 7-COOH-CBD.

The following covariates were considered in the PK analysis: age, race, sex, weight, unit dose of CBD-OS, and CLB as a concomitant AED. No covariates had any significant effect of model parameters and thus the final population PK model was identical to the base model. Parameter estimates of the final model and estimates of IIV on the model parameters are presented in Table 11and Table 12 (below).

The evaluation of the final population PK model did not reveal any bias, allowing the derivation of exposure metrics on Day 71.

Table 11

Table 2-3 GWPP19217: Parameter Estimates of the Final Model					
Description	**Unit**	**Estimate on Log Scale**	**RSE (%)**	**95% CI on Log Scale**	**Estimate on Normal Scale**
D_1	h	0.739	9.1	0.608 - 0.870	-
CL_{10}	L/h	4.03	14.7	2.87 - 5.19	-
VP1	L	9.04	5.1	8.14 - 9.94	-
Q_{12}	L/h	3.95	40.3	0.834 - 7.07	-
VP2	L	9.78	12.1	7.47 - 12.1	-
$Dose_{50}$	Mg	4.55	9.1	3.74 - 5.36	-
High fat meal effect on F1	%	1.98	84.8	-1.31 - 5.27	-
Prandial state unknown on F1	%	1.28	93.8	-1.07 - 3.63	-
$CL_{F\text{-}7\text{-}OH\text{-}CBD}$	L/h	-7.39	6.2	-8.29 - -6.49	-
$CL_{F\text{-}7\text{-}COOH\text{-}CBD}$	L/h	2.67	2.5	2.54 - 2.80	-
$CL_{E\text{-}7\text{-}COOH\text{-}CBD}$	L/h	-1.51	4.5	-1.65 - -1.38	-
RUV_{CBD}	%	-	2.6	0.426 - 0.472	44.9
$RUV_{7\text{-}OH\text{-}CBD}$	%	-	51	-0 - 0.003	0.155
$RUV_{7\text{-}COOH\text{-}CBD}$	%	-	3.5	0.397 - 0.455	42.6
Common $RUV_{CBD\text{-}7\text{-}OH\text{-}CBD\text{-}7\text{-}COOH\text{-}CBD}$	µM		5.1	0.653 - 0.799	0.726

CBD = cannabidiol; CI = Confidence interval; CL_{10} = Apparent CBD clearance not forming 7-OH-CBD; $CL_{E\text{-}7\text{-}COOH\text{-}CBD}$ = Apparent elimination clearance of 7-COOH-CBD; $CL_{F\text{-}7\text{-}COOH\text{-}CBD}$ = Apparent formation clearance of 7-COOH-CBD; $CL_{F\text{-}7\text{-}OH\text{-}CBD}$ = Apparent formation clearance of 7-OH-CBD; Common $RUV_{CDB\text{-}7\text{-}OH\text{-}CBD\text{-}7\text{-}COOH\text{-}CBD}$ = Absolute residual unexplained variability common to the 3 analytes; D_1 = Absorption duration; $Dose_{50}$ = Potency of the dose effect on bioavailable fraction of CBD; F_1 = bioavailable fraction of CBD; Q_{12} = Apparent intercompartmental clearance of CBD; RSE = percent relative standard error; $RUV_{7\text{-}COOH\text{-}CBD}$ = Percent residual unexplained variability on 7-COOH-CBD; $RUV_{7\text{-}OH\text{-}CBD}$ = Percent residual unexplained variability on 7-OH-CBD; RUV_{CBD} = Percent residual unexplained variability on CBD; VP1 = Apparent central volume of distribution of CBD; VP2 = Apparent peripheral volume of distribution of CBD.

S[redacted]

Table 12

Table 2-4 GWPP19217: Interindividual Variability in Model Parameters				
Description	**Estimate**	**RSE%**	**CV%**	**Shrinkage %**
IIV CL_{10}	0.315	44.8	56.1	22.4
Correlation IIV CL_{10} IIV VP1	0.121	30.1	44.2	-
IIV VP1	0.238	31.8	48.8	15.9
IIV $CL_{F\text{-}7\text{-}OH\text{-}CBD}$	1.55	14.1	124.5	7.1
Correlation IIV $CL_{F\text{-}7\text{-}OH\text{-}CBD}$ IIV $CL_{F\text{-}7\text{-}COOH\text{-}CBD}$	1.09	17.1	86.7	-
IIV $CL_{F\text{-}7\text{-}COOH\text{-}CBD}$	1.02	17.2	101	8.6
Correlation IIV $CL_{F\text{-}7\text{-}OH\text{-}CBD}$ IIV $CL_{E\text{-}7\text{-}COOH\text{-}CBD}$	0.965	18.4	79.6	-
Correlation IIV $CL_{F\text{-}7\text{-}COOH\text{-}CBD}$ IIV $CL_{E\text{-}7\text{-}COOH\text{-}CBD}$	0.865	19.3	87.9	-
IIV $CL_{E\text{-}7\text{-}COOH\text{-}CBD}$	0.949	17.7	97.4	8.9

CBD = cannabidiol; CV% = coefficient of variation; CL_{10} = Apparent CBD clearance not forming 7-OH-CBD; $CL_{E\text{-}7\text{-}COOH\text{-}CBD}$ = Apparent elimination clearance of 7-COOH-CBD; $CL_{F\text{-}7\text{-}COOH\text{-}CBD}$ = Apparent formation clearance of 7-COOH-CBD; $CL_{F\text{-}7\text{-}OH\text{-}CBD}$ = Apparent formation clearance of 7-OH-CBD; IIV = interindividual variability; RSE% = percent relative standard error; VP1 = Apparent central volume of distribution of CBD.

[redacted]

Within each analyte, all exposure metrics at Day 71 (Cmin, Cmax and AUC) were closely correlated so that AUC could be used as a single, representative metrics of exposure for each analyte. The resulting efficacy and safety exposure-response dataset included 82 subjects on active treatment. The exposure endpoints were derived from the model-based simulations using the individual posthoc parameters and the actual dosing history of the TSC patients included in trial GWEP1521.

Table 13

Table 2-5 AUC_{tau} (ng·h/mL) at Steady State Stratified by Dose Level and Analyte					
Dose level (mg/kg/day)		**Median (ng·h/mL)**	**Min (ng·h/mL)**	**Max (ng·h/mL)**	**Mean (ng·h/mL)**
25 (n = 46)	CBD	1274	723	2138	1327
	7-OH-CBD	459	155	1269	502
	7-COOH-CBD	28830	9300	94032	33238
50 (n = 36)	CBD	1434	597	2550	1434
	7-OH-CBD	522	172	935	552
	7-COOH-CBD	38233	7302	89554	41677

7-OH-CBD = 7-hydroxy-cannabidiol; 7-COOH-CBD = 7-carboxy-cannabidiol; AUCtau = area under the plasma concentration time curve over a dosing interval, where tau is the dosing interval; CBD = cannabidiol; Min = minimum; Max = maximum.

S[redacted]

The frequency of TSC-related seizures was then calculated for each subject on each day in each AUC group, as well as for each dose group (placebo, 25 and 50 mg/kg). The seizure rate change, i.e. the relative change from baseline in daily seizure frequency, was plotted against time and differentiated by treatment cohort or by AUC group.

2.3.5. Discussion on clinical pharmacology

CBD-OS is approved in the EU for use as an adjunctive therapy of seizures associated with LGS or DS, in conjunction with CLB, in patients aged 2 years of age and older. In this extension of indication variation, the MAH propose the use of CBD-OS in the treatment of seizures associated with TSC in patients 1 year of age and older.

Due to the risk of immature PK pathways, the supporting data for patients below the age of 2 years was discussed in regards of posology, efficacy, safety and tolerability. It was acknowledged that the pharmacokinetics of CBD have not been comprehensively studied in subjects below 2 years of age and no patients below the age of 2 have been providing PK data for CBS metabolites.

In addition, the main route of clearance of CBD is via hepatic metabolism, primarily by CYP3A4 and CYP2C19. CBD has been shown to induce major CYP450 enzymes including CYP2C19. Furthermore, CBD is an inhibitor of several CYP450 enzymes including CYP3A4, 2C9 and 2C19.

The MAH argued that CYP450 activity and expression are considered to be equivalent from the age of 12 months to adults for all major CYP450 isoforms, with the exception of CYP2E1 (Blanco 2000 and Upreti 2016), the hepatic blood flow rate is equal to that of an adult by the age of 6 months (Yokoi 2009) and, by 1 year of age, the serum protein binding rate for acidic drugs, such as cannabidiol, is reported to reach that of an adult (Yokoi 2009). However, it was agreed that the presented information should be carefully interpreted, especially in case of drugs with a narrow therapeutic range such as cannabidiol.

Overall, due to lack of PK data in paediatric patients below the age of 2 years, a complex hepatic metabolism of CBD and several potential interactions with AEDs, extrapolation from data in younger patients and adults to children below 2 years of age cannot be accepted and the proposed indication in patients below 2 years of age is not supported.

The unmet medical need in this paediatric population is however acknowledged. In order to collect the relevant PK data in this infant population, the MAH is invited to extend the recruitment for infants up to 2 years in Study 9 of the PIP, GWEP 17005, planned/ongoing in infants suffering from TSC from one month to 1 year of age and discuss its plan. This was acknowledged and agreed by the MAH.

Food intake was shown to impact the relative bioavailability of CBD with a positive 3-fold increase when CBD-OS was taken with a high-fat meal. This increase was moderate when that prandial state was not fully known i.e. 2.2-fold increase of the relative bioavailability. The importance of consistency in prandial status when CBD is administrated has been adequately addressed in the SmPC section 4.2 and 5.2.

Mean N-CLB levels in the pooled placebo group were lower than pre-dose Day 1 at all subsequent trial visits. As a result, N-CLB:CLB ratios increased from Day 1 pre-dose values in patients taking CBD-OS whereas in the pooled placebo group, N-CLB:CLB ratios were similar throughout the trial. These data are consistent with previous trial data where the interaction between CLB and CBD-OS has been evaluated (GWEP1332A, GWEP1428, GWEP1543). In these trials, CLB levels have been relatively unaffected by CBD-OS co-administration and N-CLB exposure has been shown to increase between 2- and 4-fold when CLB is combined with CBD-OS.

In the proposed TSC indication, a drug class known as mTOR inhibitors may be administered, including everolimus, sirolimus and tacrolimus (a related calcineurin inhibitor). These agents are known to be mainly metabolized by CYP3A enzymes. Despite a weak *in vitro* signal, CBD-OS did not affect CYP3A activity in a midazolam probe study (GWEP17028 submitted in the initial MAA), thus there is no expectation that combination of mTOR inhibitors (or related calcineurin inhibitors) with CBD-OS would lead to a clinically important interaction through inhibition of CYP3A. However, there have been some case studies and a retrospective study published (Wiemer-Kruel 2019; Leino 2019; Ebrahimi-Fakhari

2019) which suggest that exposures of mTOR inhibitors (and related calcineurin inhibitors) may be increased after initiating dosing with preparations of CBD, including synthetic CBD. As mTOR inhibitors (and related calcineurin inhibitors) may be administered in TSC and have a narrow therapeutic index, a dedicated DDI study trial is planned to determine the potential for CBD-OS to affect the PK of everolimus. Pending the availabilities of the DDI results, an appropriate level of caution should be provided and information regarding potential interaction and increased plasma concentrations of the mTOR inhibitors/calcineurin inhibitors has been added to the SmPC Section 4.5.

The exposure response analysis in TSC patients did not demonstrate any statistically significant relationship between the probability of being a treatment responder (> 50% reduction in TSC associated seizures) and exposure to CBD and its metabolites that may indicate that the higher dose levels may have resulted in reaching a maximal effect (see also clinical efficacy).

In an exploratory PK/PD analysis for safety endpoints in LGS and TSC, there was evidence for correlation with elevated transaminases. Increases in AST and GGT above twice the ULN were associated with higher CBD AUC in LGS patients. Similarly, for TSC, there was evidence for a correlation with AST and the 7-OH metabolite. The MAH confirms a statistically significant exposure effect relationship for both CBD and its metabolites with elevated liver transaminases (ALT and AST) in LGS (GWPP17004 report). In TSC, this correlation was only apparent for 7-OH-CBD and AST but suggests consistency for a drug-related effect. However, PK-data together with the safety evaluation on liver do indicate that the effect on liver transaminases is predictable with dose and exposure as well as other known risk factors (e.g., concomitant VPA use), and is therefore clinically manageable by appropriate dosing instructions and monitoring as provided in the SmPC.

2.3.6. Conclusions on clinical pharmacology

The CHMP agrees that the available pharmacology data support the proposed TSC indication for patients 2 years of age and older.

In order to further investigate the potential for CBD-OS to affect the PK of everolimus, the MAH will perform a DDI study trial.

2.4. Clinical efficacy

The clinical development program supporting the efficacy of CBD-OS in TSC comprises a single, Phase III, randomised, placebo-controlled trial (GWEP1521) that investigated 25 mg/kg/day and 50 mg/kg/day CBD-OS for the treatment of TSC-associated seizures.

2.4.1. Dose response study(ies)

No dose response studies were performed. Dose selection for phase III was based on clinical experience. Thus, by September 2015, when all 5 RCTs (2 LGS, 2 in DS, and 1 in TSC) were being initiated, doses of up to 50 mg/kg/day had been used in clinical practice (EAP).

2.4.2. Main study

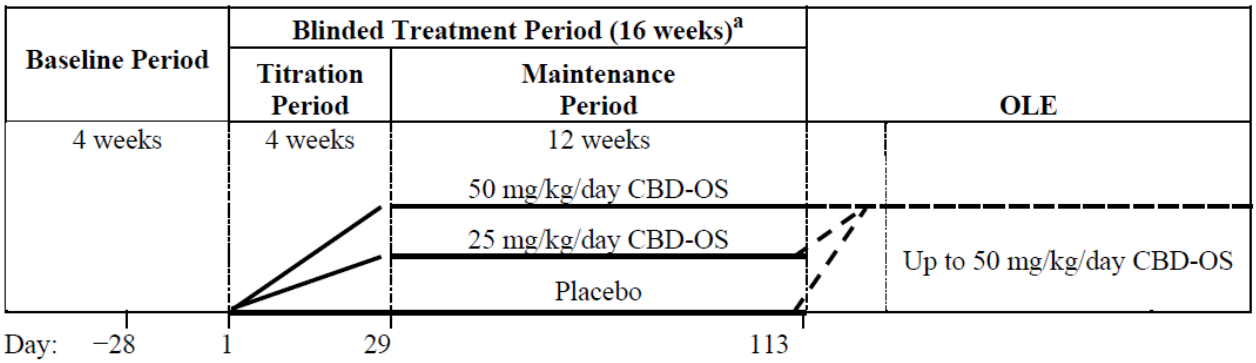
GWEP1521: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures

The GWEP1521 trial was designed to evaluate 25 mg/kg/day CBD-OS and 50 mg/kg/day CBD-OS vs. placebo as adjunctive therapy and consisted of a 4-week baseline period, followed by a 16-week treatment period comprising a 4-week titration (dose escalation) period and a 12-week maintenance (stable dosing) period (

Figure 7). Patients who completed the double-blind phase could transition to the OLE phase of the trial where all patients were titrated to 25 mg/kg/day CBD-OS; the dose could then be adjusted to find an optimal dose for each patient, with titration up to 50 mg/kg/day if required for better seizure control or a decrease in dose if the patient experienced intolerance.

Figure 7

Figure 1-1 GWEP1521 Trial Design Schematic



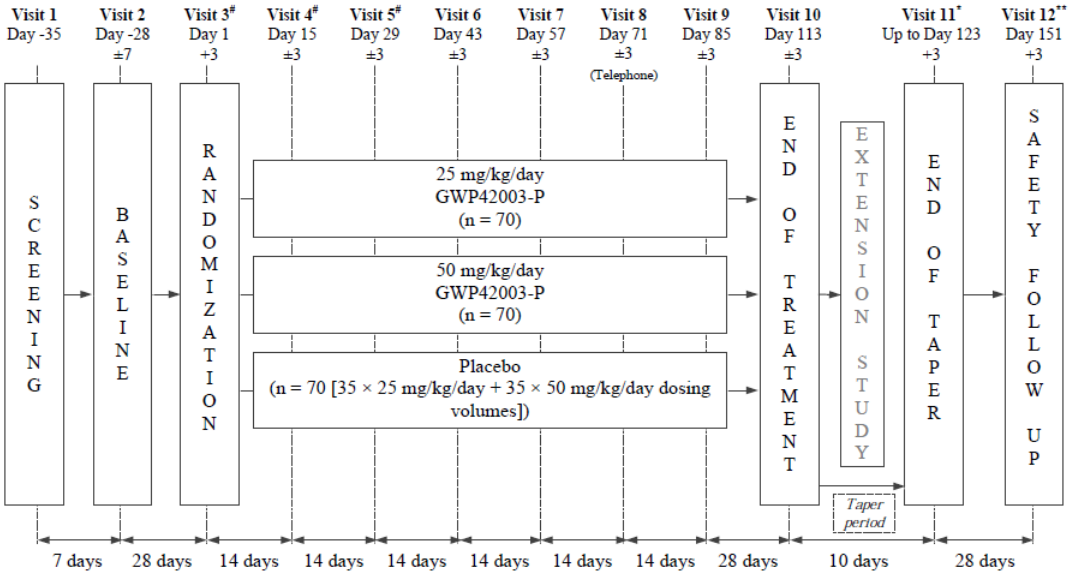
CBD-OS = cannabidiol oral solution; OLE = open-label extension.

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

Seizure counts were recorded daily during the baseline and treatment period using an IVRS telephone diary and were used in the primary and key secondary seizure endpoint analyses. Only patients who met seizure frequency criteria, and all other eligibility criteria, by the end of the baseline period could be randomised into the trial.

Figure 8

Figure 5.1-1 Trial Schematic Diagram



* For patients not entering the open-label extension on Day 113.

** For patients not entering the open-label extension; could be conducted by telephone.

Safety telephone calls were to be completed every 2 days during titration and 1 week after the end of titration. If the call fell on a weekend, it was permitted to schedule the call for the Friday before or Monday after the weekend instead.

[redacted]

Methods

Study participants

For enrolment in the GWEP1521 trial, patients had to be male or female, aged 1 to 65 years (inclusive), with a clinical diagnosis of TSC. The patients had to have well-documented clinical history of epilepsy, which was not completely controlled by their current AEDs and had to have experienced at least 8 seizures during the 4-week baseline period, with at least 1 seizure in at least 3 of the 4 weeks; TSC-associated seizures included: 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 (tonic-clonic, tonic, clonic or atonic) that were countable.

To ensure accuracy of seizure identification and reporting, seizure types were verified by members of a committee of independent experts from the Epilepsy Study Consortium (ESC). Following the screening visit, the ESC reviewed and approved a detailed clinical description of each patient's current seizures, and a list of seizures experienced by the patient in lay terms. The seizure types were either confirmed, or further information was requested, by the ESC until agreement was reached.

Table 14

Table 5.3.1-1	Inclusion Criteria
1.	Patient was male or female aged between 1 and 65 years inclusive.
2.	Patient and/or parent(s)/legal representative was willing and able to give informed consent/assent for participation in the trial.
3.	Patient and their caregiver were willing and able (in the investigator's opinion) to comply with all trial requirements (including accurate diary and IVRS completion).
4.	Well-documented clinical history of epilepsy, which was not completely controlled by their current AEDs.
5.	Clinical diagnosis of TSC according to the criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference.[26]
6.	Taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening.
7.	All medications or interventions for epilepsy (including ketogenic diet and any neurostimulation devices for epilepsy) must have been stable for 1 month prior to screening and the patient was willing to maintain a stable regimen throughout the trial.
8.	Patient was willing to keep any factors expected to affect seizures stable (such as the level of alcohol consumption and smoking).
9.	Patient and/or parent(s)/legal representative was willing to allow the responsible authorities to be notified of participation in the trial, if mandated by local law.
10.	Patient and/or parent(s)/legal representative was willing to allow his or her primary care practitioner and consultant (if they have one) to be notified of participation in the trial, if mandated by local law.
At the end of the baseline period, patients had to also meet the following criteria:	
11.	Experienced at least 8 seizures during the first 28 days of the baseline period, with at least 1 seizure occurring in at least 3 of the 4 weeks (seizures included: 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 [tonic–clonic, tonic, clonic or atonic] that were countable).
12.	Completed at least 90% of calls to IVRS during the first 28 days of the baseline period (a minimum of 25 completed calls).

Abbreviations: AEDs, antiepileptic drug; IVRS, interactive voice response system.
S[redacted]

Table 15

Table 5.3.2-1	Exclusion Criteria
1.	Patient had a history of pseudo-seizures.
2.	Patient had clinically significant unstable medical conditions other than epilepsy.
3.	Patient had an illness in the 4 weeks prior to screening or randomization, other than epilepsy, which in the opinion of the investigator could affect seizure frequency.
4.	Patient had undergone general anesthetic in the 4 weeks prior to screening or randomization.
5.	Patient had undergone surgery for epilepsy in the 6 months prior to screening.
6.	Patient was being considered for epilepsy surgery or any procedure involving general anesthesia during the blinded phase of the trial.
7.	Patient had been taking felbamate for less than one year prior to screening.
8.	Patient was taking an oral mTOR inhibitor.
9.	Patient had, in the investigator's opinion, clinically significantly abnormal laboratory values.
10.	Patient had any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.
11.	Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS in the last month or at screening.
12.	Patient was currently using or has in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the 3 months prior to screening and was unwilling to abstain for the duration for the trial.
13.	Patient had tumor growth which, in the opinion of the investigator, could affect the primary endpoint.
14.	In the opinion of the investigator the patient had clinically significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which would interfere with the ability to read their ECGs.
15.	Patient had significantly impaired hepatic function at the screening visit (Day −35) or the randomization visit (Day 1), defined as **any** of the following: i) Serum ALT or AST > 5 × ULN. ii) TBL* ≥ 2 × ULN or INR > 1.5 (*TBL ≥ 2 × ULN exclusion did not apply for patients diagnosed with Gilbert's disease). iii) Serum ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). *This criterion could only be confirmed once the laboratory results were available.*
16.	Patient was female and of child-bearing potential, or was male whose partner was of child-bearing potential, unless willing to ensure that they or their partner used a highly effective method of birth control (e.g., hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner, sexual abstinence) during the trial and for 3 months thereafter.
17.	Female patient who was pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial and for 3 months thereafter.
18.	Patient had received an IMP less than 12 weeks prior to the screening visit.
19.	Patient had any other significant disease or disorder which, in the opinion of the investigator, may have either put the patient at risk because of participation in the trial, may have influenced the result of the trial, or may have affected the patient's ability to take part in the trial.
20.	Any abnormalities identified following a physical examination of the patient that, in the opinion of the investigator, would jeopardize the safety of the patient if they took part in the trial.
21.	Patient had donated blood during the past 12 weeks and was unwilling to abstain from donation of blood during the trial.
22.	Patient had been previously randomized into this trial.
23.	Patient had any known or suspected history of alcohol or substance abuse.
24.	Patient had travel outside the country and/or state of residence planned during the trial, unless the patient had confirmation that the IMP was permitted in the destination country/state.

Treatments

Eligible patients were randomized to receive GWP42003-P 25 mg/kg/day, GWP42003-P 50 mg/kg/day, placebo 25 mg/kg/day dose-volume equivalent, or placebo 50 mg/kg/day dose-volume equivalent at a 2:2:1:1 ratio. The placebo groups were pooled for the analyses of efficacy. Randomised patients were weighed (Day 1) and the daily volumes of IMP solution to be taken during the maximum 4-week titration period and for the remainder of the trial were calculated and provided to the patient/caregiver. All doses of investigational medicinal product (IMP) were administered orally by the patient or their caregiver twice each day (morning and evening); patients who were not able to take the IMP orally and had a gastrostomy tube (G-tube) or nasogastric tube were to be discussed with and approved by the GW medical monitor prior to using the G-tube or nasogastric tube to administer IMP. The IMP could be taken with other concomitant medications, as directed by the investigator.

Each patient took their first dose of IMP on Day 1 and their final maintenance dose of IMP on Day 113 ('End of Treatment' visit) or day of early withdrawal. Patients who did not enter the OLE study on Day 113 or who withdrew early, had their IMP dose tapered gradually (10% each day) over a period of 10 days (unless continuing dosing was not possible due to an AE). Patients participating in the taper period returned used and unused IMP to the clinic on Day 123 ('End of Taper Period' visit). Patients entering the OLE transitioned to OLE IMP over a period of 2 weeks.

Table 16: Dose titration regimen for the 25 mg/kg/day dose:

Day	Dose Level 1 (25 mg/kg/day)
1	5.0 mg/kg
2	5.0 mg/kg
3	10.0 mg/kg
4	10.0 mg/kg
5	15.0 mg/kg
6	15.0 mg/kg
7	20.0 mg/kg
8	20.0 mg/kg
9	25.0 mg/kg

Objectives and Endpoints

The primary and secondary objectives with their corresponding endpoints are summarised in Table 17.

Table 17

Table 4-1 Summary of Primary, Secondary and Exploratory Objectives and Corresponding Endpoints	
Objectives	**Endpoints**
Primary	
To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures when compared with placebo in patients with TSC.	The primary endpoint is the change in number of TSC-associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo.
Secondary	
To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.	**KEY:** **1) Number of patients considered treatment responders defined as those with a ≥ 50% reduction in TSC-associated seizure frequency.** **2) Change in Caregiver Global Impression of Change (CGIC) or Subject Global Impression of Change (SGIC) score.** **3) 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, 25–50% improvement, 50–75% 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).
To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.	• Change in serum insulin-like growth factor-1 (IGF-1) levels. • Change in Tanner Staging score (for patients aged 10–17 [inclusive]).
To evaluate the effects of GWP42003-P on quality of life compared with placebo.	• Changes in the Quality of Life in Childhood Epilepsy (QOLCE; patients 2–18 years) or Quality of Life in Epilepsy (QOLIE-31-P; patients 19+ years) score. • Change in Physician Global Impression of Change (PGIC) score.
To evaluate the safety and tolerability of GWP42003-P compared with placebo.	• AEs. • Clinical laboratory parameters.

Table 4-1	Summary of Primary, Secondary and Exploratory Objectives and Corresponding Endpoints
	• 12-lead electrocardiogram (ECG). • Physical examination parameters (including height and weight). • Vital signs. • Columbia-Suicide Severity Rating Scale (C-SSRS; 19+ years) or C-SSRS Children's (6–18 years) score, where applicable. • Number of inpatient hospitalizations due to epilepsy. • Abuse liability. • Effects on menstruation cycles (in females).
Exploratory	
Antiepileptic Efficacy Measures	**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 SE (convulsive and non-convulsive). • Changes in duration of seizure subtypes as assessed by the Subject Global Impression of Change in Seizure Duration (SGIC-SD) or the Caregiver Global Impression of Change in Seizure duration (CGIC-SD).
To evaluate the effect of GWP42003-P on TSC-associated neuropsychiatric disorders (TAND), including cognitive and behavioral function and autistic features compared with placebo.	**TAND:** Cognitive and Behavioral 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.
To determine the pharmacokinetics (PK) of CBD, and its major metabolites following single and multiple doses of GWP42003-P.	**PK** • The plasma concentrations will be summarized by time window for CBD and its major metabolites following single and multiple doses of GWP42003-P. Where data allows, the area under the plasma concentration curve (AUC_{0-t}) from time zero to the last measurable time-point will be calculated.
To evaluate the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), if applicable.	Plasma concentrations of concomitant AEDs before and after treatment with GWP42003-P, where available.

Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Source: Appendix 1.1, Section 2, Section 13.6.2, Section 13.6.3.

Sample size

A total of 210 patients were planned for randomisation across 4 treatment groups (25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P, 25 mg/kg/day dose-volume equivalent placebo, or 50 mg/kg/day dose-volume equivalent placebo) at a 2:2:1:1 ratio. The randomisation was stratified by age group (1–6 years, 7–11 years, 12–17 years, and 18–65 years). The placebo groups were pooled for the analyses of efficacy.

It was assumed that patients in the placebo group would experience a mean reduction in seizure frequency of 15% (from baseline), patients receiving GWP42003-P would experience at least a 50% reduction in seizures and a common standard deviation (SD) of 60%, and therefore this sample size of 70 patients per group would be sufficient to detect a difference in response distributions with 90% power. This test was based on a 2-sided non-parametric Mann-Whitney-Wilcoxon test for continuous response data with a 5% significance level.

Randomisation

At the start of the 'Screening Visit', a unique patient number was assigned to each enrolled patient using the IVRS. After confirmation of eligibility on Day 1, patients were randomly allocated to 25 mg/kg/day GWP42003-P, 50 mg/kg/day GWP42003-P, 25 mg/kg/day dose-volume equivalent placebo, or 50 mg/kg/day dose-volume equivalent placebo using the IVRS. The randomisation scheme was generated by an independent statistician using random permuted blocks, and allocation to treatment at site was managed using the IVRS. The randomisation was stratified by age group (1–6 years, 7–11 years, 12–17 years and 18–65 years).

Blinding (masking)

IMP was provided in 100 mL amber glass bottles labelled "GWP42003–P Oral Solution or Placebo". The identity of the IMP assigned to patients was held by the IVRS. The PI at each site, or his/her designee, was responsible for ensuring that information on how to access the IVRS was available to the relevant staff in case of an emergency and unblinding being required.

A patient's treatment assignment should only have been unblinded when knowledge of the treatment was essential to make a decision on the medical management of the patient. Unblinding for any other reason was considered a protocol deviation. The investigator was encouraged to contact GW to discuss the rationale for unblinding prior to doing so. However, to prevent delays to the investigator or medical personnel responding to a potentially emergent situation, unblinding of IMP was not dependent upon the investigator receiving approval from GW (i.e., the investigator would be able to obtain the code break information independent of contacting GW). If the investigator did unblind they were to contact GW within 1 working day of the event and were to document the time, date, and reasons for unblinding in the patient's CRF.

Statistical methods

Analysis populations

The intention to treat (ITT) analysis set included all patients who were randomized and dosed with IMP in the trial and had post-baseline efficacy data. Patient data were analysed according to the treatment group

to which they were randomized. The ITT analysis set was the primary analysis set for all efficacy endpoints.

The per protocol (PP) analysis set included all patients who completed the trial with no protocol deviations deemed to compromise the assessment of efficacy. Patient data were analysed according to the treatment they received. The PP analysis set was authorized following blinded data review meetings on 22 and 25 Mar 2019, prior to unblinding of the database on 27 Apr 2019.

Primary efficacy endpoint: Change in number of TSC-associated seizures during the treatment period compared to baseline period in patients taking GWP42003-P compared with placebo

The primary endpoint will be analysed using a negative binomial regression model with the total number of TSC-associated seizures during the baseline period and treatment period as the response variables.

A mixed effect model with repeated measures will be performed modelling the observed total number of TSC-associated seizures in the baseline period and treatment period implemented within the framework of general linear models using the negative binomial response distribution. The model will include stratified age group (1–6 years, 7–11 years, 12–17 years and 18–65 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect. The log transformed number of days in which seizure data were reported will be included as an offset. The time variable corresponds to an indicator for the baseline period and treatment period. The estimated least squares mean seizure rate for each period and the estimated ratio of least squares means for treatment period to baseline period and 95% confidence intervals (CIs) will be presented for each treatment arm. In addition, the estimated ratio of each GWP42003-P arm to placebo and 95% CIs will be presented along with the p-value testing the null hypothesis that this ratio is 1. For each ratio and upper and lower bound of the 95% CI, the percentage reduction will also be presented.

Missing Data

If a patient withdraws during the treatment period, then the primary analysis variable will be calculated from all the available data, during the treatment period, including any data available after the patient withdraws.

Sensitivity Analyses for the Primary Efficacy Endpoint for the blinded phase

- Primary endpoint analysis repeated using the PP analysis set.
- Wilcoxon rank-sum test on percentage change from baseline in TSC-associated seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P arm and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.
- A rank analysis of covariance (ANCOVA) on percentage change from baseline in TSC-associated seizure frequency during the treatment period.
- ANCOVA of log transformed TSC-associated seizure frequency during the treatment period.
- ANCOVA on percentage change from baseline in TSC-associated seizure frequency during the treatment period.
- Primary endpoint analysis repeated using the maintenance period. This analysis will include only patients who have at least 7 days of seizure data within the maintenance period.
- Primary endpoint analysis repeated using the titration period. These analyses will include only patients who have at least 7 days of seizure data within each corresponding 4 week period.

- Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the mean from the non-missing data for each patient (rounded up to the nearest integer) to impute missing data arising from unreported days in IVRS during the treatment period only (not the baseline period).
- Primary endpoint analysis repeated using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption. For intermittent missing data, in which subjects have missing values for intermediate periods but have available data at subsequent periods, imputation will be based on the MCMC methodology. Assumptions underlying this partial imputation step are that patients will follow a similar outcome trajectory as patients in their respective treatment arm that have complete data. The remaining monotone missing data will then be imputed using predictive mean matching in which missing observations are imputed with an observed value from another patient whose predicated value is close to the predicated value of the patient with the missing observation. To test the robustness of the analysis to the MNAR imputations a tipping point analysis will be performed. This will be conducted by adding or subtracting a sensitivity parameter, k × standard error of the observed average daily TSC-associated seizure frequency in the placebo arm at each period, to the MNAR imputations only at the corresponding period. The tipping point analysis will be used to explore the robustness of the estimated treatment difference to the degree of decrease or increase (positive values of k represent decrease and negative values represent increase) in MNAR efficacy from the placebo patients.

In addition, the following analyses were planned in the SAP Addendum (dated 28 /11/2019):

- Time to 10th and 20th Seizure. The advantage of this proposed time to event analysis is that it is distinctly less sensitive to early withdrawals.
- Analysis using Worst Case of No Change or Observed Worsening: The negative binomial regression (NBR) primary analysis will be repeated penalizing patients in the 25 mg/kg/day or 50 mg/kg/day treatment arms who withdrew during the blinded phase treatment period. The following will be used as the analysis value for withdrawn patients in the active arms:
    - Patients with a reduction (improvement) in percentage change from baseline during the blinded phase treatment period will be imputed by setting the treatment period denominator, used in the NBR offset, to 113 days and the seizure count set to a value giving the same daily average observed during the baseline period.
    - Patients with an increase (worsening) in percentage change from baseline during the blinded phase treatment period will be imputed by setting the treatment period denominator, used in the NBR offset, to 113 days and the seizure count set to a value giving the same daily average observed during the treatment period.

  The primary endpoint analysis will be repeated using the above imputation.

1st Key Secondary Endpoint: TSC-associated Seizure Treatment Responders (≥50% Reduction in TSC-associated Seizure Frequency)

Blinded Phase: The proportion of patients considered treatment responders, defined as those with a ≥50% reduction in TSC-associated seizure frequency from baseline during the treatment period, for patients who have not withdrawn from the trial during the treatment period, will be summarized by treatment arm and analysed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group. The proportion of patients who are considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratios (GWP42003-P arms vs. placebo), 95% CI for the odds ratios, and the p-values from the CMH test will be presented.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, the titration period and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

2nd Key Secondary Endpoint: Subject/Caregiver Global Impression of Change

Blinded Phase: The SGIC and CGIC response/score, recorded at each visit, will be summarized separately, on both a categorical and continuous scale, by treatment arm. It is anticipated that only a small percentage of patients will complete the subject version of the questionnaire. Hence, no analyses will be performed for the SGIC. A combined score will be used as the primary analysis for this endpoint. The combined score will be defined as follows:

☐ If both a CGIC and SGIC are completed then the CGIC will be used.

☐ If only a CGIC is completed then the CGIC will be used.

☐ If only a SGIC is completed then the SGIC will be used.

The score at the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment arm as a factor. The estimated odds ratio (GWP42003-P vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented.

Analysis performed at the last visit will be considered the primary analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis. Since this analysis uses a combination of caregiver and subject ratings, a sensitivity analysis will be performed using only the CGIC score and using the same analyses as above.

3rd Key Secondary Endpoint: Total Seizures

Blinded Phase: Summaries and analyses of total seizures will be performed as per the primary endpoint.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance period, titration period, and during each 4 weeks of the maintenance period (Week 1 to 4, Week 5 to 8 and Week 9 to 12 of the 12 week maintenance period).

Multiplicity control

The primary and key secondary endpoints will be tested with their Type I error controlled by use of a hierarchical gate-keeping procedure, in the sequence given in Table 18.

Table 18

Table 3 Hierarchy for Analysis

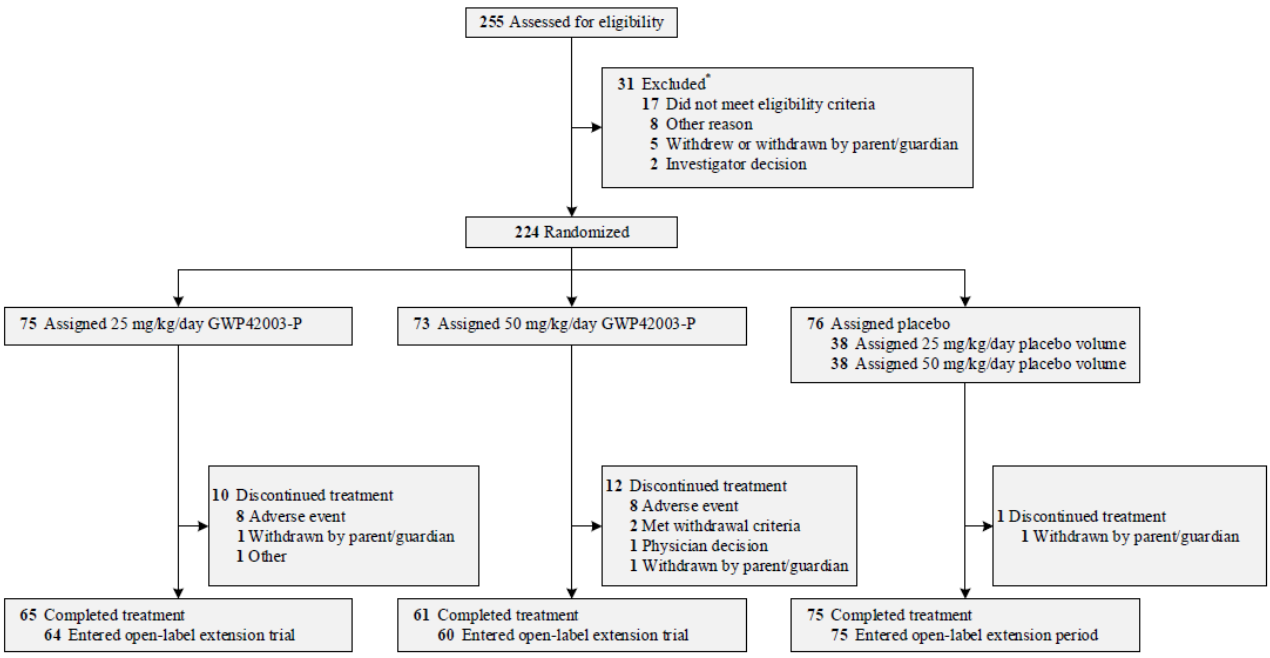
Test	Endpoint	Treatment Comparison
1	Primary endpoint	25 mg/kg/day GWP42003-P vs. Placebo
2	1st key secondary endpoint	25 mg/kg/day GWP42003-P vs. Placebo
3	Primary endpoint	50 mg/kg/day GWP42003-P vs. Placebo
4	1st key secondary endpoint	50 mg/kg/day GWP42003-P vs. Placebo
5	2nd key secondary endpoint	25 mg/kg/day GWP42003-P vs. Placebo
6	3rd key secondary endpoint	25 mg/kg/day GWP42003-P vs. Placebo
7	2nd key secondary endpoint	50 mg/kg/day GWP42003-P vs. Placebo
8	3rd key secondary endpoint	50 mg/kg/day GWP42003-P vs. Placebo

Results

Participant flow

Figure 9

Figure 7.1-1 Patient Disposition (All Randomized Patients)

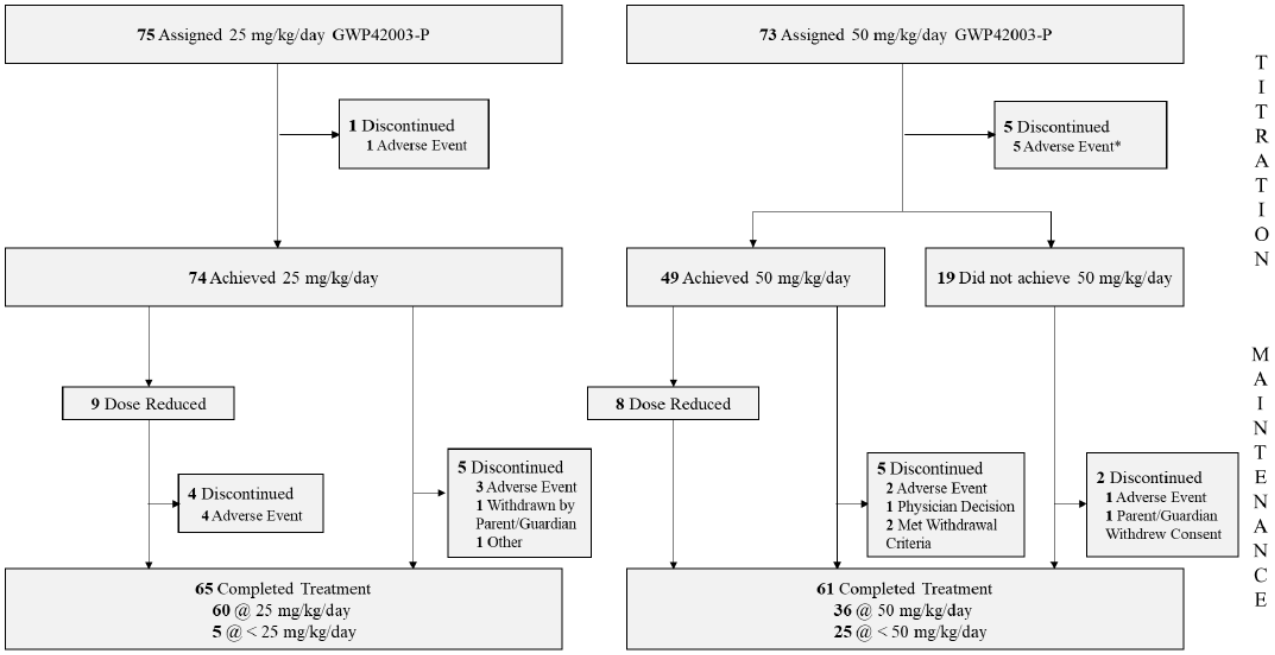


* One patient had 2 reasons recorded for screen failure: 1) did not meet inclusion criterion #2 (patient and/or parent(s)/legal representative is willing and able to give informed consent/assent for participation in the study) and 2) withdrawal by subject or parent/guardian.

A total of 255 patients were screened; 31 (12.2%) of whom were screen failures. A total of 224 patients were randomized to double-blind treatment (Figure 9); the disposition of patients in each active treatment group, illustrating the number that had their dose of IMP reduced either during titration (and did not achieve their target maintenance dose) or later in the trial is shown in Figure 10.

Figure 10

Figure 7.1-2 **Disposition of Patients Randomized to the GWP42003-P Treatment Groups by Achievement of Target Dose Throughout During the Treatment Period (ITT Analysis Set)**



* Two patients from the 50 mg/kg/day group discontinued during the titration phase when they had reached 25 mg/kg/day GWP42003-P; both as a result or TEAEs; of rash macular and angioedema in 1 patient, and urticaria, lip swelling and eye swelling in the other patient.
Note: Treatment period is defined as Day 1 to the earliest of the day of last blinded phase dose or Day 113.

[redacted]

Table 19

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%)

Recruitment

In total, 46 sites screened patients (25 in the US, 6 in Poland, 5 in Spain, 4 in Australia, 4 in the UK, 2 in the Netherlands), of which 44 sites randomised patients into the trial. Of the 224 randomized patients, 112 (50%) were randomized 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. The date of the first informed consent/assent form signed by a patient or their parent(s)/legal representative for the first patient to be enrolled into the trial was 06 April 2016, the last screening date was 31 August 2018, and the date of the

last trial observation was 15 February 2019. Overall, 201 patients (89.7%) completed the trial and 199 patients (88.8%) entered the OLE phase of the trial.

The OLE trial was conducted at 32 sites that enrolled patients in Australia, Netherlands, Poland, Spain, UK, and US. The date of first informed consent/assent was 31 August 2016. The date of the interim data cut-off was 26 February 2019.

Conduct of the study

Protocol amendments

Of the seven protocol amendments, six (Amendments 2-7) were introduced after patient enrolment had started. Amendment 2 (August 2016) changed e.g. the target sample size, the frequency of assessments, and the primary and secondary analyses. Amendment 4 (June 2017) changed secondary endpoint structure, and clarified exclusion criteria relating to mTOR inhibitors. Amendment 5 (Aug 2018) introduced a number of substantial changes of e.g. clarification of the treatment allocation ratio and inclusion criteria: An inclusion criterion was added to ensure that eligible patients must be taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening. Furthermore, inclusion criteria were amended to clarify that eligible patients must have a well-documented clinical history of epilepsy which is not completely controlled by their current AEDs. Also, it was clarified that the investigator may consider temporarily or permanently reducing the dosage in case of poor tolerability, and in cases where the transaminase elevation withdrawal criteria are not met or confirmed, the dose of IMP or a concomitant AED with known hepatoxicity should be reduced. Amendment 6 (September 2018) changed the primary analysis method from the Wilcoxon rank-sum test to a negative binomial regression analysis. Amendment 7 (April 2019) changed the testing hierarchy moving the GIC and total seizure endpoints down in the hierarchy so that all TSC-associated seizure endpoints are tested first.

Protocol deviations (selected)

Potential unblinding:

• One site unblinded a patient after they experienced an AE of rash with eosinophilia. Sponsor medical approval was not in place prior to unblinding. The patient was withdrawn.

• On Day 113 (end of treatment), 1 patient had a positive result for cannabinoids despite being on placebo. On investigation, the most plausible explanation was that they took the dispensed open-label medication in error as the predose sample was negative. Both double-blind medication and open-label medication were dispensed at this visit. There were no treatment-emergent adverse events (TEAEs) reported.

• One patient had a THC test Day 113 (end of treatment) although this was not required. The positive result was provided to the site; a positive test for THC is not necessarily unblinding as it may be due to noncompliance. The result was also provided to the sponsor, only one person in the biostatistics department, who wasn't the study statistician, reviewed the data and took steps to isolate the data. There has been no impact on the data integrity.

IMP Dosing:

• Two patients failed to properly titrate (1 in the 25 mg/kg/day GWP42003-P group and 1 in the 50 mg/kg/day GWP42003-P group).

• One patient in the 25 mg/kg/day GWP42003-P group had a dose reduction in error.

• One patient in the 25 mg/kg/day GWP42003-P group took the medication with a drink because the patient was uncooperative.

Concomitant AED Medication Changes During the Trial:

25 mg/kg/day GWP42003-P group:

• One patient had their dose of vigabatrin increased from 1000 mg QD + 1250 mg QD to 1000 mg QD + 1500 mg QD by an external neurologist.

• One patient had their dose of zonisamide increased from 75 mg b.i.d. to 100 mg b.i.d. on Day 99; the patient was removed from the PP analysis set.

• One patient had their dose of carbamazepine increased from 450 mg QD + 600 mg QD to 600 mg QD by an external hospital due to an episode of status epilepticus; the patient was removed from the PP analysis set.

• One patient had their dose of valproic acid increased from 1000 mg QD to 1000 mg QD + 500 mg QD on Day 24; the patient was removed from the PP analysis set.

50 mg/kg/day GWP42003-P group:

• One patient had their dose of vigabatrin increased from 750 mg b.i.d. to 750 mg QD + 1000 mg QD on Day 108; the patient was removed from the PP analysis set.

• One started taking CLB on Day 62; the patient was removed from the PP analysis set.

• One patient had their dose of levetiracetam increased from 5 mL b.i.d to 6 mL b.i.d. during the baseline period; the patient was removed from the PP analysis set.

Placebo group:

• One patient had their dose of CLB increased from 20 mg QD + 30 mg QD to 20 mg TID on Day 13; the patient was removed from the PP analysis set.

Baseline data

The demographic characteristics were similar across the treatment groups. Overall, there was a slightly higher proportion of male (58.1%) than female (41.9%) patients; the majority were White/Caucasian (89.6%) with the highest proportion coming from the US (49.5%); the mean (SD) age was 13.659 (10.0) years.

Table 20

Table 8.2-1 Demographics and Baseline Characteristics (Safety Analysis Set)				
Demographic Characteristic Statistics	**25 mg/kg/day GWP42003-P (N=75)**	**50 mg/kg/day GWP42003-P[a] (N=73)**	**Pooled Placebo[a] (N=76)**	**Total[a] (N=224)**
Age (years)				
n	75	72	75	222
Mean (SD)	14.112 (10.8131)	12.915 (8.5324)	13.918 (10.6302)	13.659 (10.0324)
Median	11.573	10.778	11.055	11.369
Min, Max	1.05, 56.78	1.80, 34.92	1.20, 55.77	1.05, 56.78
Age Group [n (%)]				
1–6 years	21 (28.0)	20 (27.8)	21 (28.0)	62 (27.9)
7–11 years	18 (24.0)	18 (25.0)	18 (24.0)	54 (24.3)
12–17 years	16 (21.3)	16 (22.2)	16 (21.3)	48 (21.6)
18–65 years	20 (26.7)	18 (25.0)	20 (26.7)	58 (26.1)
Sex [n (%)]				
Female	32 (42.7)	30 (41.7)	31 (41.3)	93 (41.9)
Male	43 (57.3)	42 (58.3)	44 (58.7)	129 (58.1)
Race [n (%)]				
White/Caucasian	68 (90.7)	65 (90.3)	66 (88.0)	199 (89.6)
Black/African American	2 (2.7)	3 (4.2)	0	5 (2.3)
American Indian/Alaska Native	1 (1.3)	0	0	1 (0.5)
Asian	1 (1.3)	0	3 (4.0)	4 (1.8)
Other	3 (4.0)	4 (5.6)	6 (8.0)	13 (5.9)
Country [n (%)]				
Australia	5 (6.7)	9 (12.5)	10 (13.3)	24 (10.8)
Netherlands	3 (4.0)	3 (4.2)	3 (4.0)	9 (4.1)
Poland	23 (30.7)	22 (30.6)	16 (21.3)	61 (27.5)
Spain	6 (8.0)	3 (4.2)	2 (2.7)	11 (5.0)
US	36 (48.0)	33 (45.8)	41 (54.7)	110 (49.5)
UK	2 (2.7)	2 (2.8)	3 (4.0)	7 (3.2)
Region [n (%)]				
Rest of the World	39 (52.0)	39 (54.2)	34 (45.3)	112 (50.5)
US	36 (48.0)	33 (45.8)	41 (54.7)	110 (49.5)
Weight at Baseline (kg)				
n	75	72	75	222
Mean (SD)	42.79 (23.988)	42.37 (23.747)	44.90 (27.972)	43.37 (25.240)
Median	40.40	38.00	36.90	38.70
Min, Max	12.1, 143.7	13.0, 130.0	10.4, 115.7	10.4, 143.7

Table 8.2-1 Demographics and Baseline Characteristics (Safety Analysis Set)				
Demographic Characteristic Statistics	**25 mg/kg/day GWP42003-P (N=75)**	**50 mg/kg/day GWP42003-P[a] (N=73)**	**Pooled Placebo[a] (N=76)**	**Total[a] (N=224)**
Height at Baseline (cm)				
n	75	70	75	220
Mean (SD)	142.08 (27.072)	138.51 (28.620)	138.67 (29.490)	139.78 (28.325)
Median	146.00	147.65	140.60	145.75
Min, Max	81.0, 196.0	85.0, 184.0	80.0, 182.0	80.0, 196.0
Body Mass Index at Baseline (kg/m^2)				
n	75	70	75	220
Mean (SD)	19.66 (5.823)	20.07 (5.011)	20.90 (6.359)	20.21 (5.771)
Median	18.39	18.73	19.20	18.73
Min, Max	8.4, 44.4	12.6, 38.4	13.2, 40.5	8.4, 44.4

[a] 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.

[redacted].

The distribution of current seizure types reported during the 28-day baseline period was similar across the treatment groups, with Type 2 focal seizures being most common, followed by Type 1 focal motor, Type 3 focal and tonic.

Table 21

Table 8.2-2 Summary of Current Seizure Types (Safety and ITT Analysis Sets)				
Seizure Group Seizure Type	25 mg/kg/day GWP42003-P (N=75) n (%)	50 mg/kg/day GWP42003-P (N=73) n (%)	Pooled Placebo (N=76) n (%)	Total (N=224) n (%)
TSC-associated Seizures	**75 (100)**	**73 (100)**	**76 (100)**	**224 (100)**
Atonic	10 (13.3)	5 (6.8)	13 (17.1)	28 (12.5)
Clonic	3 (4.0)	3 (4.1)	2 (2.6)	8 (3.6)
Tonic	27 (36.0)	23 (31.5)	15 (19.7)	65 (29.0)
Tonic–Clonic	22 (29.3)	16 (21.9)	14 (18.4)	52 (23.2)
Type 1 Focal Motor	29 (38.7)	39 (53.4)	33 (43.4)	101 (45.1)
Type 2 Focal	46 (61.3)	54 (74.0)	50 (65.8)	150 (67.0)
Type 3 Focal	17 (22.7)	24 (32.9)	24 (31.6)	65 (29.0)
Other Seizures	**12 (16.0)**	**24 (32.9)**	**15 (19.7)**	**51 (22.8)**
Absence	5 (6.7)	14 (19.2)	7 (9.2)	26 (11.6)
Infantile or Epileptic Spasms	5 (6.7)	7 (9.6)	3 (3.9)	15 (6.7)
Myoclonic	3 (4.0)	6 (8.2)	4 (5.3)	13 (5.8)
Partial (Focal) Sensory	2 (2.7)	1 (1.4)	3 (3.9)	6 (2.7)

Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Note: Other seizures include absence, myoclonic, partial (focal) sensory seizures, and infantile or epileptic spasms.

Note: The placebo arms were pooled for the analysis of efficacy.

[redacted]

A small proportion of patients received concomitant non-pharmacological antiepileptic therapies during the trial; 25 patients (11.2%) used VNS and 3 patients (1.3%) used a ketogenic diet, spread fairly evenly across the 3 treatment groups.

A total of 114 patients (50.9%) had significant non-epilepsy medical or surgical history that had resolved prior to starting the trial, with similar numbers in each group (40 [53.3%] 25 mg/kg/day GWP42003-P patients, 37 [50.7%] 50 mg/kg/day GWP42003-P patients and 37 [48.7%] placebo patients); however, some epilepsy-related conditions were recorded as non-epilepsy medical or surgical history on the CRF. The most common resolved non-epilepsy medical conditions were from the surgical and medical procedures SOC (30 [40.0%] 25 mg/kg/day GWP42003-P patients, 26 [35.6%] 50 mg/kg/day GWP42003-P patients and 26 [34.2%] placebo patients), and the infections and infestations SOC (11 [14.7%] 25 mg/kg/day GWP42003-P patients, 9 [12.3%] 50 mg/kg/day GWP42003-P patients and 5 [6.6%] placebo patients).

The most common ongoing non-epilepsy medical conditions by PT (i.e., reported in > 10% of patients overall) are presented in Table 22; the distribution was similar across the treatment groups.

Table 22

Table 8.2-4 Most Common Significant Ongoing Non-Epilepsy Medical Conditions or Surgical History (Safety Analysis Set)				
Preferred Term	**25 mg/kg/day GWP42003-P (N=75) n (%)**	**50 mg/kg/day GWP42003-P (N=73) n (%)**	**Placebo (N=76) n (%)**	**Total (N=224) n (%)**
Developmental delay	14 (18.7)	20 (27.4)	23 (30.3)	57 (25.4)
Angiofibroma	21 (28.0)	19 (26.0)	16 (21.1)	56 (25.0)
Autism spectrum disorder	17 (22.7)	15 (20.5)	21 (27.6)	53 (23.7)
Rhabdomyoma	16 (21.3)	17 (23.3)	20 (26.3)	53 (23.7)
Kidney angiomyolipoma	15 (20.0)	17 (23.3)	15 (19.7)	47 (21.0)
Skin hypopigmentation	14 (18.7)	10 (13.7)	14 (18.4)	38 (17.0)
Renal cyst	10 (13.3)	8 (11.0)	17 (22.4)	35 (15.6)
Hamartoma	8 (10.7)	8 (11.0)	12 (15.8)	28 (12.5)
Intellectual disability	9 (12.0)	10 (13.7)	7 (9.2)	26 (11.6)
Constipation	12 (16.0)	7 (9.6)	5 (6.6)	24 (10.7)

S[redacted]

The most common classes of AEDs now discontinued (i.e., reported in > 50% of patients overall) were other antiepileptics (172 [76.8%] patients), and fatty acid derivatives (152 [67.9%] patients).

For all of the treatment groups, the median number of AEDs no longer taken was 4 (range 0 to 15) and the median number of current AEDs was 3 (range 0 to 5) (Table 23). One patient was enrolled into the trial while not taking any ongoing concomitant AEDs. The patient was enrolled under protocol version 5 which did not explicitly state that patients had to be taking 1 or more other AEDs; the protocol was subsequently updated via substantial amendment to clarify this.

Table 23

Table 8.2-5 Baseline Characteristics: Antiepileptic Drugs (Safety Analysis Set)				
Baseline Characteristic Statistics	**25 mg/kg/day GWP42003-P (N=75)**	**50 mg/kg/day GWP42003-P (N=73)**	**Pooled Placebo (N=76)**	**Total (N=224)**
Number of Prior AEDs Patient No Longer Taking				
n	75	73	76	224
Mean (SD)	4.84 (3.162)	4.25 (3.166)	4.59 (3.327)	4.56 (3.215)
Median	4	4	4	4
Min, Max	0, 13	0, 13	0, 15	0, 15
Number of AEDs Patient Currently Taking				
n	75	73	76	224
Mean (SD)	2.65 (0.979)	2.77 (1.048)	2.58 (0.898)	2.67 (0.975)
Median	3	3	3	3
Min, Max	0[a], 4	1, 5	1, 5	0[a], 5

[a] One patient was enrolled into the trial while not taking any ongoing concomitant AEDs. The patient was enrolled under protocol version 5 which did not explicitly state in Section 6.1 that patients had to be taking 1 or more other AEDs; the protocol was subsequently updated via substantial amendment to clarify this.

S[redacted]

The most common AEDs taken concomitantly during the trial were VPA and VGB (Table 24). Overall, 99.6% of patients were taking at least 1 AED concomitantly during the trial.

The concomitant AEDs used were similar across the treatment groups for most AEDs; however, CLB was taken by fewer patients in each GWP42003-P group than in the pooled placebo group and VGB was taken by more patients in each GWP42003-P group than in the pooled placebo group.

Table 24

Table 8.2-6 Concomitant Antiepileptic Medications (Excluding Rescue Medications) (Safety Analysis Set)				
Therapeutic Class Preferred Term	**25 mg/kg/day GWP42003-P (N=75) n (%)**	**50 mg/kg/day GWP42003-P (N=73) n (%)**	**Pooled Placebo (N=76) n (%)**	**Total (N=224) n (%)**
Patients taking any concomitant medications	**74 (98.7)[a]**	**73 (100)**	**76 (100)**	**223 (99.6)**
Barbiturates and derivatives	**3 (4.0)**	**3 (4.1)**	**2 (2.6)**	**8 (3.6)**
Phenobarbital	2 (2.7)	3 (4.1)	1 (1.3)	6 (2.7)
Primidone	1 (1.3)	0	1 (1.3)	2 (0.9)
Benzodiazepine derivatives	**25 (33.3)**	**30 (41.1)**	**32 (42.1)**	**87 (38.8)**
Clobazam	17 (22.7)	19 (26.0)	25 (32.9)	61 (27.2)
Clonazepam	6 (8.0)	9 (12.3)	4 (5.3)	19 (8.5)
Lorazepam	2 (2.7)	1 (1.4)	2 (2.6)	5 (2.2)
Midazolam	1 (1.3%)	0	1 (1.3%)	2 (0.9)
Clorazepate dipotassium	0	1 (1.4)	0	1 (0.4)
Nitrazepam	0	1 (1.4)	0	1 (0.4)

Table 8.2-6 Concomitant Antiepileptic Medications (Excluding Rescue Medications) (Safety Analysis Set)				
Therapeutic Class Preferred Term	**25 mg/kg/day GWP42003-P (N=75) n (%)**	**50 mg/kg/day GWP42003-P (N=73) n (%)**	**Pooled Placebo (N=76) n (%)**	**Total (N=224) n (%)**
Patients taking any concomitant medications	**74 (98.7)[a]**	**73 (100)**	**76 (100)**	**223 (99.6)**
Carboxamide derivatives	**30 (40.0)**	**22 (30.1)**	**24 (31.6)**	**76 (33.9)**
Oxcarbazepine	13 (17.3)	12 (16.4)	10 (13.2)	35 (15.6)
Carbamazepine	11 (14.7)	9 (12.3)	6 (7.9)	26 (11.6)
Rufinamide	7 (9.3)	1 (1.4)	8 (10.5)	16 (7.1)
Eslicarbazepine acetate	2 (2.7)	0	1 (1.3)	3 (1.3)
Fatty acid derivatives	**42 (56.0)**	**50 (68.5)**	**46 (60.5)**	**138 (61.6)**
Valproic acid	29 (38.7)	36 (49.3)	35 (46.1)	100 (44.6)
Vigabatrin	28 (37.3)	29 (39.7)	17 (22.4)	74 (33.0)
Tiagabine hydrochloride	0	0	1 (1.3)	1 (0.4)
Hydantoin derivatives	**0**	**0**	**3 (3.9)**	**3 (1.3)**
Phenytoin	0	0	3 (3.9)	3 (1.3)
Other antiepileptics	**56 (74.7)**	**55 (75.3)**	**58 (76.3)**	**169 (75.4)**
Levetiracetam	19 (25.3)	22 (30.1)	24 (31.6)	65 (29.0)
Lamotrigine	17 (22.7)	15 (20.5)	18 (23.7)	50 (22.3)
Lacosamide	16 (21.3)	15 (20.5)	12 (15.8)	43 (19.2)
Topiramate	7 (9.3)	14 (19.2)	12 (15.8)	33 (14.7)
Zonisamide	9 (12.0)	2 (2.7)	7 (9.2)	18 (8.0)
Felbamate	6 (8.0)	3 (4.1)	4 (5.3)	13 (5.8)
Perampanel	4 (5.3)	5 (6.8)	1 (1.3)	10 (4.5)
Gabapentin	1 (1.3)	2 (2.7)	1 (1.3)	4 (1.8)
Pregabalin	0	2 (2.7)	1 (1.3)	3 (1.3)
Brivaracetam	0	1 (1.4)	1 (1.3)	2 (0.9)
Selective immunosuppressants	**1 (1.3)**	**0**	**1 (1.3)**	**2 (0.9)**
Everolimus[b]	1 (1.3)	0	0	1 (0.4)
Sirolimus[c]	0	0	1 (1.3)	1 (0.4)
Succinimide derivatives	**1 (1.3)**	**0**	**0**	**1 (0.4)**
Ethosuximide	1 (1.3)	0	0	1 (0.4)

Note: Preferred terms of ergenyl chrono, valproate semisodium, valproate sodium, and valproate magnesium have been combined with the preferred term of valproic acid.

[a] One patient was enrolled into the trial while not taking any ongoing concomitant AEDs. The patient was enrolled under protocol version 5 which did not explicitly state in Section 6.1 that patients had to be taking 1 or more other AEDs; the protocol was subsequently updated via substantial amendment to clarify this.

[b] Oral everolimus was not allowed per protocol. One patient in the 25 mg/kg/day GWP42003-P group was listed as taking everolimus but was withdrawn from the treatment phase of the trial and abruptly stopped taking GWP42003-P on Day 9; the patient started taking everolimus on Day 21. Refer to [redacted] One patient in the placebo group was listed [redacted] as taking oral everolimus throughout the DB phase of the trial but the site confirmed that they did not start taking everolimus until Day 148, after they had transitioned into the OLE phase of the trial (where oral everolimus was allowed).

[c]Oral sirolimus was not allowed during the DB phase per protocol. One patient was listed as taking sirolimus but they did not commence treatment until after the patient had been withdrawn from the trial (Day 143).

A total of 27 patients received concomitant non-pharmacological antiepileptic therapies during the trial. Of these patients, 3/26 (11.5%) used ketogenic diet and 25/26 (96.2%) used vagus nerve stimulation (VNS); 2/26 [7.7%] used both. Ketogenic diet was used by 1 patient (1.4%) in the 50 mg/kg/day GWP42003-P treatment group and 2 patients (2.6%) in the pooled placebo group. VNS was used by 10 patients (13.3%) in the 25 mg/kg/day GWP42003-P group, 7 patients (9.6%) in the 50 mg/kg/day GWP42003-P group, and 8 patients (10.5%) in the pooled placebo group.

Sixteen patients (4 in the 25 mg/kg/day GWP42003-P group, 6 in the 50 mg/kg/day GWP42003-P group, and 6 in the placebo group) had previously used cannabis. The majority (11/16) of these patients were reported to have used cannabis more than 12 times per year. There were 4 patients who had taken cannabis within 6 months of the screening visit.

Numbers analysed

All randomised patients who received at least 1 dose of IMP and had post-baseline efficacy data were included in the ITT analysis set according to the treatment group to which they were randomised. No randomised patients were excluded from the ITT analysis set which comprised a total of 224 patients: 75 patients in the 25 mg/kg/day GWP42003-P group, 73 patients in the 50 mg/kg/day GWP42003-P group, and 76 patients in the placebo group.

All patients who completed the trial with no protocol deviations deemed to compromise the assessment of efficacy were included in the PP analysis set according to the actual treatment they received. The PP analysis set excluded 30 patients (13 patients in the 25 mg/kg/day GWP42003-P group, 15 patients in the 50 mg/kg/day GWP42003-P group, and 2 patients in the placebo group) comprising 23 patients who withdrew from the trial early, 1 patient in the 50 mg/kg/day GWP42003-P group who had new AEDs initiated during the trial (reported as an important protocol deviation), and 6 patients who had their AED dose increased during the trial (reported as important protocol deviations in 3 patients in the 25 mg/kg/day, 2 patients in the 50 mg/kg/day GWP42003-P groups and 1 patient in the placebo group). Accordingly, the PP analysis set comprised a total of 194 patients: 62 patients in the 25 mg/kg/day GWP42003-P group, 58 patients in the 50 mg/kg/day GWP42003-P group, and 74 patients in the placebo group.

Outcomes and estimation

Primary endpoint:

Following treatment, the percentage reduction in TSC-associated seizures was greater in both active treatment groups (25 mg/kg/day and 50 mg/kg/day) compared with the placebo group (Table 25). As shown in Figure 11 the difference between the 25 mg/kg/day CBD-OS group and placebo was statistically significant while the difference between the 50 mg/kg/day CBD-OS group and placebo could not be regarded as formally significant due to the rules associated with the hierarchical testing approach.

Table 25

Table 8.4.1.1-1 Primary Endpoint: Change in TSC-associated Seizures During the Treatment Period Compared to Baseline (ITT Analysis Set)			
Variable Statistics	**25 mg/kg/day GWP42003-P (N=75)**	**50 mg/kg/day GWP42003-P (N=73)**	**Placebo (N=76)**
Percent Change from Baseline in TSC-associated Seizure Frequency			
Median	−43.36	−36.55	−20.08
Q1, Q3	−67.8, −13.6	−67.0, −5.5	−47.1, 3.1
Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods			
Percentage Reduction	48.6	47.5	26.5
95% CI	40.4, 55.8	39.0, 54.8	14.9, 36.5

Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.

Note: The placebo arms were pooled for the analysis of efficacy.

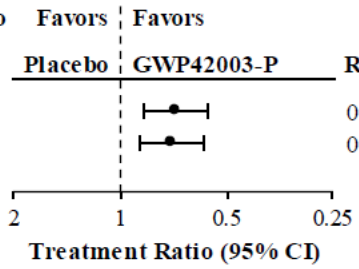
Note: Model includes total number of seizures as a response variable, age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[redacted]

Figure 11

Figure 8.4.1.1-1 Primary Endpoint: Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods (ITT Analysis Set)

Comparison vs. Placebo	GWP42003-P (N)	Placebo (N)	Ratio (95% CI)	P-value[a]
25 mg/kg/day GWP42003-P	75	76	0.699 (0.567, 0.861)	0.0009
50 mg/kg/day GWP42003-P	73	76	0.715 (0.580, 0.881)	0.0018



[a] Nominal P-value presented for the 50 mg/kg/day GWP42003-P group.

Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.

Note: The placebo arms were pooled for the analysis of efficacy.

Note: Model includes total number of seizures as a response variable, age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[redacted]

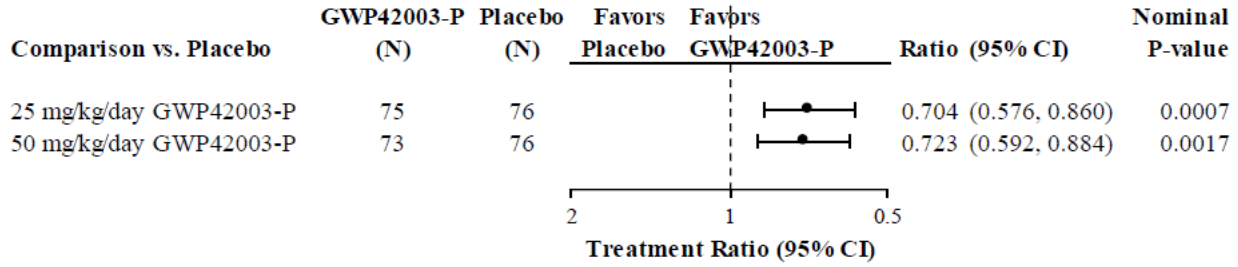
Sensitivity Analyses for the Primary Endpoint

Results of various sensitivity analyses were consistent with the primary analysis e.g. when using the PP analysis set, when analysing the percentage change from baseline in TSC-associated seizure frequency (28-day average) using a rank ANCOVA approach or when analysing seizure frequency using a log-transformed ANCOVA approach.

Results of the primary analysis after imputing unreported days in the IVRS are presented in Figure 12. For this analysis, missing data from the treatment period arising from unreported days in the IVRS were imputed using the worst (highest number of seizures) of the following for each patient on active treatment who withdrew during the treatment period: LOCF, NOCB, and the mean daily number of seizures during the treatment period (using the non-missing data). The treatment ratio was in favor of CBD-OS over placebo for both GWP42003-P groups (25 mg/kg/day and 50 mg/kg/day) (Figure 12).

Figure 12

Figure 8.4.1.1.1-7 Sensitivity Analyses of the Primary Endpoint: Negative Binomial Regression Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods After Imputing Unreported Days in IVRS (ITT Analysis Set)



Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.
Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: Missing data from the treatment period arising from unreported days in the IVRS are imputed using the worst (highest number of seizures) of the following for each patient: last observation carried forward, next observation carried backward, and the mean daily number of seizures during the treatment period (using the non-missing data).
Note: Model includes total number of seizures as a response variable, age group, time (baseline and treatment period), treatment and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[redacted]

Secondary endpoints:

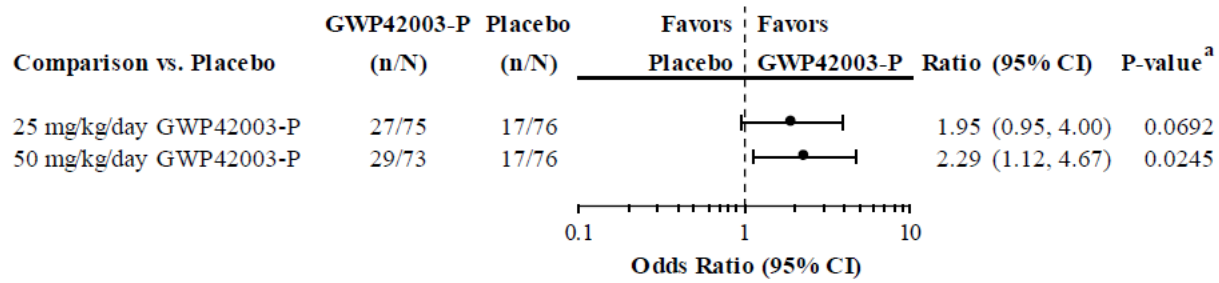
No tests reached formal statistical significance.

Key secondary endpoint #1: Patients with a ≥ 50% Reduction from Baseline in TSC-associated Seizure Frequency

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 did not reach statistical significance for the 25 mg/kg/day group (P=0.0692) and therefore the hierarchical testing ended.

Figure 13

Figure 8.4.1.2.1.1-1 Key Secondary Endpoint #1: TSC-associated Seizure Responders (≥ 50% Reduction from Baseline) During the Treatment Period (ITT Analysis Set)



[a] Nominal P value presented for the 50 mg/kg/day GWP42003-P group.

Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Note: Treatment period was defined as Day 1 to Day 113.

Note: The placebo arms were pooled for the analysis of efficacy.

Note: P-value calculated from a CMH test stratified by age group (1–6, 7–11, 12–17, and 18–65 years).

[redacted]

Table 26

[redacted]

Table 9.1.1: Summary and Analysis of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom During the Treatment Period (ITT Analysis Set)

Endpoint		25 mg/kg (N=75)	50 mg/kg (N=73)	Placebo (N=76)
	No Baseline Period Seizures	0	0	0
	>25% (Increase)	6 (8.0%)	8 (11.0%)	6 (7.9%)
	>=0% to <=25% (Increase)	11 (14.7%)	6 (8.2%)	15 (19.7%)
	>-25% to <0% (Reduction)	7 (9.3%)	12 (16.4%)	22 (28.9%)
	>-50% to <=-25% (Reduction)	18 (24.0%)	16 (21.9%)	16 (21.1%)
	>-75% to <=-50% (Reduction)	19 (25.3%)	17 (23.3%)	17 (22.4%)
	<=-75% (Reduction)	14 (18.7%)	14 (19.2%)	0
>=25% Reduction*	Yes	43 (57.3%)	43 (58.9%)	33 (43.4%)
	No	32 (42.7%)	30 (41.1%)	43 (56.6%)
	Difference in Proportions (95% CI) [Active-Placebo]	0.139 (-0.019, 0.297)	0.155 (-0.004, 0.313)	
	Odds Ratio (95% CI) [Active/Placebo]	1.75 (0.92, 3.33)	1.87 (0.97, 3.58)	
	p-value^	0.0910	0.0622	
>=50% Reduction*	Yes	27 (36.0%)	29 (39.7%)	17 (22.4%)
	No	48 (64.0%)	44 (60.3%)	59 (77.6%)
	Difference in Proportions (95% CI) [Active-Placebo]	0.136 (-0.007, 0.280)	0.174 (0.027, 0.320)	
	Odds Ratio (95% CI) [Active/Placebo]	1.95 (0.95, 4.00)	2.29 (1.12, 4.67)	
	p-value^	0.0692	0.0245	

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.
Treatment period is defined as Day 1 to Day 113.
^ p-value calculated from a Cochran-Mantel-Haenszel test stratified by age group (1-6, 7-11, 12-17 and 18-65 years).
* Subjects who withdrew from the trial during the treatment period are considered non-responders.

[redacted]

Page 1 of 2

Table 9.1.1: Summary and Analysis of TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom During the Treatment Period (ITT Analysis Set)

Endpoint		25 mg/kg (N=75)	50 mg/kg (N=73)	Placebo (N=76)
>=75% Reduction*	Yes	12 (16.0%)	13 (17.8%)	0
	No	63 (84.0%)	60 (82.2%)	76 (100.0%)
	Difference in Proportions (95% CI) [Active-Placebo]	0.160 (0.077, 0.243)	0.178 (0.090, 0.266)	
	p-value^	0.0003	0.0001	
100% Reduction*	Yes	1 (1.3%)	0	0
	No	74 (98.7%)	73 (100.0%)	76 (100.0%)
	Difference in Proportions (95% CI) [Active-Placebo]	0.013 (-0.013, 0.039)		
	Odds Ratio (95% CI) [Active/Placebo]			
	p-value^	0.3173		

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.
Treatment period is defined as Day 1 to Day 113.
^ p-value calculated from a Cochran-Mantel-Haenszel test stratified by age group (1-6, 7-11, 12-17 and 18-65 years).
* Subjects who withdrew from the trial during the treatment period are considered non-responders.

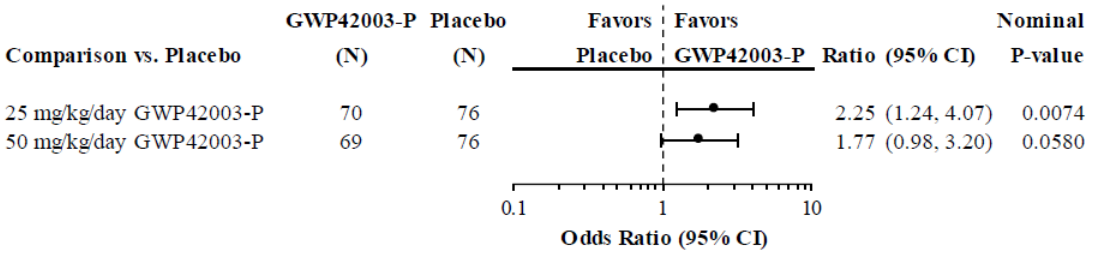
[redacted]

Other secondary endpoints:

Subject/Caregiver Global Impression of Change Score

Figure 14

Figure 8.4.1.2.1.2-2 Key Secondary Endpoint #2: Ordinal Logistic Regression Analysis of Subject/Caregiver Global Impression of Change in Overall Condition at Last Visit (ITT Analysis Set)



Note: The combined caregiver and subject summary uses either the caregiver or subject version if only one version was completed, or the caregiver version if both a caregiver and subject versions were completed.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: The S/CGIC was analyzed using an ordinal logistic regression model with treatment group as a fixed factor.

[redacted]

Change in Total Seizures During the Treatment Period Compared to Baseline

Table 27

Table 8.4.1.2.1.3-1 Key Secondary Endpoint #3: Change in Total Seizures During the Treatment Period Compared to Baseline (ITT Analysis Set)			
Variable Statistics	25 mg/kg/day GWP42003-P (N=75)	50 mg/kg/day GWP42003-P (N=73)	Placebo (N=76)
Total Seizure Frequency (Average per 28 Days) During the Baseline Period			
Median	56.00	70.00	56.48
Q1, Q3	22.6, 101.0	38.0, 130.0	27.5, 138.1
Total Seizure Frequency (Average per 28 Days) During the Treatment Period			
Median	32.96	32.25	44.03
Q1, Q3	9.0, 63.3	14.6, 91.3	18.3, 84.9
% Reduction in Seizure Frequency (Average per 28 Days) During the Treatment Period Compared to Baseline Period			
% Reduction	48.1	47.6	26.9
95% CI	39.8, 55.3	39.3, 54.8	15.4, 36.8

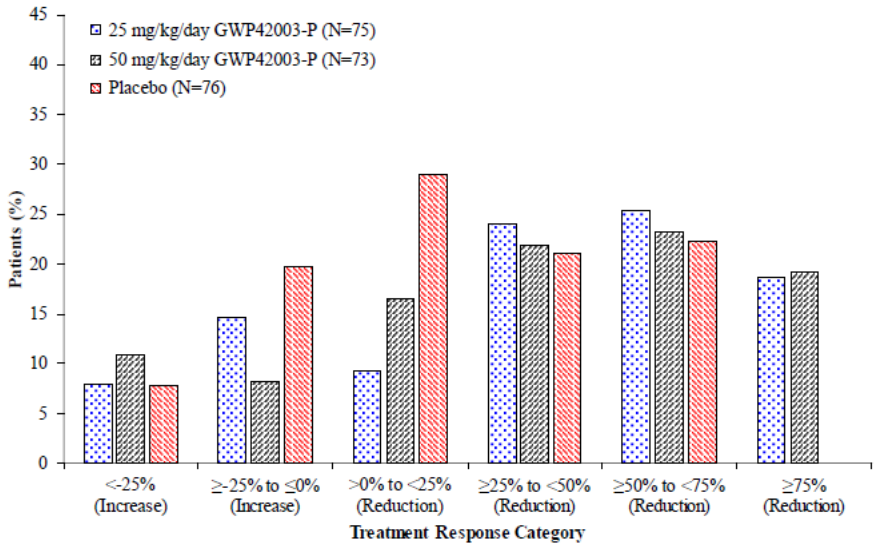
Note: Total seizures include all seizure types combined.
Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.

[redacted]

TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom

Figure 15

Figure 8.4.1.2.2.1-1 Proportion of Patients Experiencing Increase or Reduction from Baseline in TSC-associated Seizure Frequency During the Treatment Period (ITT Analysis Set)



Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.
Note: Baseline period included all data from Day −28 to Day 1. Maintenance period was defined as Day 29 to Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.

[redacted]

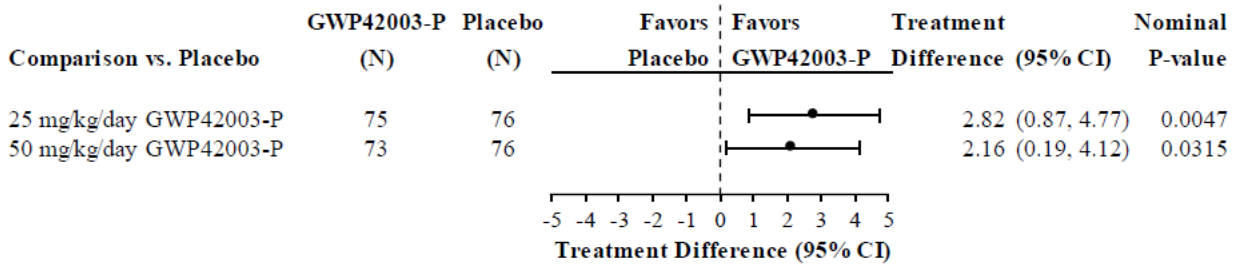
Overall, 1 patient, randomised to the 25 mg/kg/day group, experienced complete TSC-associated seizure freedom during the treatment period. Cannabidiol was associated with an increase in the percentage of

subjects (16.0%) experiencing a greater than or equal to 75% reduction in TSC-associated seizure frequency during the treatment period compared with the placebo group (0%).

Number of TSC-associated Seizure Free Days

Figure 16

Figure 8.4.1.2.2.2-1 Change from Baseline in TSC-associated Seizure Free Days per 28 Days During the Treatment Period (ITT Analysis Set)



Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.

Note: The placebo arms were pooled for the analysis of efficacy.

Note: Nominal p-value calculated using an ANCOVA model with baseline number of TSC-associated seizure free days and age group (1–6, 7–11, 12–17 and 18–65 years) as covariates and treatment group as fixed factor.

[redacted]

Other Seizures

Other seizures were defined as absence, myoclonic, partial (focal) sensory seizures, and infantile or epileptic spasms.

Of those patients who had other seizures reported during the baseline period, a higher proportion of patients in the 50 mg/kg/day GWP42003-P treatment group (91.7%) experienced any reduction in their other seizure frequency during the treatment period compared with in the placebo group (86.7%) or the 25 mg/kg/day GWP42003-P treatment group (75.0%). A higher proportion of 25 mg/kg/day GWP42003-P patients (25.0%) than placebo patients (13.3%) or 50 mg/kg/day GWP42003-P patients (8.3%) reported any increase in other seizures from baseline during the treatment period.

Overall 14 patients experienced complete freedom from other seizures during the treatment period; 2 randomized to 25 mg/kg/day, 7 randomized to 50 mg/kg/day and 5 randomized to placebo.

Table 28

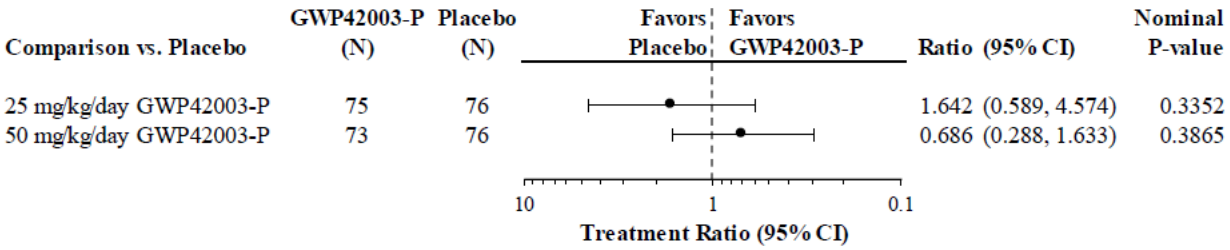
Table 8.4.1.2.2.3-1 Change in Other Seizures During the Treatment Period Compared to Baseline (ITT Analysis Set)			
Variable Statistics	25 mg/kg/day GWP42003-P (N=75)	50 mg/kg/day GWP42003-P (N=73)	Placebo (N=76)
Percentage Change from Baseline in Other Seizure Frequency (Average per 28 Days) During the Treatment Period			
n (%)	12 (16.0)	24 (32.9)	15 (19.7)
Median	−39.67	−89.92	−77.73
Q1, Q3	−100.0, 14.6	−100.0, −51.4	−100.0, −32.9
Negative Binomial Regression Analysis of Other Seizure Count During Baseline and Treatment Periods			
Percentage Reduction	51.8	79.9	70.6
95% CI	-3.8, 77.6	65.4, 88.3	42.2, 85.1

Note: Other seizures include absence, myoclonic, partial (focal) sensory seizures, and infantile or epileptic spasms.
Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[redacted]

Figure 17

Figure 8.4.1.2.2.3-1 Negative Binomial Regression Analysis of Other Seizure Count During Baseline and Treatment Periods (ITT Analysis Set)



Note: Other seizures include absence, myoclonic, partial (focal) sensory seizures, and infantile or epileptic spasms.
Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: Model includes total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[redacted]

Total Seizure Treatment Responders and Total Seizure Freedom

Overall 1 patient, randomised to the 25 mg/kg/day group, experienced complete total seizure freedom during the whole treatment period (Day 1 to Day 113).

Patients receiving cannabidiol experienced a greater percentage reduction in total seizures (48.1%) compared with placebo (26.9%).

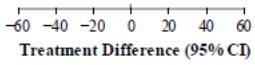
Quality of Life in Childhood Epilepsy (2–18 Years)

Quality of Life in Epilepsy, Version 2 (19 Years and Above)

Figure 18

Figure 8.4.1.2.2.6-1 ANCOVA of Change from Baseline to End of Treatment in Quality of Life in Epilepsy, Version 2 Score (19 Years and Above) by Subscale (ITT Analysis Set)

Subscale Comparison vs. Placebo	GWP42003-P (N)	Placebo (N)	Treatment Difference (95% CI)	Nominal P-value
Overall Quality of Life[a]				
25 mg/kg/day GWP42003-P	13	10	-4.2 (−25.1, 16.8)	0.6868
50 mg/kg/day GWP42003-P	9	10	-7.9 (−30.7, 14.8)	0.4803
Energy				
25 mg/kg/day GWP42003-P	13	10	6.4 (−11.7, 24.5)	0.4762
50 mg/kg/day GWP42003-P	9	10	-0.9 (−20.1, 18.3)	0.9237
Mood				
25 mg/kg/day GWP42003-P	14	10	-19.6 (−40.6, 1.5)	0.0675
50 mg/kg/day GWP42003-P	9	10	-13.0 (−35.6, 9.6)	0.2490
Daily Activities				
25 mg/kg/day GWP42003-P	13	10	-3.3 (−25.9, 19.3)	0.7644
50 mg/kg/day GWP42003-P	8	10	-8.7 (−34.6, 17.2)	0.4966
Cognition				
25 mg/kg/day GWP42003-P	12	10	-12.7 (−44.0, 18.6)	0.4098
50 mg/kg/day GWP42003-P	8	10	-10.8 (−44.1, 22.5)	0.5095
Medication Effects				
25 mg/kg/day GWP42003-P	13	10	-10.6 (−39.3, 18.2)	0.4562
50 mg/kg/day GWP42003-P	8	10	-25.7 (−58.4, 6.9)	0.1172
Seizure Worry				
25 mg/kg/day GWP42003-P	12	10	7.9 (−16.5, 32.2)	0.5121
50 mg/kg/day GWP42003-P	8	10	-14.7 (−41.6, 12.2)	0.2712
Total[b]				
25 mg/kg/day GWP42003-P	12	10	-3.7 (−16.6, 9.2)	0.5606
50 mg/kg/day GWP42003-P	8	10	-10.4 (−23.8, 3.0)	0.1227



[a] The overall quality of life score is calculated by taking the mean of the subscale scores.

[b] The total score is calculated as:
(Sum of all subscale weighted scores ÷ Sum of all subscale 'distress' item converted scores) × 100

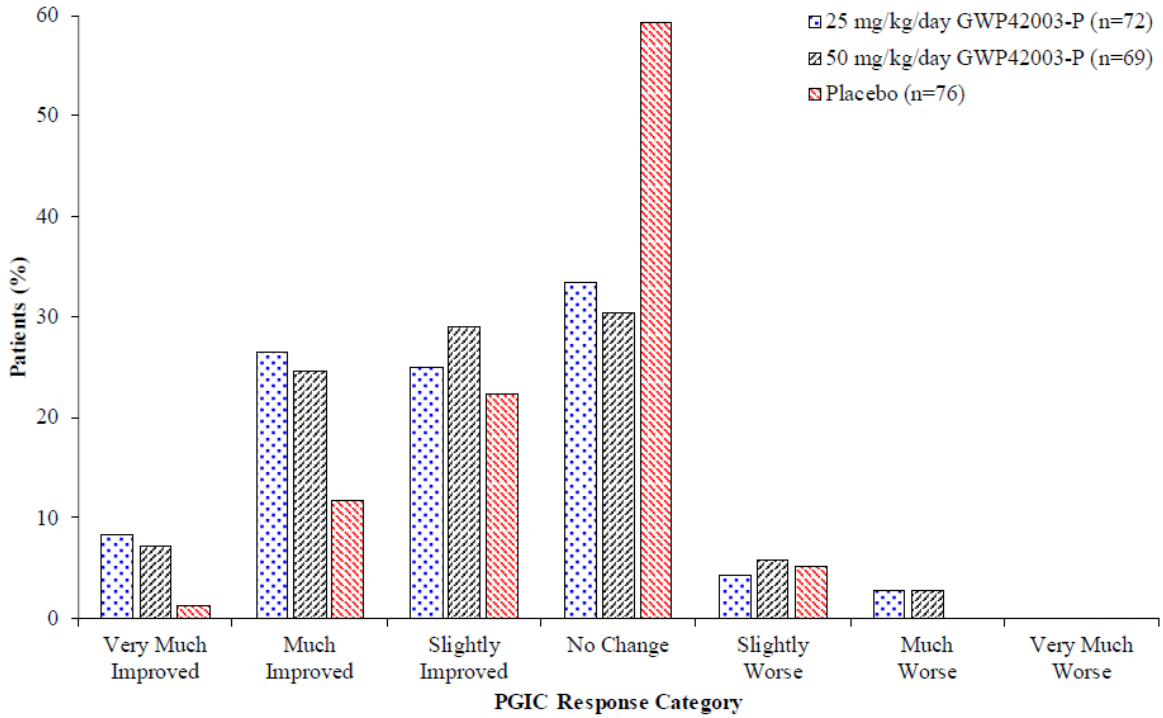
Note: The placebo arms were pooled for the analysis of efficacy.
Note: 0 represents the lowest or poorest category and 100 represents the highest level of functioning.
Note: The change from baseline is analyzed using an ANCOVA model with baseline as covariate and treatment group as a fixed factor.

[redacted]

Physician Global Impression of Change

Figure 19

Figure 8.4.1.2.2.7-1 Physician Global Impression of Change in the Patient's General Functional Abilities at Last Visit by Category (ITT Analysis Set)



Note: The combined caregiver and subject summary used either the caregiver or subject version if only one version was completed, or the caregiver version if both a caregiver and subject versions were completed.

Note: The placebo arms were pooled for the analysis of efficacy.

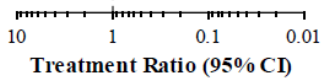
Selected exploratory endpoints:

Individual TSC-associated Seizure Types

Figure 20

Figure 8.4.1.2.3.2.1-1 Negative Binomial Regression Analysis of Seizure Count During Baseline and Treatment Periods by TSC-associated Seizure Type (ITT Analysis Set)

Seizure Type Comparison vs. Placebo	GWP42003-P (N)	Placebo (N)	Ratio (95% CI)	Nominal P-value
Type 1 Focal				
25 mg/kg/day GWP42003-P	29	33	1.021 (0.527, 1.979)	0.9506
50 mg/kg/day GWP42003-P	39	33	0.766 (0.408, 1.437)	0.4020
Type 2 Focal				
25 mg/kg/day GWP42003-P	46	50	0.666 (0.481, 0.921)	0.0145
50 mg/kg/day GWP42003-P	54	50	0.716 (0.524, 0.977)	0.0354
Type 3 Focal				
25 mg/kg/day GWP42003-P	17	24	0.525 (0.294, 0.938)	0.0300
50 mg/kg/day GWP42003-P	24	24	0.815 (0.485, 1.369)	0.4338
Tonic-Clonic				
25 mg/kg/day GWP42003-P	22	14	0.837 (0.396, 1.769)	0.6342
50 mg/kg/day GWP42003-P	16	14	0.842 (0.377, 1.884)	0.6700
Tonic				
25 mg/kg/day GWP42003-P	27	15	0.559 (0.322, 0.968)	0.0382
50 mg/kg/day GWP42003-P	23	15	0.657 (0.375, 1.151)	0.1393



Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Note: Baseline period included all data from Day −28 to Day 1. For each seizure type, only patients with seizures during the baseline period are included. Treatment period was defined as Day 1 to Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: Models include total number of seizures as a response variable and age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

[redacted]

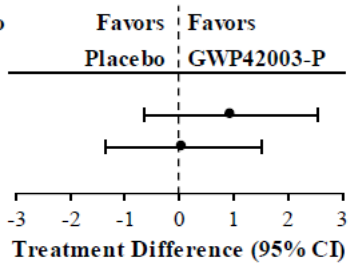
Rescue Medication Use

The number of patients who reported any rescue medication use within a 28-day period during the treatment period increased in all groups vs. the baseline period (25 mg/kg/day GWP42003-P: 68 vs. 16 patients; 50 mg/kg/day GWP42003-P: 71 vs. 24 patients; Placebo: 73 vs. 20 patients). The treatment difference for the change from baseline in the number of days of reported rescue medication use in patients who had been taking rescue medications during the baseline period was numerically in favour of GWP42003-P for the 25 mg/kg/day (Figure 21).

Figure 21

Figure 8.4.1.2.3.3-1 Analysis of Change from Baseline in the Number of Days of Rescue Medication Use (ITT Analysis Set)

Comparison vs. Placebo	GWP42003-P (N)	Placebo (N)	Treatment Difference (95% CI)	Nominal P-value
25 mg/kg/day GWP42003-P	16	20	0.96 (−0.65, 2.56)	0.2371
50 mg/kg/day GWP42003-P	24	20	0.07 (−1.37, 1.51)	0.9258



Note: Treatment period includes all data between Day 1 and Day 113.
Note: The placebo arms were pooled for the analysis of efficacy.
Note: The change from baseline period in number of days rescue medication was taken per 28 days is analyzed using an ANCOVA model with baseline period and age group (1-6, 7-11, 12-17 and 18-65 years) as covariates and treatment group as a fixed factor.

[redacted]

Status Epilepticus

Table 29

Table 8.4.1.2.3.4-1 Summary of Patients with Status Epilepticus (ITT Analysis Set)

Parameter Analysis Period	25 mg/kg/day GWP42003-P (N=75)	50 mg/kg/day GWP42003-P (N=73)	Placebo (N=76)
Number of Patients with Status Epilepticus [n (%)]			
Baseline (all patients)	0	2 (2.7)	3 (3.9)
Treatment (all patients)	5 (6.7)	2 (2.7)	7 (9.2)
Treatment (patients without an occurrence at baseline)	5 (6.7)	2 (2.7)	6 (9.2)

Note: The placebo arms were pooled for the analysis of efficacy.

[redacted]

Vineland Adaptive Behaviour Scales, Second Edition

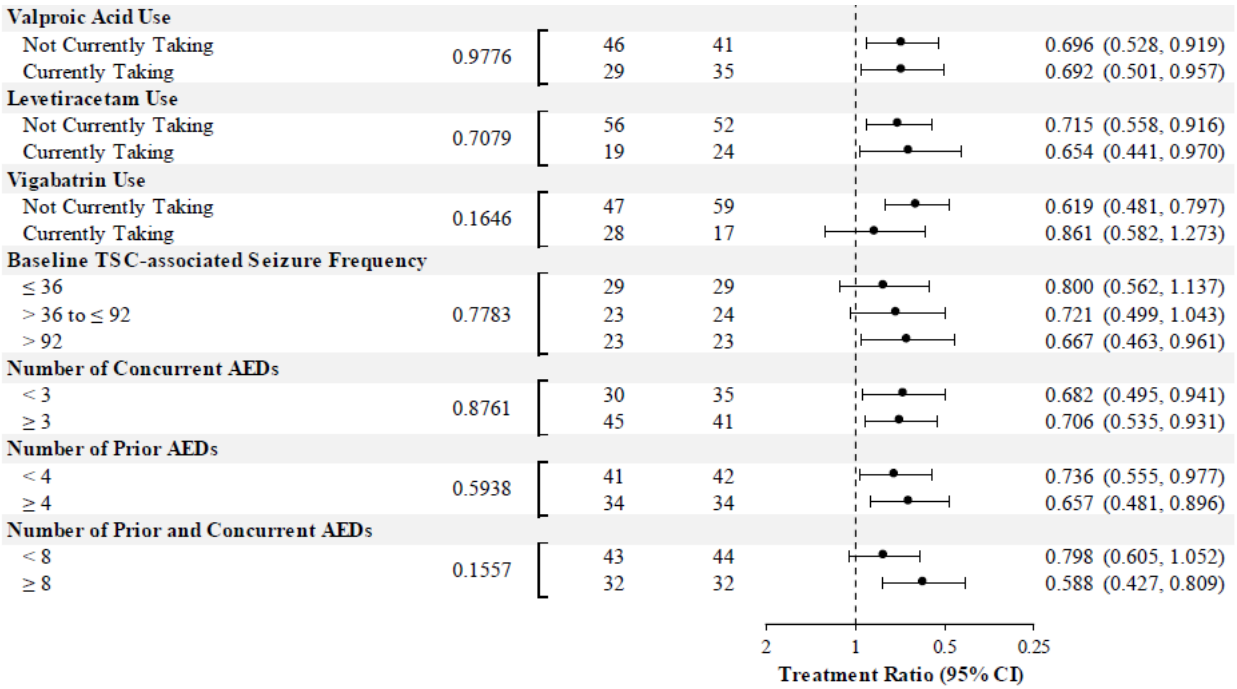
For all adaptive behaviour domain scores and the adaptive behaviour composite score, the adjusted mean differences between treatments were small, the majority being in favour of placebo.

Subgroup Analysis of the primary and key secondary endpoints

Figure 22

Figure 8.4.1.3.1-1 Subgroup Analysis of the Primary Endpoint (25 mg/kg/day GWP42003-P vs. Placebo): Negative Binomial Regression Effect Modification Analysis of TSC-associated Seizure Count During Baseline and Treatment Periods (ITT Analysis Set)

Subgroup	Interaction P-value	GWP42003-P (N)	Placebo (N)	Favors Placebo / Favors GWP42003-P	Ratio (95% CI)
Overall		75	76		0.699 (0.567, 0.861)
Age Group					
1–6 Years	0.9287	21	22		0.698 (0.472, 1.032)
7–11 Years		18	18		0.776 (0.504, 1.192)
12–17 Years		16	16		0.626 (0.394, 0.995)
18–65 Years		20	20		0.686 (0.453, 1.039)
Sex					
Female	0.4653	32	31		0.768 (0.554, 1.063)
Male		43	45		0.655 (0.498, 0.863)
Region					
USA	0.0813	36	42		0.583 (0.435, 0.781)
Rest of the World		39	34		0.846 (0.627, 1.141)
Clobazam Use					
Not Currently Taking	0.1535	58	51		0.753 (0.589, 0.963)
Currently Taking		17	25		0.534 (0.356, 0.800)



Note: TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.

Note: Baseline period included all data from Day −28 to Day 1. Treatment period was defined as Day 1 to Day 113.

Note: The placebo arms were pooled for the analysis of efficacy.

Note: Model includes total number of seizures as a response variable and age group (only when age is not the factor being tested), time (baseline and treatment period), treatment, factor, treatment by time interaction, factor by treatment interaction, factor by time interaction, and factor by time by treatment interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as an offset.

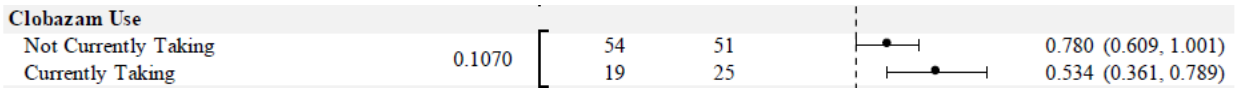
[redacted]

In the GWEP1521 study, 22.7% of TSC patients in the 25 mg/kg/day group and 32.9% in the placebo group were taking concomitant clobazam. Results of subgroup analysis by clobazam use showed additive anticonvulsant effects of cannabidiol in the presence of clobazam.

In the subgroup of patients treated with concomitant clobazam, patients receiving cannabidiol 25 mg/kg/day experienced a 61.1% reduction from baseline in TSC-associated seizure frequency compared to a 27.1 % reduction in the placebo group, based on a negative binomial regression analysis. Compared with placebo, cannabidiol was associated with a 46.6% reduction (nominal p=0.0025) in TSC-associated seizures (95% CI: 20.0%, 64.4%).

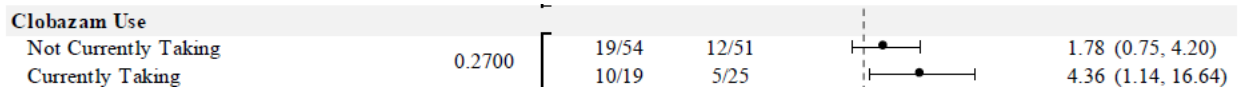
In the subgroup of patients treated without concomitant clobazam, patients receiving cannabidiol 25 mg/kg/day experienced a 44.4 % reduction from baseline in TSC associated seizure frequency compared to a 26.2% reduction in the placebo group; based on a negative binomial regression analysis. Compared with placebo, cannabidiol was associated with a 24.7% reduction (nominal p=0.0242) in TSC-associated seizures (95% CI: 3.7%, 41.1%).

Subgroup Analysis of the Primary Endpoint (50 mg/kg/day GWP42003-P vs. Placebo), clobazam use:



Subgroup Analysis of Key Secondary Endpoint #1 (25 mg/kg/day GWP42003-P vs. Placebo), clobazam use:

Subgroup Analysis of Key Secondary Endpoint #1 (50 mg/kg/day GWP42003-P vs. Placebo), clobazam use:



Ancillary analyses

NA

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30: Summary of Efficacy for trial GWEP1521 (Tuberous Sclerosis Complex)

Title: 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	
Trial Identifier	Protocol Number: GWEP1521 EudraCT Number: 2015-002154-12 ClinicalTrials.gov Identifier: NCT02544763
Design	Trial GWEP1521 was a 16-week treatment period, multisite, randomized, double-blind trial of 2 dose levels of cannabidiol oral solution (CBD-OS) (25 mg/kg/day and 50 mg/kg/day) vs. placebo. An interactive voice response system was used daily to record information on seizures. A paper diary was used daily to record information on investigational medicinal product (IMP) usage, rescue medication, concomitant antiepileptic drugs, and adverse events. Following a 1-week screening period and a 4-week baseline period, eligible patients were randomized to receive CBD-OS 25 mg/kg/day, CBD-OS 50 mg/kg/day, or equivalent volumes of placebo. Patients completed a 4-week dose escalation period, titrating up to their assigned dose, before continuing on a stable dose of blinded IMP for 12 weeks. Patients who discontinued before the end of the treatment phase completed a 10-day taper period (down-titrating 10% per day for 10 days). Following completion of the trial, patients were invited to continue to receive CBD-OS in an open-label extension (OLE) trial under the same protocol. Those who opted to enter the OLE first entered a 2-week blinded transition period where all patients were transitioned to 25 mg/kg/day, followed by a 3-week titration period for dose optimization, a subsequent maintenance period, and a 10-day taper period (down-titrating 10% per day for 10 days) following either the end of treatment or early discontinuation from the trial. Those who opted not to enter the OLE completed the 10-day taper period

	Duration of Main Phase:	16-week treatment period (12 weeks dose maintenance)	
	Duration of Run-in Phase: Duration of Extension Phase:	4-week dose titration period before maintenance phase Up to 3 years' duration (Poland) or 4 years' duration (US)	
Hypothesis	Superiority: The hypothesis underlying this trial was that CBD-OS, as an adjunctive treatment of tuberous sclerosis complex (TSC), has a positive risk/benefit outcome in the change in number of TSC-associated seizures compared with placebo.		
Treatment Groups	CBD-OS 25 mg/kg/day	Treatment: 25 mg/kg/day CBD-OS Treatment duration: 16 weeks including a 4-week dose titration period and a 12-week maintenance phase Number randomized: 75	
	CBD-OS 50 mg/kg/day	Treatment: 50 mg/kg/day CBD-OS Treatment duration: 16 weeks including a 4-week dose titration period and a 12-week maintenance phase Number randomized: 73	
	Placebo	Treatment: Placebo Treatment duration: 16 weeks including a 4-week dose titration period and a 12-week maintenance phase Number randomized: 76 (38 patients each in the 25 and 50 mg/kg/day dose equivalent volume groups)	
Endpoints and Definitions	Primary endpoint:	Primary Analysis: Change in TSC-associated seizures during the treatment period compared with baseline	The prespecified primary endpoint was the change in number of TSC-associated seizures during the treatment period (Day 1 to Day 113, including the initial dose titration period) compared with baseline period. The primary endpoint was analyzed using negative binomial regression; therefore, results were presented with an estimated ratio of the ratios of least squares (LS) means (treatment period to baseline period) and 95% confidence interval (CI) for the ratio, along with the p-value testing the null hypothesis that the ratio of each CBD-OS group to placebo was 1. A hierarchical procedure was used to control the Type 1 error; for further details see 'Hierarchical Analyses' section in this table.
	Key secondary endpoint #1	Key secondary analysis: TSC-associated treatment responders (patients with a ≥ 50% reduction in TSC-associated seizure frequency)	The first prespecified key secondary endpoint was the proportion of patients considered treatment responders, defined as those with ≥ 50% reduction from baseline in TSC-associated seizure frequency, during the treatment period, for patients who had not withdrawn from the trial during the treatment period, and was summarized by treatment group and analyzed using a Cochran Mantel Haenszel (CMH) test stratified by age group.

			The proportion of patients considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratio (OR) (CBD-OS arms vs. placebo), 95% CI for the OR, and the p-value from the CMH test were presented. If no patients in a treatment group were considered responders, then the OR and 95% CI for the OR were not calculated. A hierarchical procedure was used to control the Type 1 error; for further details see 'Hierarchical Analyses' section in this table.
	Key secondary endpoint #2	Key secondary analysis: Subject/caregiver global impression of change (S/CGIC)	The second prespecified key secondary endpoint was the S/CGIC score at the last visit comparing CBD-OS vs. placebo treatment. The scores at the end of treatment visit and last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. Proportional odds modelling was carried out by including treatment group as a factor. The estimated OR (CBD-OS vs. placebo), 95% CI for the OR, and the p-value testing the null hypothesis that OR is equal to 1, were presented. The analysis of the patient's last visit data was considered the main analysis for this endpoint, with the analysis of the patient's end of treatment visit data considered a sensitivity analysis. A hierarchical procedure was used to control the Type 1 error; for further details see 'Hierarchical Analyses' section in this table.
	Key secondary endpoint #3	Key secondary analysis: Change in total seizures during the treatment period compared with baseline	The third prespecified key secondary endpoint was the change in total seizures comparing CBD-OS vs. placebo treatment. The endpoint was analyzed using negative binomial regression; therefore, results were presented with an estimated ratio of the ratios of LS means (treatment period to baseline period) and 95% CI for the ratio, along with the p-value testing the null hypothesis that the ratio of each CBD-OS group to placebo was 1. A hierarchical procedure was used to control the Type 1 error; for further details see 'Hierarchical Analyses' section in this table.
Hierarchical Analyses	Each endpoint, including the primary endpoint, had 2 comparisons against placebo (25 mg/kg/day CBD OS and 50 mg/kg/day CBD OS vs. placebo) and 3 key secondary endpoints were defined. The primary and key secondary endpoints were tested with their type I error controlled using a hierarchical gate-keeping procedure, in the following sequence: 1) Primary endpoint; CBD-OS 25 mg/kg/day vs. placebo. 2) 1st key secondary endpoint; CBD OS 25 mg/kg/day vs. placebo. 3) Primary endpoint; CBD OS 50 mg/kg/day vs. placebo. 4) 1st key secondary endpoint; CBD-OS 50 mg/kg/day vs. placebo.		

	5) 2nd key secondary endpoint; CBD OS 25 mg/kg/day vs. placebo. 6) 3rd key secondary endpoint; CBD-OS 25 mg/kg/day vs. placebo. 7) 2nd key secondary endpoint; CBD OS 50 mg/kg/day vs. placebo. 8) 3rd key secondary endpoint; CBD OS 50 mg/kg/day vs. placebo. The null hypothesis of an endpoint had to be rejected at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis was not rejected, then all subsequent analyses would be declared nominally significant or not statistically significant, depending on whether the subsequent P-value was ≤ 0.05 or > 0.05.			
Database Lock	23 Apr 2019			
Results and Analysis				
Analysis Description	**Primary Analysis:** Change in TSC-associated seizures during the treatment period compared with baseline			
Analysis Population and Time Point Description	Intention-to-treat (ITT): All patients who were randomized and dosed with IMP and had post-baseline efficacy data were included in the ITT analysis set according to their randomized treatment group. Time Point: 16-week treatment period (including 4-week dose titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment group	25 mg/kg/day CBD-OS	50 mg/kg/day CBD-OS	Placebo[a]
	Number of patients	75	73	76
	Percent change from baseline in TSC-associated seizure[b] frequency			
	Median Q1, Q3	−43.36 −67.8, −13.6	−36.55 −67.0, −5.5	−20.08 −47.1, 3.1
	Negative binomial regression analysis of TSC-associated seizure count during baseline and treatment periods			
	Percentage reduction 95% CI	48.6 40.4, 55.8	47.5 39.0, 54.8	26.5 14.9, 36.5
Effect Estimate Per Comparison	Primary endpoint (Hierarchical analysis #1)	Comparison groups	25 mg/kg/day CBD-OS vs. placebo	
		Treatment ratio	0.699	
		95% CI	0.567, 0.861	
		P-value	0.0009	
	Co-primary endpoint (Hierarchical analysis #3)	Comparison groups	50 mg/kg/day CBD-OS vs. placebo	
		Treatment ratio	0.715	
		95% CI	0.580, 0.881	
		Nominal P-value	0.0018	
Notes	[a] The placebo arms were pooled for the analysis of efficacy. [b] TSC-associated seizures include focal motor seizures without impairment of consciousness or awareness (Type 1 focal motor); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures.			

	Patient Withdrawals A total of 23 patients withdrew from the trial (10 from the 25 mg/kg/day CBD-OS group, 12 from the 50 mg/kg/day CBD-OS group; and 1 patient from the placebo group). The most common primary reason for withdrawal was adverse events (8 patients each from the 25 and 50 mg/kg/day CBD-OS group). Withdrawn patients were included in the ITT analysis set.			
Analysis Description	**Key Secondary Analysis #1:** Patients with a ≥ 50% reduction from baseline in TSC-associated seizure frequency			
Analysis Population and Time Point Description	ITT: All patients who were randomized and dosed with IMP and had post-baseline efficacy data were included in the ITT analysis set according to their randomized treatment group. Time Point: 16-week treatment period (including 4-week dose titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment group	25 mg/kg/day CBD-OS	50 mg/kg/day CBD-OS	Placebo[a]
	Number of patients	75	73	76
	Patients with a ≥ 50% reduction from baseline in TSC-associated seizure frequency			
	Yes (%) No (%)	27 (36.0) 48 (64.0)	29 (39.7) 44 (60.3)	17 (22.4) 59 (77.6)
Effect Estimate Per Comparison	Key secondary endpoint #1 (Hierarchical analysis #2)	Comparison groups	25 mg/kg/day CBD-OS vs. placebo[b]	
		OR	1.95	
		95% CI	0.95, 4.00	
		P-value	0.0692	
	Key secondary endpoint #1 (Hierarchical analysis #4)	Comparison groups	50 mg/kg/day CBD-OS vs. placebo	
		OR	2.29	
		95% CI	1.12, 4.67	
		Nominal P-value	0.0245	
Notes	[a] The placebo arms were pooled for the analysis of efficacy. [b] The OR did not reach statistical significance for the 25 mg/kg/day CBD-OS group (P=0.0692) and therefore the OR for the 50 mg/kg/day CBD-OS group vs. placebo was considered nominally significant according to the rules associated with the hierarchical testing approach. A step-down procedure was used to control the type 1 error; for further details see the 'Hierarchical Analyses' section in this table. For information on patient withdrawals please see 'Notes' in the primary analysis section in this table. Patients who withdrew were considered non-responders.			
Analysis Description	**Key Secondary Analysis #2:** Subject/caregiver global impression of change score			
Analysis Population and Time Point Description	ITT: All patients who were randomized and dosed with IMP and had post-baseline efficacy data were included in the ITT analysis set according to their randomized treatment group. Time Point: Patient's last visit.			
	Treatment group	25 mg/kg/day CBD-OS	50 mg/kg/day CBD-OS	Placebo[a]

Descriptive Statistics and Estimate Variability	Number of patients	70	69	76
	S/CGIC score at last visit by category, n (%)			
	Very much improved	10 (14.3)	9 (13.0)	3 (3.9)
	Much improved	13 (18.6)	12 (17.4)	10 (13.2)
	Slightly improved	25 (35.7)	22 (31.9)	17 (22.4)
	No change	14 (20.0)	15 (21.7)	42 (55.3)
	Slightly worse	4 (5.7)	6 (8.7)	3 (3.9)
	Much worse	3 (4.3)	3 (4.3)	1 (1.3)
	Very much worse	1 (1.4)	2 (2.9)	0

Effect Estimate Per Comparison[b]	Key secondary endpoint #2 (Hierarchical analysis #5)	Comparison groups	25 mg/kg/day CBD-OS vs. placebo
		OR	2.25
		95% CI	1.24, 4.07
		Nominal P-value	0.0074
	Key secondary endpoint #2 (Hierarchical analysis #7)	Comparison groups	50 mg/kg/day CBD-OS vs. placebo
		OR	1.77
		95% CI	0.98, 3.20
		Nominal P-value	0.0580

Notes	[a] The placebo arms were pooled for the analysis of efficacy. [b] The global impression of change was analyzed using an ordinal logistic regression model with treatment group as a fixed factor (ordinal values were as follows: 1 = very much improved; 2 = much improved; 3 = slightly improved; 4 = no change; 5 = slightly worse; 6 = much worse; 7 = very much worse). The combined caregiver and subject summary uses either the caregiver or subject version if only one version was completed, or the caregiver version if both a caregiver and subject versions were completed. A step-down procedure was used to control the type 1 error; for further details see the 'Hierarchical Analyses' section in this table. For information on patient withdrawals please see 'Notes' in the primary analysis section in this table.
Analysis Description	**Key Secondary Analysis #3:** Change in total seizures during the treatment period compared with baseline
Analysis Population and Time Point Description	ITT: All patients who were randomized and dosed with IMP and had post-baseline efficacy data were included in the ITT analysis set according to their randomized treatment group. Time Point: 16-week treatment period (including 4-week dose titration period and 12-week maintenance period).

	Treatment group	25 mg/kg/day CBD-OS	50 mg/kg/day CBD-OS	Placebo[a]

Descriptive Statistics and Estimate Variability	Number of patients	75	73	76
	Total seizure frequency (average per 28 days) during the baseline period			
	Median	56.00	70.00	56.48
	Q1, Q3	22.6, 101.0	38.0, 130.0	27.5, 138.1
	Total seizure frequency (average per 28 days) during the treatment period			
	Median	32.96	32.25	44.03
	Q1, Q3	9.0, 63.3	14.6, 91.3	18.3, 84.9
	% Reduction in seizure frequency (average per 28 days) during the treatment period compared to baseline period			
	% Reduction	48.1	47.6	26.9
	95% CI	39.8, 55.3	39.3, 54.8	15.4, 36.8

Effect Estimate Per Comparison	Key secondary endpoint #3 (Hierarchical analysis #6)	Comparison groups	25 mg/kg/day CBD-OS vs. placebo
		Treatment ratio	0.709
		95% CI	0.576, 0.873
		Nominal P-value	0.0013
	Key secondary endpoint #3 (Hierarchical analysis #8)	Comparison groups	50 mg/kg/day CBD-OS vs. placebo
		Treatment ratio	0.716
		95% CI	0.582, 0.882
		Nominal P-value	0.0018
Notes	[a] The placebo arms were pooled for the analysis of efficacy. Total seizures include all seizure types combined. A step-down procedure was used to control the type 1 error; for further details see the 'Hierarchical Analyses' section in this table. For information on patient withdrawals please see 'Notes' in the primary analysis section in this table.		

2.4.3. Discussion on clinical efficacy

The MAH is seeking approval for CBD-OS in TSC with dose titration steps at 5 mg/kg/day and 10 mg/kg/day after which the clinical response and tolerability are assessed up to a maximum recommended maintenance dosage of 25 mg/kg/day. The single pivotal trial in TSC (GWEP1521) tested the doses 25 mg/kg/day and 50 mg/kg/day, with a titration regimen was much faster than that in the proposed SmPC.

Design and conduct of clinical studies

The clinical development program supporting the efficacy of CBD-OS in TSC comprises a single, Phase III, randomised, placebo-controlled trial (GWEP1521) that investigated 25 mg/kg/day and 50 mg/kg/day

CBD-OS for the treatment of TSC-associated seizures. Except for dose levels and titration schedule, the trial design adopted resembled that used for the CBD-OS trials in previously authorised indications.

There is a significant unmet need for new therapies in TSC and the patients randomised in the study are representative of a highly refractory patient population.

Stratification by the use of clobazam would have been preferable given the known interaction between clobazam and CBD-OS. However, the trial was initiated before the importance of this interaction had been fully realised.

Discontinuations and dose reductions due to AEs were common in the active treatment arms, and in a considerable proportion of cases, caregivers and physicians may thus have been aware of the treatment assignment due to AEs (both reported and unreported).

Primary efficacy endpoint is not fully in line with the EU Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders and the recommendation that "Two important variables should be specified in the protocol. The primary endpoint should be responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency (e.g. a 50% reduction is commonly used). The other variable should be some parameterisation using the actual change in seizure frequency." Nonetheless, the use of 50% responder rate as a key secondary endpoint instead of primary endpoint was accepted by PDCO and included in the agreed PIP. For the primary analysis, several sensitivity analyses which would have been informative could not be performed because of lack of detailed data e.g. about missing visits or rescue medication.

Efficacy data and additional analyses

The efficacy of the 50 mg/kg/day dose was found to be similar to that of the 25 mg/kg/day dose. The safety and tolerability burden was however greater with the 50 mg/kg/day dose. Only the 25 mg/kg/day dose of Epidyolex has been proposed for approval.

There is no evidence of efficacy available for the lower dose level of 10 mg/kg/day in GWEP1521, and the similar efficacy profile of 50 mg/kg/day dose to 25 mg/kg/day dose is precluding establishment of a dose-response relationship or low or high doses to be approved or used for treatment of TSC.

The primary analysis demonstrated greater reduction in TSC-associated seizures in the active treatment groups as compared with the placebo group. The percent decrease in TSC-associated seizure frequency was 43.36% in the 25 mg/kg/day group and 20.08% in the placebo group compared to their baseline. The sensitivity analyses performed appeared to support the primary analysis. A similar pattern was seen for the percent decrease in total seizures for patients who received CBD-OS compared to placebo (treatment ratio 0.709, 95% CI: 0.576-0.873; p=0.0013).

Clinical relevance was not fully supported by the most important key secondary analysis, the 50% responder analysis, where the OR for achieving a ≥ 50% reduction in TSC-associated seizure frequency did not reach statistical significance for the 25 mg/kg/day group (proportion of responders was 36.0 % and 22.4% in the 25 mg/kg/day and the placebo group respectively, P=0.0692). If patients who took rescue medication are also considered non-responders only 24.0% in the 25 mg/kg/day vs. 17.1% of patients in the placebo group were responders. This is still considered supportive as these results are in accordance with the European Medicines Agency (EMA) Guideline on Multiplicity Issues in Clinical Trials (EMA/CHMP/44762/2017): "In a situation in which the primary endpoint establishes a statistically significant effect, "the results of the 'responder' analysis need not be statistically significant, but the difference in the proportions of responders should support a statement that the investigated treatment

induces clinically relevant effects." Actually, 16.0% of patients in the 25 mg/kg/day Epidyolex group achieved the ≥ 75% response level, compared to no patients in the placebo group (nominal p=0.0003).

As also observed in studies in other indications, for 25 mg/kg/day group the point estimates for efficacy were larger in the subgroup of patients on concomitant clobazam treatment than in the subgroup of patients not receiving clobazam. The treatment ratio was 0.753 (95% CI 0.589-0.963) in the subgroup of patients not on clobazam but 0.534 (95% CI 0.356-0.800) in the subgroup of patients on clobazam, suggesting a treatment effect twice as large in patients on clobazam. Patients receiving cannabidiol 25 mg/kg/day in conjunction with clobazam experienced a 61.1 % reduction from baseline in TSC-associated seizure frequency compared to 27.1 % in the placebo group. The proportion of patients with at least a 50% reduction in TSC associated seizure frequency in patients receiving cannabidiol 25 mg/kg/day in conjunction with clobazam was 47.1% compared to 20.0 % in the placebo group. Concomitant administration of cannabidiol and CLB causes an approximate 3-fold elevation in the active metabolite N-CLB with little or no increase in CLB likely mediated by CYP2C19 inhibition. Literature indicate that both pharmacodynamic and pharmacokinetic interactions between CBD and clobazam may contribute to its efficacy in Dravet syndrome. Nevertheless, in the TSC study, 73% of patients did not receive CLB (in contrast to 36% in clinical trials with Dravet syndrome) and the results from this subgroup still reached nominal statistical significance with CI (0.589-0.963) and the effect can be considered clinically relevant. Thus, the clinical efficacy of cannabidiol observed in patients with TSC does not appear only to be driven by an interaction with clobazam.

2.4.4. Conclusions on the clinical efficacy

The efficacy of CBD-OS in TSC has been demonstrated with the proposed dose level of 25 mg/kg/day.

The recommended posology, with a titration regimen as agreed for LGS/DS indications and with a maximum recommended dose of 25 mg/kg/day, is considered acceptable.

Although the treatment effect was found to be greater with concomitant clobazam treatment, which can well be explained by the known PK interaction, the treatment effect of CBD-OS without concomitant CLB therapy is statistically significant and clinically relevant. Taking into account that CLB is rarely used in TCS and has considerable safety issues, the decision to use concomitantly with CLB should be made individually according to patient needs and treatment response, which can be easily monitored. In order to support this decision, the relevant data are correctly reflected in the SmPC section 5.1.

2.5. Clinical safety

Introduction

In this extension of indication, the clinical safety data are coming from:

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

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

- completed data from 4 double-blind, placebo-controlled trials in LGS/DS

- interim data from an ongoing, long-term OLE trial in LGS/DS (Trial GWEP1415 OLE, cut-off date 03 Feb 2019)

Supportive safety data are also provided separately from

- 14 Phase 1 clinical pharmacology trials, as of 30 Apr 2019

- expanded access and compassionate use programs (EAP) (cut-off date 31 Jan 2019).

The EAP is a series of physician-initiated and state-supported applications for compassionate access in the US and a CAS in New South Wales, Australia, for treatment of patients with drug-resistant epilepsy. At the data cut-off, the CBD-OS EAP consisted of 38 different sites; 20 sites in the US under physician-initiated IND applications, some of which also treated patients under state-initiated IND applications, a further 7 US sites under state-initiated IND applications only, and 11 sites under the CAS in Australia. Results of pooled EAP data were presented in the original MAA; updates are presented in this extension of indication, along with new data from European EAPs.

Table 31: Overview of Clinical Trials in TSC, DS, and LGS

Trial	Trial Design and Objectives	No. of Patients Randomized to CBD-OS	No. of Patients Randomized to Placebo	Treatment Duration	Inclusion in Pools
Controlled					
GWEP1332	Randomized, double-blind, placebo-controlled, 2-part trial to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of CBD-OS in children and young adults with DS	Part A: 5 mg/kg/day: 10 10 mg/kg/day: 8 20 mg/kg/day: 9	Part A: 7	21 days	DS; DS/LGS; DS/LGS/TSC
		Part B: 20 mg/kg/day: 61	Part B: 59	14 weeks	
GWEP1414	Randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of CBD-OS as adjunctive treatment for seizures associated with LGS in children and adults	10 mg/kg/day: 73 20 mg/kg/day: 76	76	14 weeks	LGS; DS/LGS; DS/LGS/TSC
GWEP1423	Randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of CBD-OS as adjunctive treatment for seizures associated with LGS in children and adults	20 mg/kg/day: 86	85	14 weeks	LGS; DS/LGS; DS/LGS/TSC
GWEP1424	Randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of CBD-OS in children and young adults with Dravet syndrome	10 mg/kg/day: 67 20 mg/kg/day: 67	65	14 weeks	DS; DS/LGS; DS/LGS/TSC
GWEP1521	Double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of CBD-OS as add-on therapy in patients with TSC who experience inadequately controlled seizure	25 mg/kg/day: 75 50 mg/kg/day: 73	76	16 weeks	TSC; DS/LGS/TSC
Total Number of Patients		544	368		
Open label		**No. of Patients Exposed to CBD-OS[a]**	**No. of Patients Newly Exposed to CBD-OS[b]**	**Maximum Treatment Duration**	
GWEP1415	Open-label extension trial to investigate the safety of CBD-OS in children and adults with inadequately controlled DS or LGS	681	282	2 years[c]	DS/LGS OLE; DS/LGS/TSC OLE
GWEP1521 OLE	Open-label extension portion of GWEP1521 to investigate the safety of CBD-OS as add-on therapy in children and adults with seizures associated with TSC	199	75	1 year	TSC OLE; DS/LGS/TSC OLE

CBD-OS = cannabidiol oral solution, DB = double-blind, DS = Dravet syndrome; LGS = Lennox-Gestaut sydrome; OLE = open-label extension, TSC = tuberous sclerosis complex; US = United States.
[a] Number exposed as of the cutoff dates: GWEP1415, 03 February 2019; GWEP1521, 26 February 2019.
[b] Unique exposures represent patients randomized to placebo in the previous double-blind trials (GWEP1332 Part A, GWEP1332 Part B, GWEP1414, GWEP1423, and GWEP1521) who transitioned to CBD-OS in the open-label trial GWEP1415 or GWEP1521 OLE.
[c] Two years in the US, Poland, and France; 1 year in the UK, Spain, Netherlands, and Israel

[redacted].

Patient exposure

Table 32: Overall Summary of CBD-OS Exposures in the Clinical Development and Supportive Programs[a]

Population Source	Total CBD-OS Exposures	Number of Unique CBD-OS Exposures
Controlled trials in the target indications		
Pool DS/LGS	456	—[b]
Pool DS	221	221
Pool LGS	235	235
Pool TSC (controlled portion of GWEP1521)	148	148
Pool DS/LGS/TSC	604	—[b]
Long-term open-label trials in the target indications		
GWEP1415-DS/LGS	681	282
GWEP1521 OLE (TSC)	199	75
Phase 1 clinical pharmacology trials (healthy patients and special patient populations)[c]		
Pool H-SD	417	224
Pool H-MD	189	189
Pool PP1-SD	163	87
Trials in other patient populations with epilepsy		
GWEP1428 (Placebo-controlled DDI trial in patients with epilepsy)	16	16
GWEP1447	28	28
Total for GW clinical development	2297	1505
EAP and other compassionate use programs (drug-resistant epilepsy)		
Pool EAP	1067	1067
Grand Total		2572

CBD-OS = cannabidiol oral solution, DB = double-blind, DDI = drug-drug interaction, EAP = expanded access program; OLE = open-label extension, TSC = tuberous sclerosis complex.
[a] Trials in exploratory indications are not included; these trials include schizophrenia, infantile spasms, and Rett syndrome.
[b] Exposures in pools with combined indications are not considered unique.
[c] Phase 1 clinical pharmacology trials include patients from crossover trials (GWEP1544, GWEP1448, GWEP1541, GWEP1431) having multiple treatment periods separated by washout periods. Therefore, patients from these trials can be counted more than once such that the total exposures are larger than the sum of the actual number of patients who participated in the trials.

In the TSC development program, 148 patients have been exposed to CBD-OS at the doses and durations shown in Table 33.

Table 33

Summary of CBD-OS Exposures in the TSC Clinical Development Program: Trial GWEP1521				
	CBD-OS			
Controlled phase	**25 mg/kg/day (N=75)**	**50 mg/kg/day (N=73)**	**All CBD-OS (N=148)**	**Placebo (N=76)**
Patient-years (on treatment)	21.11	20.34	41.45	23.61
Mean ± SD time on study (weeks)	15.2 ± 3.0	15.3 ± 3.0	15.2 ± 3.0	16.3 ± 0.6
CBD-OS Modal Dose				
Open-label phase	**≤ 20 mg/kg/day (N = 19)**	**> 20–30 mg/kg/day (N = 150)**	**> 30 mg/kg/day (N = 30)**	**All CBD-OS (N = 199)**
Patient-years (on treatment)	18.12	103.89	30.90	152.91
Mean ± SD time on study (weeks)	49.8 ± 34.2	36.4 ± 27.5	53.8 ± 30.0	40.3 ± 29.3

CBD-OS = cannabidiol oral solution; SD = standard deviation; TSC = tuberous sclerosis complex.

Summary of exposure from TSC study GWEP1521 (double-blind phase and OLE)

Table 34

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 (N=223)
	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	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)

Overall, 88 patients across the double-blind phase and OLE have been exposed to CBD-OS > 1 year.

Long-term exposure in TSC patients in the EAP

In addition to trial GWEP1521, there was 37 patients with TSC in the EAP with long-term exposure to CBD-OS, of which 17 patients achieved a modal dose of > 40 mg/kg/day (maximum 50 mg/kg/day) . There were 27 EAP TSC patients who were exposed to CBD-OS for > 1 year duration – of which 16 patients achieved > 40 mg/kg/day modal dose.

If all EAP patients are accounted for, then 706 patients with > 1 year exposure to CBD-OS in a more real world setting, at doses up to 50 mg/kg/day.

When combined with trial GWEP1521, duration of exposure can be summarised as in, where 115 TSC patients have been exposed to CBD-OS > 1 year duration.

Table 35

Exposure by Duration of Exposure in Patients with TSC		
Duration of Exposure	**Patients (N)**	**Patient-years**
1–14 days	7	0.22
15–28 days	5	0.31
29–42 days	5	0.48
43–84 days	21	3.32
85–182 days	39	14.74
183–364 days	68	50.92
365–729 days	77	99.62
> 730 days	38	99.58
Total person-time		**269.19**

Demographics

Demographic and baseline characteristics of Trial GWEP1521 are summarized in the following tables.

Table 36

2. Demographic and Baseline Data
TSC.2.1.1 Demographics
Pool TSC (controlled TSC) - Safety Analysis Set

Parameter	Statistics	CBD-OS 25 mg/kg/day (N=75)	CBD-OS 50 mg/kg/day (N=73)	All CBD-OS (N=148)	Placebo (N=76)
Age (years)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	Mean ± SD	14.1 ± 10.8	12.8 ± 8.6	13.5 ± 9.8	13.8 ± 10.6
	Median	11.6	10.2	11.4	10.9
	Q1 ; Q3	6.2 ; 18.4	5.8 ; 17.9	6.0 ; 18.2	6.4 ; 18.4
	Min ; Max	1.1 ; 56.8	1.8 ; 35.0	1.1 ; 56.8	1.2 ; 55.8
Age Categories, n (%)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	<2 years	2 (2.7)	1 (1.4)	3 (2.0)	5 (6.6)
	2-5 years	16 (21.3)	18 (24.7)	34 (23.0)	13 (17.1)
	6-11 years	21 (28.0)	20 (27.4)	41 (27.7)	22 (28.9)
	12-17 years	16 (21.3)	16 (21.9)	32 (21.6)	16 (21.1)
	18-45 years	18 (24.0)	18 (24.7)	36 (24.3)	19 (25.0)
	46-55 years	1 (1.3)	0	1 (0.7)	1 (1.3)
	56-65 years	1 (1.3)	0	1 (0.7)	0
	>=66 years	0	0	0	0
Sex, n (%)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	Male	43 (57.3)	43 (58.9)	86 (58.1)	45 (59.2)
	Female	32 (42.7)	30 (41.1)	62 (41.9)	31 (40.8)
Race[1], n (%)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	White/Caucasian	68 (90.7)	66 (90.4)	134 (90.5)	67 (88.2)
	Black/African American	2 (2.7)	3 (4.1)	5 (3.4)	0
	Asian	1 (1.3)	0	1 (0.7)	3 (3.9)
	Other	4 (5.3)	4 (5.5)	8 (5.4)	6 (7.9)
Country, n (%)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	US	36 (48.0)	34 (46.6)	70 (47.3)	42 (55.3)
	Australia	5 (6.7)	9 (12.3)	14 (9.5)	10 (13.2)
	Spain	6 (8.0)	3 (4.1)	9 (6.1)	2 (2.6)
	UK	2 (2.7)	2 (2.7)	4 (2.7)	3 (3.9)
	Netherlands	3 (4.0)	3 (4.1)	6 (4.1)	3 (3.9)
	Poland	23 (30.7)	22 (30.1)	45 (30.4)	16 (21.1)
Region, n (%)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	US	36 (48.0)	34 (46.6)	70 (47.3)	42 (55.3)
	ROW	39 (52.0)	39 (53.4)	78 (52.7)	34 (44.7)

[1] When multiple races were reported in the CRF, the race is reported as 'Other'.

Table 37

2. Demographic and Baseline Data
TSC.2.1.2 Baseline Characteristics
Pool TSC (controlled TSC) - Safety Analysis Set

Parameter	Statistics	CBD-OS 25 mg/kg/day (N=75)	CBD-OS 50 mg/kg/day (N=73)	All CBD-OS (N=148)	Placebo (N=76)
Previous use of Cannabis, n (%)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	Yes	4 (5.3)	6 (8.2)	10 (6.8)	6 (7.9)
	No	71 (94.7)	67 (91.8)	138 (93.2)	70 (92.1)
Time in months from last use of Cannabis to first dose of study medication	N (missing)	4 (0)	6 (0)	10 (0)	6 (0)
	Mean ± SD	14.3 ± 8.2	13.3 ± 12.5	13.7 ± 10.4	41.6 ± 66.8
	Median	14.0	9.0	10.8	16.7
	Q1 ; Q3	8.4 ; 20.2	4.9 ; 14.5	4.9 ; 16.0	6.5 ; 28.6
	Min ; Max	4.8 ; 24.3	4.6 ; 37.7	4.6 ; 37.7	4.3 ; 176.7
Body Weight (kg)	N (missing)	75 (0)	73 (0)	148 (0)	76 (0)
	Mean ± SD	42.79 ± 23.99	42.06 ± 23.72	42.43 ± 23.78	44.56 ± 27.94
	Median	40.40	37.50	38.75	36.90
	Q1 ; Q3	24.00 ; 56.00	21.90 ; 59.40	23.05 ; 57.95	19.95 ; 65.90
	Min ; Max	12.10 ; 143.70	13.00 ; 130.00	12.10 ; 143.70	10.40 ; 115.70
BMI (kg/m2)	N (missing)	75 (0)	71 (2)	146 (2)	76 (0)
	Mean ± SD	19.66 ± 5.82	21.32 ± 11.64	20.46 ± 9.13	22.08 ± 12.05
	Median	18.39	18.75	18.73	19.24
	Q1 ; Q3	15.99 ; 22.19	16.82 ; 22.07	16.35 ; 22.09	16.42 ; 24.51
	Min ; Max	8.37 ; 44.35	12.60 ; 108.71	8.37 ; 108.71	13.17 ; 110.32

Demographic and baseline characteristics by dose group (≤ 20, > 20–30, and > 30 mg/kg/day) for the OLE phase of GWEP1521 are summarized in the following Table 38:

Table 38

2. Demographic and Baseline Data
OLETSC.2.10.1 Demographics
OLE-TSC - Safety Analysis Set

Parameter	Statistics	OLE-TSC CBD-OS <= 20 mg/kg/day (N=19)	OLE-TSC CBD-OS > 20-30 mg/kg/day (N=150)	OLE-TSC CBD-OS > 30 mg/kg/day (N=30)	OLE-TSC CBD-OS All CBD-OS (N=199)
Age (years)	N (missing)	19 (0)	150 (0)	30 (0)	199 (0)
	Mean ± SD	16.9 ± 8.8	12.9 ± 10.6	12.0 ± 7.4	13.2 ± 10.0
	Median	16.3	10.1	9.9	10.8
	Q1 ; Q3	11.4 ; 18.6	5.3 ; 17.3	6.6 ; 17.1	5.9 ; 17.6
	Min ; Max	3.7 ; 40.2	1.1 ; 56.8	1.7 ; 26.6	1.1 ; 56.8
Age Categories, n (%)	N (missing)	19 (0)	150 (0)	30 (0)	199 (0)
	<2 years	0	4 (2.7)	4 (13.3)	8 (4.0)
	2-5 years	1 (5.3)	39 (26.0)	2 (6.7)	42 (21.1)
	6-11 years	5 (26.3)	43 (28.7)	11 (36.7)	59 (29.6)
	12-17 years	7 (36.8)	31 (20.7)	6 (20.0)	44 (22.1)
	18-45 years	6 (31.6)	30 (20.0)	7 (23.3)	43 (21.6)
	46-55 years	0	2 (1.3)	0	2 (1.0)
	56-65 years	0	1 (0.7)	0	1 (0.5)
	>=66 years	0	0	0	0
Sex, n (%)	N (missing)	19 (0)	150 (0)	30 (0)	199 (0)
	Male	7 (36.8)	94 (62.7)	17 (56.7)	118 (59.3)
	Female	12 (63.2)	56 (37.3)	13 (43.3)	81 (40.7)
Race[1], n (%)	N (missing)	19 (0)	150 (0)	30 (0)	199 (0)
	White/Caucasian	16 (84.2)	134 (89.3)	27 (90.0)	177 (88.9)
	Black/African American	0	2 (1.3)	2 (6.7)	4 (2.0)
	Asian	1 (5.3)	2 (1.3)	1 (3.3)	4 (2.0)

Race[1], n (%)	Other	2 (10.5)	12 (8.0)	0	14 (7.0)
Country, n (%)	N (missing)	19 (0)	150 (0)	30 (0)	199 (0)
	US	12 (63.2)	71 (47.3)	20 (66.7)	103 (51.8)
	Australia	3 (15.8)	17 (11.3)	2 (6.7)	22 (11.1)
	Spain	0	9 (6.0)	1 (3.3)	10 (5.0)
	UK	0	6 (4.0)	0	6 (3.0)
	Netherlands	0	5 (3.3)	2 (6.7)	7 (3.5)
	Poland	4 (21.1)	42 (28.0)	5 (16.7)	51 (25.6)
Region, n (%)	N (missing)	19 (0)	150 (0)	30 (0)	199 (0)
	US	12 (63.2)	71 (47.3)	20 (66.7)	103 (51.8)
	ROW	7 (36.8)	79 (52.7)	10 (33.3)	96 (48.2)

[1] When multiple races were reported in the CRF, the race is reported as 'Other'.

Prior to entering Trial GWEP1521, the largest proportion of patients had used ≥4 AEDs, ranging from 54.8% in the CBD-OS 50 mg/kg/day group to 60.0% in the 25 mg/kg/day group. In Pool TSC, the largest proportion of patients in all treatment groups currently used 3 AEDs, ranging from 35.6% in the CBD-OS 50 mg/kg/day group to 42.1% in the placebo group.

Concomitant medications are summarized in Table 39 in terms of AEDs used by ≥ 10% of patients in any treatment group. All patients used concomitant AEDs. In the All CBD-OS group, the 3 AEDs used by the most patients were valproic acid, vigabatrin, and levetiracetam. In the placebo group the 3 AEDs used by most patients were valproic acid, clobazam, and levetiracetam.

In the OLE TSC, 58 patients (29.1%) used 0 to 2 AEDs, 62 patients (31.2%) used 3 AEDs, and 79 (39.7%) used ≥4 AEDs).

Table 39

Table 2-2 Concomitant Antiepileptic Drugs Used by ≥10% of Patients in Any Treatment Group: Pool TSC (Safety Analysis Set)

	Number of Patients (%)			
	CBD-OS			
ATC Level 2 Preferred Term	25 mg/kg/day (N = 75)	50 mg/kg/day (N = 73)	All CBD-OS (N = 148)	Placebo (N = 76)
Valproic acid	29 (38.7)	36 (49.3)	65 (43.9)	35 (46.1)
Vigabatrin	28 (37.3)	29 (39.7)	57 (38.5)	17 (22.4)
Levetiracetam	19 (25.3)	22 (30.1)	41 (27.7)	24 (31.6)
Clobazam	17 (22.7)	19 (26.0)	36 (24.3)	25 (32.9)
Lamotrigine	17 (22.7)	15 (20.5)	32 (21.6)	18 (23.7)
Lacosamide	16 (21.3)	15 (20.5)	31 (20.9)	12 (15.8)
Oxcarbazepine	13 (17.3)	12 (16.4)	25 (16.9)	10 (13.2)
Topiramate	7 (9.3)	14 (19.2)	21 (14.2)	12 (15.8)
Carbamazepine	11 (14.7)	9 (12.3)	20 (13.5)	6 (7.9)
Clonazepam	6 (8.0)	9 (12.3)	15 (10.1)	4 (5.3)
Zonisamide	9 (12.0)	2(2.7)	11 (7.4)	7 (9.2)
Rufinamide	7(9.3)	1(1.4)	8 (5.4)	8 (10.5)

ATC = anatomic therapeutic class; CBD-OS = cannabidiol oral solution; TSC = tuberous sclerosis complex.

Adverse events

Overview in Pool TSC

Table 40 summarizes treatment emergent adverse events in Pool TSC. No deaths occurred.

Table 40

Table 2-3 Summary of Treatment-Emergent Adverse Events: Pool TSC (Safety Analysis Set)

	CBD-OS			
Number of Patients (%) with:	**25 mg/kg/day (N = 75)**	**50 mg/kg/day (N = 73)**	**All CBD-OS (N = 148)**	**Placebo (N = 76)**
At least 1 TEAE	70 (93.3)	73 (100)	143 (96.6)	72 (94.7)
Treatment-related TEAEs	52 (69.3)	64 (87.7)	116 (78.4)	40 (52.6)
TEAEs leading to permanent discontinuation of IMP	8 (10.7)	10 (13.7)	18 (12.2)	2 (2.6)
Treatment-related TEAEs leading to permanent discontinuation of IMP	8 (10.7)	10 (13.7)	18 (12.2)	2 (2.6)
Serious TEAEs	16 (21.3)	10 (13.7)	26 (17.6)	2 (2.6)
Treatment-related serious TEAEs	8 (10.7)	6 (8.2)	14 (9.5)	0

Overview in OLE TSC

Table 41 summarizes treatment emergent adverse events in OLE TSC. One death occurred due to cardiopulmonary failure.

Table 41

Table 2-4 Summary of Treatment-Emergent Adverse Events: OLE TSC (Safety Analysis Set)

	CBD-OS Modal Dose (mg/kg/day)			
No. of Patients (%) with:	**≤20 (N = 19)**	**>20-30 (N = 150)**	**>30 (N = 30)**	**All CBD-OS (N = 199)**
At least 1 TEAE	18 (94.7)	136 (90.7)	30 (100)	184 (92.5)
Treatment-related TEAEs	13 (68.4)	86 (57.3)	28 (93.3)	127 (63.8)
TEAEs leading to permanent discontinuation of IMP	1 (5.3)	10 (6.7)	0	11 (5.5)
Treatment-related TEAEs leading to permanent discontinuation of IMP	1 (5.3)	8 (5.3)	0	9 (4.5)
Serious TEAEs	2 (10.5)	18 (12.0)	9 (30.0)	29 (14.6)
Treatment-related serious TEAEs	0	5 (3.3)	4 (13.3)	9 (4.5)

Common TEAEs

Treatment-emergent adverse events reported for ≥10% of patients in any dose group for Pool TSC and OLE TSC are summarized in Table 42 and Table 43 (Table 44 with updated groups).

Table 42: Treatment-Emergent Adverse Events Reported for ≥10% of Patients in Any Dose Group: Pool TSC (Safety Analysis Set)

	Number of Patients (%)			
	CBD-OS			
Preferred Term	25 mg/kg/day (N = 75)	50 mg/kg/day (N = 73)	All CBD-OS (N = 148)	Placebo (N = 76)
Diarrhoea	23 (30.7)	41 (56.2)	64 (43.2)	19 (25.0)
Decreased appetite	15 (20.0)	17 (23.3)	32 (21.6)	9 (11.8)
Somnolence	10 (13.3)	19 (26.0)	29 (19.6)	7 (9.2)
Vomiting	13 (17.3)	13 (17.8)	26 (17.6)	7 (9.2)

	Number of Patients (%)			
	CBD-OS			
Pyrexia	14 (18.7)	12 (16.4)	26 (17.6)	6 (7.9)
Alanine aminotransferase increased	9 (12.0)	16 (21.9)	25 (16.9)	0
Aspartate aminotransferase increased	8 (10.7)	14 (19.2)	22 (14.9)	0
Gamma-glutamyltransferase increased	12 (16.0)	10 (13.7)	22 (14.9)	0
Seizure	5 (6.7)	8 (11.0)	13 (8.8)	5 (6.6)
Constipation	8 (10.7)	5 (6.8)	13 (8.8)	6 (7.9)
Cough	8 (10.7)	3 (4.1)	11 (7.4)	5 (6.6)

Table 43: Treatment-Emergent Adverse Events Reported for ≥10% of Patients in Any Modal Dose Category: OLE TSC (Safety Analysis Set)

	Number of Patients (%)			
	CBD-OS Modal Dose (mg/kg/day)			
Preferred Term	≤20 (N = 19)	>20-30 (N = 150)	>30 (N = 30)	All CBD-OS (N = 199)
Diarrhoea	6 (31.6)	62 (41.3)	15 (50.0)	83 (41.7)
Seizure	7 (36.8)	27 (18.0)	10 (33.3)	44 (22.1)
Decreased appetite	4 (21.1)	27 (18.0)	8 (26.7)	39 (19.6)
Vomiting	4 (21.1)	19 (12.7)	9 (30.0)	32 (16.1)
Pyrexia	1 (5.3)	22 (14.7)	9 (30.0)	32 (16.1)
Somnolence	2 (10.5)	23 (15.3)	6 (20.0)	31 (15.6)
Nasopharyngitis	2 (10.5)	21 (14.0)	5 (16.7)	28 (14.1)
Upper respiratory tract infection	2 (10.5)	19 (12.7)	5 (16.7)	26 (13.1)
Fatigue	3 (15.8)	9 (6.0)	2 (6.7)	14 (7.0)
Fall	0	9 (6.0)	5 (16.7)	14 (7.0)
Alanine aminotransferase increased	1 (5.3)	7 (4.7)	5 (16.7)	13 (6.5)
Aspartate aminotransferase increased	1 (5.3)	5 (3.3)	4 (13.3)	10 (5.0)
Cough	1 (5.3)	7 (4.7)	4 (13.3)	12 (6.0)
Constipation	3 (15.8)	7 (4.7)	1 (3.3)	11 (5.5)
Nasal congestion	3 (15.8)	4 (2.7)	4 (13.3)	11 (5.5)
Weight decreased	2 (10.5)	5 (3.3)	3 (10.0)	10 (5.0)
Gastroenteritis viral	2 (10.5)	5 (3.3)	2 (6.7)	9 (4.5)
Oropharyngeal pain	0	6 (4.0)	3 (10.0)	9 (4.5)
Otitis media	2 (10.5)	5 (3.3)	2 (6.7)	9 (4.5)
Rhinorrhea	0	5 (3.3)	3 (10.0)	8 (4.0)
Agitation	2 (10.5)	4 (2.7)	1 (3.3)	7 (3.5)
Liver function test increased	4 (21.1)	2 (1.3)	1 (3.3)	7 (3.5)
Abdominal pain	2 (10.5)	5 (3.3)	0	7 (3.5)
Viral upper respiratory tract infection	2 (10.5)	4 (2.7)	1 (3.3)	7 (3.5)
Viral infection	2 (10.5)	3 (2.0)	1 (3.3)	6 (3.0)
Ataxia	0	3 (2.0)	3 (10.0)	6 (3.0)
Lethargy	2 (10.5)	1 (0.7)	2 (6.7)	5 (2.5)

The most commonly occurring TEAEs (reported for ≥ 10% of patients) were generally the same events between the ≤ 25 mg/kg/day and > 25 mg/kg/day modal dose groups, although many of these events showed a dose relationship (Table 44).

Table 44

Treatment-emergent Adverse Events Reported for ≥ 10% of Patients in the ≤ 25 mg/kg/day CBD-OS Modal Dose Group in GWEP1521 OLE			
	Number of Patients (%)		
	CBD-OS Modal Dose		
Preferred Term	≤ 25 mg/kg/day (N = 156)	> 25 mg/kg/day (N = 43)	All CBD-OS (N = 199)
Diarrhoea	63 (40.4)	20 (46.5)	83 (41.7)
Vomiting	20 (12.8)	12 (27.9)	32 (16.1)
Pyrexia	21 (13.5)	11 (25.6)	32 (16.1)
Nasopharyngitis	22 (14.1)	6 (14.0)	28 (14.1)
Upper respiratory tract infection	19 (12.2)	7 (16.3)	26 (13.1)
Decreased appetite	26 (16.7)	13 (30.2)	39 (19.6)
Seizure	30 (19.2)	14 (32.6)	44 (22.1)
Somnolence	19 (12.2)	12 (27.9)	31 (15.6)

For comparison of common TEAE profile to safety profile in previous indications Table 45 is included.

Table 45: Treatment-Emergent Adverse Events Reported for > 10% of Patients in Any CBD-OS Dose Group: Pool DS/LGS/TSC (Safety Analysis Set)

	DS/LGS, No. of Patients (%)			TSC, No. of Patients (%)		
	CBD-OS			CBD-OS		
Preferred Term	10 mg/kg/day (N=139)	20 mg/kg/day (N=307)	Placebo (N=292)	25 mg/kg/day (N=75)	50 mg/kg/day (N=73)	Placebo (N=76)
Diarrhoea	18 (12.9)	65 (21.2)	28 (9.6)	23 (30.7)	41 (56.2)	19 (25.0)
Vomiting	9 (6.5)	40 (13.0)	30 (10.3)	13 (17.3)	13 (17.8)	7 (9.2)
Constipation	5 (3.6)	12 (3.9)	12 (4.1)	8 (10.7)	5 (6.8)	6 (7.9)
Pyrexia	24 (17.3)	45 (14.7)	35 (12.0)	14 (18.7)	12 (16.4)	6 (7.9)
Nasopharyngitis	8 (5.8)	25 (8.1)	18 (6.2)	11 (14.7)	11 (15.1)	12 (15.8)
Upper respiratory tract infection	14 (10.1)	24 (7.8)	25 (8.6)	7 (9.3)	7 (9.6)	10 (13.2)
Alanine aminotransferase increased	6 (4.3)	21 (6.8)	3 (1.0)	9 (12.0)	16 (21.9)	0
Aspartate aminotransferase increased	5 (3.6)	20 (6.5)	2 (0.7)	8 (10.7)	14 (19.2)	0
Gamma-glutamyltransferase increased	6 (4.3)	14 (4.6)	6 (2.1)	12 (16.0)	10 (13.7)	0
Decreased appetite	23 (16.5)	73 (23.8)	22 (7.5)	15 (20.0)	17 (23.3)	9 (11.8)
Somnolence	33 (23.7)	76 (24.8)	28 (9.6)	10 (13.3)	19 (26.0)	7 (9.2)
Seizure	9 (6.5)	23 (7.5)	22 (7.5)	5 (6.7)	8 (11.0)	5 (6.6)

CBD-OS = cannabidiol oral solution; DS = Dravet syndrome; LGS = Lennox-Gestaut syndrome; TSC = tuberous sclerosis complex.

Note: The 5-mg dose from pilot trial GWEP1332 Part A for DS/LGS patients has been omitted due to low patient numbers and shorter duration of exposure.

Adverse Events of Special Interest

Diarrhoea

In Pool TSC, 64 (43.2%) patients in all CBD-OS group reported diarrhoea while 19 (25.0%) patients in placebo group did. 54 patients (36.5%) in all CBD-OS group had diarrhoea that was considered related to treatment. One patient had a serious TEAE of diarrhoea, and discontinued IMP due to this event. Diarrhoea was considered treatment related in all 13 out of 19 placebo patients who experienced the event. No patients in the placebo group had severe or serious diarrhoea, and none discontinued due to diarrhoea. Resolution of diarrhoea in Pool TSC was variable. The largest proportion of patients in both

dose groups had resolution of diarrhoea > 4 weeks (25 mg/kg: 7 out of 23 patients; 50 mg/kg: 12 out of 41 patients). Diarrhoea was ongoing at the end of the controlled phase of the study for 5 out of 23 patients in the 25 mg/kg/day group and 3 out of 41 patients in the 50 mg/kg/day group.

In the OLE TSC, 83 patients (41.7%) in the all CBD-OS group had diarrhoea. The incidence of diarrhoea increased with increasing dose, ranging from 31.6% in the ≤20 mg/kg/day category to 50.0% in the >30 mg/kg/day category.

Treatment-emergent AEs of diarrhoea were far more common in the TSC population (25 mg/kg/day, 23 patients, 30.7%; 50 mg/kg/day, 41 patients, 56.2%; placebo, 19 patients, 25.0%) than in the LGS/DS population (10 mg/kg/day, 18 patients, 12.9%; 25 mg/kg/day, 65 patients, 21.2%; placebo, 9.6%) (Table 45). Diarrhoea exhibited a dose-response relationship in both populations. Time of onset of diarrhoea showed a similar pattern in both populations, with the majority of patients having onset between 1 and 6 weeks after first dose of IMP.

Decreased Appetite and Weight Loss

In Pool TSC, 15 patients (20.0%) in the 25 mg/kg/day group, 17 patients (23.3%) in the 50 mg/kg/day group, and 9 patients (11.8%) in the placebo group had decreased appetite. Among the all CBD-OS group, 27 patients (18.2%) had an AESI of decreased appetite considered related to treatment. No patient had a serious TEAE of decreased appetite or discontinued due to this event. The onset of decreased appetite was generally evenly distributed over Weeks 1 to 10. Resolution was > 4 weeks and in 25 mg/kg/day group for 8 out of 15 patients, in 50 mg/kg/day group for 7 out of 17 patients decreased appetite was resolved before the end of the double-blind phase of the trial.

Among the OLE TSC all CBD-OS group, 31 patients (15.6%) had an AESI of decreased appetite considered related to treatment, and 1 patient (0.5%) had a TEAE leading to discontinuation. No patient had a severe or serious TEAE of decreased appetite.

In Pool TSC, a greater proportion of CBD-OS patients met criteria for decreases in weight from baseline, whereas a greater proportion of placebo patients met criteria for weight increases from baseline. In the all CBD-OS group, 26.4% of patients (30.7% in the 25 mg/kg/day CBD OS group and 21.9% in the 50 mg/kg/day CBD OS group) had a ≥ 5% decrease in weight, compared with 7.9% of placebo patients. Overall, 16.2% of patients receiving CBD-OS (16.0% in the 25 mg/kg/day CBD OS group and 16.4% in the 50 mg/kg/day CBD OS group) had a weight decrease of ≥ 7%, compared with 3.9% of placebo patients. Eleven CBD-OS patients (7.4%) had TEAEs of weight decreased: 5 (6.7%) in the 25 mg/kg/day group and 6 (8.2%) in the 50 mg/kg/day group; no patients in the placebo group experienced a TEAE of weight decreased.

In the OLE TSC, 32.7% of patients overall had a ≥ 5% decrease in weight from baseline; 23.6% had a ≥ 7% decrease; and 15.1% had a ≥ 10% decrease. For All CBD-OS patients, 50.8% had a ≥ 5% increase from baseline. A total of 10 patients (5.0%) had TEAEs of weight decreased: 2 (10.5%) in the ≤ 20 mg/kg/day category; 5 (3.3%) in the > 20–30 mg/kg/day category; and 3 (10.0%) in the > 30 mg/kg/day category (5 (3.2%) in the ≤ 25 mg/kg/day category and 5 (11.6%) in the > 25 mg/kg/day category). Higher proportions of patients met weight decrease criteria in the > 25 mg/kg/day modal dose group than in the ≤ 25 mg/kg/day dose group (Table 46).

Table 46: Number of Patients Meeting Criteria for Decreased Weight in GWEP1521 OLE

Weight Criterion	Number of Patients (%)		
	CBD-OS Modal Dose		
	≤ 25 mg/kg/day (N = 156)	> 25 mg/kg/day (N = 43)	All CBD-OS (N = 199)
Decrease of ≥5% from baseline	48 (30.8)	17 (39.5)	65 (32.7)
Decrease of ≥7% from baseline	34 (21.8)	13 (30.2)	47 (23.6)
Decrease of ≥10% from baseline	21 (13.5)	9 (20.9)	30 (15.1)
Decrease of ≥15% from baseline	10 (6.4)	1 (2.3)	11 (5.5)

Among all CBD-OS patients, decreased appetite affected 21.1% and 21.6% of the LGS/DS and TSC populations respectively (7.5% and 11.8% of placebo patients, respectively). In the LGS/DS population, 14.7% of CBD-OS patients (8.6% of placebo patients) had a ≥ 5% decrease in weight, compared with 26.4% (7.9% of placebo patients) in the TSC population.

Weight loss and height and failure to thrive

In the GWEP1521 pivotal trial approximately 75% of the study participants were below 18 years of age. It is agreed and accepted in the DS, LGS and TSC populations that treatment with CBD-OS has the potential to lead to weight loss or decreased weight gain when compared with placebo and as such decreased weight is an ADR in the SmPC and described below the ADR table.

The GWEP1521 study mandated height measurements as part of study procedures. The median change in height was 1 cm for both the all CBD-OS group and the placebo group by end of treatment in the double-blind phase of the study. The mean change in Height z score for the all CBD-OS group was 0.1 compared with 0.2 for the placebo population. The median change in Height z scores for both all CBD-OS and placebo group was 0 at the end of treatment. Although these values do not suggest a concerning variation between active and placebo groups and does not indicate an effect on growth, the short time interval between the baseline and the last assessment makes assessment of these changes of limited value. Data on height change in the OLE on the population shows mean and median increases, however inspection of the data also yields outliers which make firm conclusions difficult. The nature of the patient population may have made taking such assessments logistically difficult.

Safety endpoints relating to failure to thrive are limited, however to date, no signal has emerged from the Tanner endpoint staging for sexual maturation across the DS, LGS and TSC pivotal trials in the paediatric population.

Somnolence, Fatigue, Lethargy, Sedation

In Pool TSC, 41 patients (27.7%) in the All CBD-OS group and 13 patients (17.1%) in the placebo group had at least 1 AESI of somnolence, fatigue, lethargy, or sedation. The incidence of this AESI was higher in the 50 mg/kg/day group (34.2% of patients) than in the 25 mg/kg/day group (21.3% of patients). In the All CBD-OS group, 35 patients (23.6%) had an AESI of somnolence, fatigue, lethargy, or sedation considered related to treatment; 1 patient had a serious TEAE; and 2 patients had a TEAE leading to discontinuation. The AESI began 1 to 2 weeks after the first dose for 16.9% of patients in the All CBD-OS group. Clobazam use has been identified as a risk factor for somnolence-related TEAEs.

In the OLE TSC, 49 patients (24.6%) in the All CBD-OS group had an AESI of somnolence, fatigue, lethargy, or sedation. The incidence was 36.8% in ≤ 20 mg/kg/day group, 20.7% in > 20–30 mg/kg/day group, and 36.7% in >30 mg/kg/day group. Two patients had serious AESIs of somnolence; and 1 patient had a TEAE leading to discontinuation.

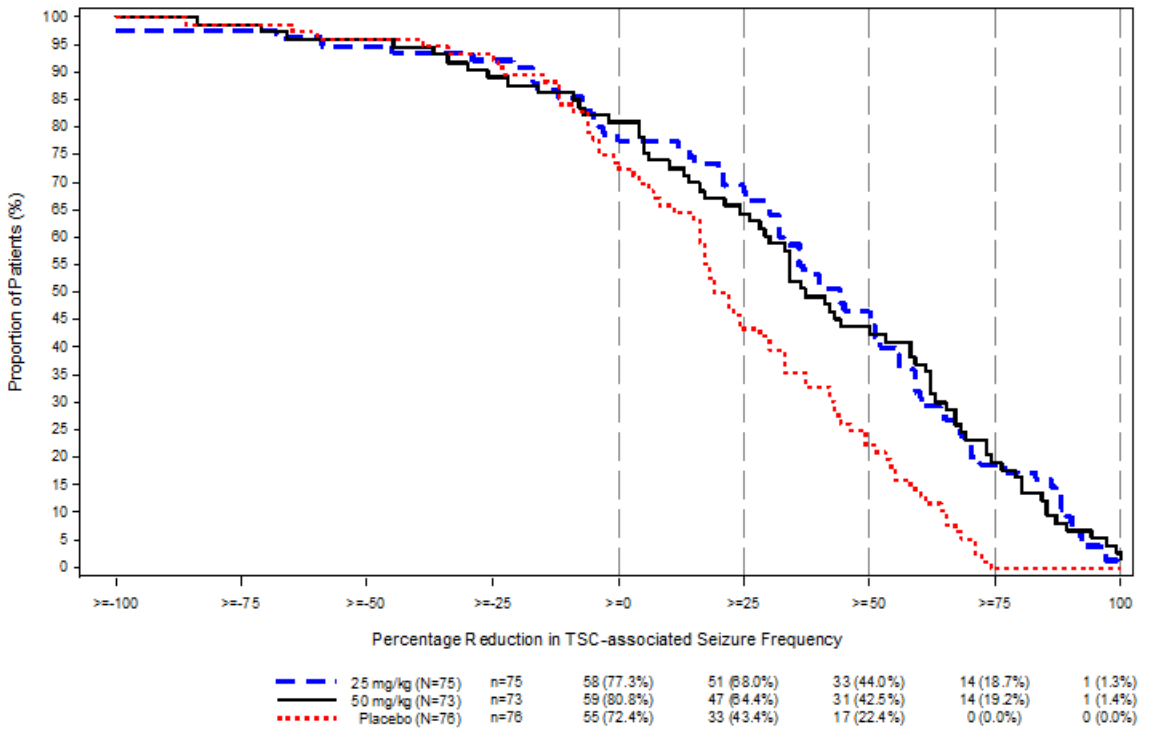
The AESI of somnolence, fatigue, lethargy, sedation was more common in LGS/DS population than in the TSC population (39.5% vs. 27.7%, respectively) for CBD-OS treated patients. Larger proportions of LGS/DS patients than TSC patients used CLB concomitantly.

Seizure Worsening

In Pool TSC, 8 patients (10.7%) in the 25 mg/kg/day group, 13 patients (17.8%) in the 50 mg/kg/day group, and 7 patients (9.2%) in the placebo group had seizure worsening. 6 patients (4.1%) in the All CBD-OS group and 2 patients (2.6%) in the placebo group had an AESI of seizure worsening considered related to treatment. Two patients (1.4%) had severe events. Five patients (3.4%) in the All CBD-OS group and 1 patient (1.3%) in the placebo group had serious AESIs of seizure worsening. No patient permanently discontinued IMP due to this AESI. The onset of seizure worsening was generally evenly distributed over Weeks 1 to 14 in both CBD-OS dose groups, with fewer patients having onset at ≥14 weeks.

The risk of seizure frequency increases was also evaluated by using seizure count data that was captured as part of primary endpoint in trial GWEP1521 (Figure 23).

Figure 23. Cumulative Distribution Function for TSC-associated Seizures During the Treatment Period: GWEP 1521 RCT (ITT Analysis Set)



In the OLE TSC, 50 patients (25.1%) in the All CBD-OS group had seizure worsening, 19 patients (9.5%) are considered related to treatment, 3 patients (1.5%) had severe events, and 4 patients (2.0%) discontinued due to seizure worsening. Twelve patients (6.0%) had serious TEAEs of seizure worsening. The onset was evenly distributed over time, from Weeks 1 to 2 to > 52 weeks.

Status Epilepticus

In Pool TSC, 2 patients (2.7%) in the 25 mg/kg/day group and 1 patient (1.3%) in the placebo group had status epilepticus. Status epilepticus was a serious TEAE for all 3 patients in Pool TSC, but it was not

considered related to IMP. For no patients was the event severe in intensity, and none of the patients permanently discontinued IMP due to this AESI.

Abnormal Liver Findings

CBD-OS caused dose-dependent elevations in serum ALT and AST in some TSC patients, including some elevations meeting the consensus criteria for DILI (Table 47 and Table 48). These typically occurred within the first 2 months of treatment with CBD-OS. Clear risk factors for ALT elevations included concomitant use of VPA, dose of CBD-OS, and elevated ALT at baseline.

There were no Hy`s Law cases (ALT or AST ≥ 3 × ULN and TBL > 2 × ULN) in either Pool TSC or TSC OLE. The ALT elevations were generally accompanied by normal ALP and bilirubin values. R values were generally > 5 indicating a hepatocellular pattern of DILI. There was no clear increased risk associated with concomitant use of AEDs other than VPA. The estimated time required for a peak ALT elevation (≥ 5 × ULN) to recover to a value of 2.9 × ULN was calculated for each patient. The recovery times estimated were commonly less than 2 weeks for patients who had treatment with CBD-OS abruptly discontinued, continued and/or tapered then discontinued, or continued at the same or lower daily dose.

Table 47

Frequency of ALT Elevations by Baseline ALT in Patients With or Without Concomitant Valproate in the TSC RCT				
Treatment Group Peak ALT (× ULN)	**No Concomitant Valproate**		**Concomitant Valproate**	
	Baseline ALT ≤ ULN	**Baseline ALT > ULN**	**Baseline ALT ≤ ULN**	**Baseline ALT > ULN**
CBD-OS 25 mg/kg/day [n / N (%)]				
> 3 ×	1/39 (2.6)	1/7 (14.3)	7/27 (25.9)	0/2
> 5 ×	0/39	1/7 (14.3)	4/27 (14.8)	0/2
CBD-OS 50 mg/kg/day [n / N (%)]				
> 3 ×	1/30 (3.3)	2/7 (28.6)	12/32 (37.5)	3/4 (75.0)
> 5 ×	0/30	1/7 (14.3)	5/32 (15.6)	2/4 (50.0)
Placebo [n / N (%)]				
> 3 ×	0/37	0/3	0/32	0/3
> 5 ×	0/37	0/4	0/32	0/3

Table 48

Table 5-6	**Frequency of Treatment-emergent ALT Test Elevations (Observed Peak) Any Time Post-baseline in Pool LGS/DS/TSC**				
	LGS/DS		**TSC**		**LGS/DS/TSC**
Multiple of ULN	**CBD-OS 10 mg/kg/day (N=131) *n / N* (%)**	**CBD-OS 20 mg/kg/day (N=298) *n / N* (%)**	**CBD-OS 25 mg/kg/day (N=75) *n / N* (%)**	**CBD-OS 50 mg/kg/day (N=73) *n / N* (%)**	**Placebo (N=361) *n / N* (%)**
> 3 ×	4 /131 (3.1)	47 /296 (15.9)	9 /75 (12.0)	18 /73 (24.7)	2 /359 (0.6)
> 5 ×	2 /131 (1.5)	20 /298 (6.7)	5 /75 (6.7)	8 /73 (11.0)	2 /361 (0.6)

N corresponds to the total number of patients in the treatment group. n/N: *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at baseline.

Renal Effects

No TEAEs but increases from baseline in creatinine were noted among patients receiving CBD-OS. Mean increases in creatinine from baseline to end of treatment were approximately 10%, occurring by Day 15

and tending to plateau, with no clear increase over the duration of the pivotal trial. Dose-relationship was unclear during the maintenance phase of treatment.

Significant Cardiovascular Disease (CVD)

In Pool TSC, 4 patients (5.3%) in 25 mg/kg/day group, 2 patients (2.7%) in the 50 mg/kg/day group, and no patients in the placebo group had at least 1 AESI of significant CVD. 1 patient in the All CBD-OS group had a significant CVD AESI (preferred term: electrocardiogram abnormal) considered related to IMP and permanently discontinued IMP.

In the OLE TSC, 15 patients (7.5%) in the All CBD-OS group had at least 1 AESI of significant CVD, 4 patients (2.0%) had events considered related to IMP. Three patients (1.5%) had a severe event, and 3 patients had serious events. No patient permanently discontinued IMP.

It is important to consider the underlying pathophysiology in patients with TSC, as there is often a clinical presentation of rhabdomyoma and tumours across the body, which may present or increase cardiovascular events. The heart is one of the more common target organs for the rhabdomyomas. In totality, 6 patients in the double-blind phase had at least one AESI significant of CVD, and additionally 15 patients in the OLE had an AESI significant of CVD.

Rash, Generalized Maculopapular Rash

In Pool TSC, 5 patients (6.7%) in the 25 mg/kg/day group, 9 patients (12.3%) in the 50 mg/kg/day group, (9.5% of all CBD-OS patients) and 3 patients (3.9%) in the placebo group had at least 1 event of rash, generalized maculopapular rash. 1 additional patient with a generalized rash was reported as Type IV hypersensitivity reaction. Rash events were considered related to IMP for 9 CBD-OS patients (6.1%) and 1 (1.3%) placebo patient. Two CBD-OS patients (1.4%) had severe events, and 3 CBD-OS patients (2.0%) had serious events; 1 patient had a serious hypersensitivity reaction, and 1 patient had serious urticaria, concomitant with serious diarrhoea. Six patients (4.1%) permanently discontinued IMP due to a rash AESI. For all patients except one, onset of rash was during Weeks 1 to 10.

Aggression, Irritability

In Pool TSC, 6 patients (8.0%) in the 25 mg/kg/day group, 7 patients (9.6%) in the 50 mg/kg/day group, and 6 patients (7.9%) in the placebo group had at least 1 event of aggression, irritability. Events for 7 all CBD-OS patients (4.7%) and 5 (6.6%) placebo patients were considered related to IMP.

In the OLE TSC, 14 patients (7.0%) in the All CBD-OS group had at least 1 aggression AESI, 1 patient (0.5%) permanently discontinued IMP.

Agitation and Psychosis

In Pool TSC, 2 patients (2.7%) in the 25 mg/kg/day group, 6 patients (8.2%) in the 50 mg/kg/day group, and 5 patients (6.6%) in the placebo group had at least 1 event of agitation and pyschosis. Events were considered related to IMP for 8 All CBD-OS patients (5.4%) and 2 (2.6%) placebo patients.

Pneumonia

In Pool TSC, 3 patients (4.0%) in the CBD-OS 25 mg/kg/day group, 2 patients (2.7%) in the 50 mg/kg/day group, and 1 patient (1.3%) in the placebo group had at least 1 event of pneumonia.

DRESS

DRESS was defined as a reaction including acute skin rash, involvement of an internal organ, enlarged lymph nodes at 2 sites, certain blood count abnormalities, and fever.

In Pool TSC, 3 patients (4.0%) in the CBD-OS 25 mg/kg/day group, 1 patient (1.4%) in the 50 mg/kg/day group, and no patients in the placebo group had at least 1 event corresponding to individual AESIs relating to DRESS. All considered related to IMP. One patient (0.7%) in the All CBD-OS group had a severe event, which was also serious (PT: rash erythematous). Two patients permanently discontinued IMP due to a DRESS AESI (PTs: eosinophil count increased; rash; rash erythematous.

Overdose and Abuse

The data from the human abuse liability trial, GWEP1431, demonstrate that even at supratherapeutic doses, the relative abuse potential of CBD-OS is significantly lower than that of dronabinol and alprazolam. The incidence of abuse liability AESIs was < 2% in both the LGS/DS and TSC populations.

The MADDERS program conclusions for the TSC population were the same as those for the LGS/DS population: CBD-OS poses minimal abuse potential.

Discontinuation of CBD-OS in TSC, DS and LGS clinical trials did not show clinical symptoms associated with psychological or physical drug dependence.

Serious adverse event/deaths/other significant events

No deaths occurred in Pool TSC. In OLE TSC, one death occurred, giving a rate of 6.54 per 1000 patient-years. The patient died due to cardiopulmonary failure due to TSC. The patient had a history of idiopathic dilated cardiomyopathy, congestive heart failure, left ventricular hypertrophy, hypertension, and TSC with cardiac involvement.

Table 49 summarizes SAEs reported for more than 1 patient in Pool TSC. 16 patients (21.3%) in the 25 mg/kg/day group, 10 patients (13.7%) in the 50 mg/kg/day group, and 2 patients (2.6%) in the placebo group experienced at least 1 serious TEAE. For 8 patients (10.7%) in the 25 mg/kg/day group and 6 patients (8.2%) in the 50 mg/kg/day group, serious TEAEs were considered related to treatment. The only treatment-related serious TEAEs that occurred in more than 1 patient were ALT increased (1 patient in the 25 mg/kg/day group and 2 patients in the 50 mg/kg/day group) and AST increased (1 patient in the 25 mg/kg/day group and 2 patients in the 50 mg/kg/day group).

Table 49

Serious Adverse Events Reported for > 1 Patient in Any Treatment Group: Pool TSC (Safety Analysis Set)

	CBD-OS			
Preferred Term	**25 mg/kg/day (N=75)**	**50 mg/kg/day (N=73)**	**All CBD-OS (N=148)**	**Placebo (N=76)**
Vomiting	2 (2.7)	0	2 (1.4)	0
Gastroenteritis viral	2 (2.7)	0	2 (1.4)	0
Alanine aminotransferase increased	2 (2.7)	2 (2.7)	4 (2.7)	0
Aspartate aminotransferase increased	2 (2.7)	2 (2.7)	4 (2.7)	0
Transaminases increased	0	2 (2.7)	2 (1.4)	0
Seizure	1 (1.3)	1 (1.4)	2 (1.4)	0
Status epilepticus	2 (2.7)	0	2 (1.4)	1 (1.3)

In the OLE TSC, serious TEAEs reported for more than 1 patient are listed in Table 50. 9 patients (30.0%) in the > 30 mg/kg/day category, 18 patients (12.0%) in the > 20–30 mg/kg/day category, and 2 patients (10.5%) in the ≤20 mg/kg/day category experienced at least 1 serious TEAE. For 4 patients (13.3%) in the > 30 mg/kg/day category and 5 patients (3.3%) in the > 20–30 mg/kg/day category in the OLE TSC, serious TEAEs were considered treatment related. Treatment-related serious TEAEs that

occurred in more than 1 patient were ALT increased, AST increased, and transaminases increased (all reported for 1 patient each in the > 20–30 mg/kg/day and > 30 mg/kg/day categories).

Table 50

Serious Adverse Events Reported for > 1 Patient in the OLE TSC (Safety Analysis Set) Number of Patients (%)				
CBD-OS Modal Dose (mg/kg/day)				
Preferred Term	**≤20 (N = 19)**	**> 20-30 (N = 150)**	**> 30 (N = 30)**	**All CBD-OS (N = 199)**
Influenza	0	2 (1.3)	0	2 (1.0)
Alanine aminotransferase increased	0	1 (0.7)	1 (3.3)	2 (1.0)
Aspartate aminotransferase increased	0	1 (0.7)	1 (3.3)	2 (1.0)
Transaminases increased	0	1 (0.7)	1 (3.3)	2 (1.0)
Dehydration	0	1 (0.7)	1 (3.3)	2 (1.0)
Seizure	1 (5.3)	3 (2.0)	2 (6.7)	6 (3.0)
Status epilepticus	0	4 (2.7)	1 (3.3)	5 (2.5)
Mental status changes	0	0	2 (6.7)	2 (1.0)

In the updated tables for OLE TSC, 29 patients (14.6%) experienced at least 1 serious TEAE. More patients receiving > 25 mg/kg/day CBD-OS (23.3%) experienced a serious TEAE than did patients receiving ≤ 25 mg/kg/day (12.2%). Serious TEAEs that occurred in > 1 patient in the OLE are shown in Table 51.

Table 51

Serious Treatment-emergent Adverse Events Occurring in ≥ 1 Patient in GWEP1521 OLE			
	Number of Patients (%)		
	CBD-OS Modal Dose		
Preferred Term	**≤ 25 mg/kg/day (N = 156)**	**> 25 mg/kg/day (N = 43)**	**All CBD-OS (N = 199)**
Influenza	2 (1.3)	0	2 (1.0)
ALT increased	1 (0.6)	1 (2.3)	2 (1.0)
AST increased	1 (0.6)	1 (2.3)	2 (1.0)
Platelet count decreased	1 (0.6)	1 (2.3)	2 (1.0)
Transaminases increased	1 (0.6)	1 (2.3)	2 (1.0)
Dehydration	2 (1.0)	2 (1.0)	2 (1.0)
Seizure	3 (1.9)	3 (7.0)	6 (3.0)
Status epilepticus	4 (2.6)	1 (2.3)	5 (2.5)
Mental status changes	0	2 (4.7)	2 (1.0)

The absolute rate of LGS/DS patients treated with CBD-OS who experienced at least one serious TEAE was 19.7% in all CBD-OS, 8.9% in placebo groups, while it was 17.6% in all CBD-OS, 2.6% in placebo groups for TSC patients. The relative risk of experiencing a serious TEAE was greater in the TSC population than in the LGS/DS population. Liver-related TEAEs contributed to the higher relative risk in TSC patients. A larger proportion of TSC patients had serious TEAEs considered related to IMP (All CBD-OS, 9.5%; placebo, 0) than did LGS/DS patients (All CBD-OS, 6.6%; placebo, 0.3%). Treatment-related skin and subcutaneous disorders and liver-related TEAEs contributed to this difference.

Laboratory findings

Potentially Clinically Significant Electrocardiogram Findings

In Pool TSC, 9 patients (12.0%) in the CBD-OS 25 mg/kg/day group, 2 patients (2.7%) in the 50 mg/kg/day group, and 4 patients (5.3%) in the placebo group had changes in QTc from baseline > 480 msec. Six patients (8.0%) in the 25 mg/kg/day group, 2 patients (2.7%) in the 50 mg/kg/day group, and 3 patients (3.9%) in the placebo group had QTc changes from baseline > 500 msec.

The following TEAEs related to ECG findings were each reported for 1 patient in Pool TSC (treatment group in parentheses): ECG signs of ventricular hypertrophy (50 mg/kg/day); ECG QT prolonged (25 mg/kg); ECG abnormal (25 mg/kg); ECG QRS complex prolonged (placebo).

In the OLE TSC, 8 patients overall (4.0%) had changes in QTc from baseline > 480 msec. Six patients (3.0%) had QTc changes from baseline > 500 msec. One patient, in the > 20–30 mg/kg/day category, had a TEAE of ECG QT prolonged.

Safety in special populations

The safety profile of CBD-OS was generally similar across the age or sex subgroups and did not appear to influence the tolerability of CBD OS. Because of low heterogeneity in race composition in the RCTs, it was not possible to form safety conclusions based on race. Region in the GWEP1521 trial did not appear to affect the safety profile of CBD-OS.

No pregnancies or instances of lactation occurred during Trial GWEP1521 as of the cut-off date.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions were not formally investigated in the trial GWEP1521 but have been explored in clinical pharmacology studies.

Concomitant Antiepileptic Drugs

There was a higher TEAE burden, either serious or leading to discontinuation, when patients were taking a greater number of concomitant AEDs.

In both LGS/DS and TSC patients, the number of AEDs did have some effect on the overall safety profile. Across the disease populations, the use of > 4 AEDs was associated with increased incidences of serious TEAEs and AEs leading to discontinuation, as well as with somnolence-related AESIs.

Among All CBD-OS patients, 56.1% of those with LGS/DS used CLB, compared with 24.3% of patients with TSC. Valproic acid was used by 52.4% of All CBD-OS patients with LGS/DS and 43.9% of patients with TSC. VGB was used by far more TSC patients (All CBD OS: LGS/DS, 2.4%; TSC, 38.5%). Valproic acid and VGB were the most commonly prescribed concomitant AEDs in Pool TSC.

Valproic Acid

More patients taking VPA had serious TEAEs and TEAEs leading to permanent discontinuation of IMP than did patients not taking the drug. Liver-related TEAEs were more frequent and the risk of hepatocellular injury was clearly increased in patients taking VPA. There was evidence of a higher relative risk of decreased appetite and an increased incidence of decreases in platelet count. It should also be noted that in the placebo group of both populations, there was also an increased incidence of decreases in platelet count, suggesting an independent effect of VPA.

Vigabatrin

VGB was the second most commonly prescribed concomitant AED in the TSC population, it was used by < 3% of LGS/DS patients. Patients on VGB more frequently had normal-to-low shifts in platelet count than those patients off VGB.

Clobazam

Clobazam is an important risk factor for AEs such as somnolence/sedation, pneumonia, and rash, and there are known PK-based drug-drug interactions between CLB and CBD-OS. The incidence of AEs and serious AEs were higher for CBD-OS vs. placebo, and highest in patients taking CBD-OS and concomitant CLB.

An effect of CLB use was evident in both TSC and LGS/DS populations. Higher percentages of patients using CLB had serious TEAEs than those not using CLB, across all dose groups and placebo groups for both populations.

The incidence of potential ADRs in patients on vs. off CLB in the TSC RCT is presented in Table 52.

Table 52

Table 2-22 Incidence of Potential ADRs in Patients on Clobazam: Pool TSC (Safety Analysis Set) CBD-OS						
	25 mg/kg/day		50 mg/kg/day		Placebo	
Preferred Term	With CLB (n = 18)	Without CLB (n = 57)	With CLB (n = 20)	Without CLB (n = 53)	With CLB (n = 25)	Without CLB (n = 51)
Anaemia	2 (11.1)	3 (5.3)	1 (5.0)	2 (3.8)	0	1 (2.0)
Diarrhoea	5 (27.8)	18 (31.6)	12 (60.0)	29 (54.7)	3 (12.0)	16 (31.4)
Vomiting	1 (5.6)	12 (21.1)	2 (10.0)	11 (20.8)	2 (8.0)	5 (9.8)
Abdominal pain upper	0	0	2 (10.0)	1 (1.9)	0	1 (2.0)
Constipation	0	8 (14.0)	1 (5.0)	4 (7.5)	3 (12.0)	3 (5.9)
Nausea	1 (5.6)	6 (10.5)	0	2 (3.8)	0	2 (3.9)
Pyrexia	5 (27.8)	9 (15.8)	7 (35.0)	5 (9.4)	4 (16.0)	2 (3.9)
Gait disturbance	2 (11.1)	2 (3.5)	1 (5.0)	2 (3.8)	1 (4.0)	1 (2.0)
Fatigue	2 (11.1)	2 (3.5)	0	4 (7.5)	1 (4.0)	0
Ear infection	0	2 (3.5)	2 (10.0)	2 (3.8)	0	0
Gastroenteritis	0	3 (5.3)	2 (10.0)	1 (1.9)	0	2 (3.9)
Urinary tract infection	1 (5.6)	3 (5.3)	0	1 (1.9)	0	0
Viral infection	1 (5.6)	2 (3.5)	0	0	0	2 (3.9)
Laceration	0	0	1 (5.0)	2 (3.8)	0	0
ALT increased	2 (11.1)	7 (12.3)	2 (10.0)	14 (26.4)	0	0
AST increased	2 (11.1)	6 (10.5)	2 (10.0)	12 (22.6)	0	0
Eosinophil count increased	2 (11.1)	2 (3.5)	1 (5.0)	0	0	0
GGT increased	2 (11.1)	10 (17.5)	1 (5.0)	9 (17.0)	0	0
Platelet count decreased	1 (5.6)	2 (3.5)	1 (5.0)	2 (3.8)	0	0
Transaminases increased	0	1 (1.8)	1 (5.0)	2 (3.8)	0	0
Weight decreased	1 (5.6)	4 (7.0)	0	6 (11.3)	0	0
Hepatic enzyme increased	0	0	0	3 (5.7)	0	0
Decreased appetite	3 (16.7)	12 (21.1)	4 (20.0)	13 (24.5)	2 (8.0)	7 (13.7)
Somnolence	5 (27.8)	5 (8.8)	10 (50.0)	9 (17.0)	3 (12.0)	4 (7.8)
Seizure	0	5 (8.8)	2 (10.0)	6 (11.3)	1 (4.0)	4 (7.8)
Ataxia	2 (11.1)	1 (1.8)	2 (10.0)	0	2 (8.0)	0
Irritability	1 (5.6)	3 (5.3)	1 (5.0)	4 (7.5)	3 (12.0)	1 (2.0)
Rhinorrhea	0	3 (5.3)	3 (15.0)	0	0	0
Cough	1 (5.6)	7 (12.3)	1 (5.0)	2 (3.8)	2 (8.0)	3 (5.9)
Rash	3 (16.7)	1 (1.8)	2 (10.0)	5 (9.4)	2 (8.0)	0

Everolimus

In GWEP1521, 6 TSC patients in the OLE were taking concomitant CBD-OS and everolimus. One patient had elevated everolimus concentrations reported as an AE that resulted in an everolimus dose interruption and dose reduction at restart, 1 patient had a dose interruption for everolimus and resumed treatment at the same dose. Two other patients had a dose reduction for everolimus, and 1 patient discontinued everolimus treatment. For the remaining patient, the everolimus dose was not changed or interrupted.

In the 1415 OLE, 3 patients with LGS were taking mTOR inhibitors (1 everolimus and 2 tacrolimus) concomitantly with CBD-OS. The patient taking everolimus had a reduction in everolimus dose; 1 patient taking tacrolimus had a dose reduction, and the other had various tacrolimus dose modifications.

There were reports of 3 patients in the EAP of patients taking concomitant CBD OS and everolimus. Each of the patients had an increase in everolimus trough levels approximately 2- to 3-fold from baseline, with 1 patient discontinuing everolimus treatment due to elevated trough levels.

In all the cases, AEs commonly associated with mTOR or calcineurin inhibitors such as non-infectious pneumonitis or stomatitis were not reported.

The mechanism of drug–drug interaction between concomitant CBD and everolimus is still unknown and a DDI study of CBD-OS and everolimus has been initiated.

Discontinuation due to adverse events

In Pool TSC, dose was temporarily reduced for 17.8% of patients in the 50 mg/kg/day group and for 5.3% of patients in the 25 mg/kg/day group and was permanently reduced for 26.0% of patients in the 50 mg/kg/day group and 8.0% in the 25 mg/kg/day group. 10 patients (13.7%) in the 50 mg/kg/day group, 8 patients (10.7%) in the 25 mg/kg/day group, and 2 patients (2.6%) in the placebo group permanently discontinued IMP due to TEAEs. Events leading to discontinuation that occurred in more than

1 patient were ALT increased, somnolence, rash, and urticaria. All TEAEs leading to discontinuation in Pool TSC were considered treatment related.

In the OLE TSC, 10 patients (6.7%) in the >20–30 mg/kg/day category and 1 patient (5.3%) in the ≤ 20 mg/kg/day category permanently discontinued IMP due to TEAEs. In updated groups for OLE TSC, 11 patients (5.5%) permanently discontinued CBD-OS; all of these patients were receiving ≤ 25 mg/kg/day CBD-OS. The only TEAE leading to discontinuation that occurred in more than 1 patient was seizure (4 patients in the ≤ 25 mg/kg/day category). This TEAE was considered related to treatment for 2 patients (1.3%).

Larger proportions of TSC patients compared with LGS/DS patients had the IMP temporarily reduced (All CBD-OS, 11.5% vs. 2.9%, respectively), permanently reduced (16.9% vs. 7.5%), interrupted (3.4% vs. 0.9%), or permanently discontinued (12.2% vs. 7.7%). The increase in permanent discontinuations in the TSC population compared to the LGS/DS population was driven by a higher incidence of permanent discontinuations in the CBD-OS 50 mg/kg/day group, which had a higher incidence of SAEs.

In the LGS/DS population, 7.7% of all CBD-OS patients (1.0% of placebo) permanently discontinued IMP due to a TEAE, compared with 12.2% of all CBD-OS patients (2.6% of placebo) in the TSC population. In both populations, the most common events leading to discontinuation included liver related events and somnolence.

Post marketing experience

CBD-OS was approved in June 2018 in the USA and launch in November 2018. Patient exposure to Epidiolex in the USA is estimated at 100,000 patient-months. No new validated safety signals have arisen from the post-marketing data as of the data cut-offs for this submission.

Epidyolex was approved in Europe on 19 September 2019. No post-marketing data are available from Europe as of the data cut-offs for this variation. The first periodic benefit-risk evaluation report/periodic safety update report was submitted 03 March 2020, with a cut-off date of 24 December 2019, and did contain a small amount of post-marketing safety data from the EU, although the majority arose from the USA.

2.5.1. Discussion on clinical safety

The primary source of safety data with CBD-OS in the TSC target population consists of the pivotal Phase III study GWEP1521 (Pool TSC) and GWEP1521 OLE as open label extension (OLE TSC). The number of all TSC patients exposed to 25 and 50 mg/kg/day for 16 weeks in the clinical program is 75 and 73 patients respectively, while there are no patients exposed to 10 mg/kg/day dose.

The ICH E1 guidance (CPMP/ICH/375/95) states that "100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety database. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use." According to the recommended dosing, the number of TSC patients exposed to CBD-OS in a double-blind randomized clinical trial setting, for 6 months or 1 year, is therefore not sufficient. There are no TSC patients who were tested for 10 mg/kg/day maintenance dose and 75 patients for 25 mg/kg/day dose for 16 weeks. However, in the context of the orphan designation of TSC, TSC OLE and long-term exposure from EAP has been taken into consideration and, in total, 115 TSC patients have been exposed to CBD-OS > 1 year duration. The CHMP agrees that the patient exposure is acceptable.

In TSC population, the largest proportion of patients were aged 6 to 11 years (27.7% in the All CBD-OS group; 28.9% in placebo), mostly white and male (90.5% and 58.1% respectively in CBD-OS group). Mean age of patients in the 25 mg/kg/day group was slightly older (14.1 years) than in the 50 mg/kg/day group (12.8 years). More patients were from US in placebo group (55.3%), compared to CBD-OS group (47.3%). In the CBD-OS groups, mean body weight (42.43 kg) and mean BMI (20.46 kg/m2) were slightly higher in the placebo group (44.56 kg and 22.08 kg/m2). The MAH explains that the lower BMI in the CBD-OS 25 mg/kg/day group than in the 50 mg/kg/day group may reflect the taller height (at older mean age) of patients in this group. In the CBD-OS 25 mg/kg/day group, 5.3% of patients reported previous use of cannabis, compared to 8.2% of patients in the 50 mg/kg/day group and 7.9% of patients in the placebo group. Among patients reporting previous cannabis use, mean time since last use to first dose of IMP was 14.3 months for the CBD-OS 25 mg/kg/day group, 13.3 months for the 50 mg/kg/day group, and 41.6 months for the placebo group.

In OLE phase most of the patients were in the 20-30 mg/kg/day group (n=150) and other two groups were small in number (n=19 in <=20 mg/kg/day group, n=30 in >30 mg/kg/day group), so any comparisons should be made carefully. There seems to be a reverse correlation of dose and mean or median age (16.9 or 16.3 years for <=20 mg/kg/day group, 12.9 or 10.1 for n=30 in >20-30 mg/kg/day group, 12.0 or 9.9 years for >30 mg/kg/day group), higher dose in younger patients. Sex distribution was imbalanced between dose groups, especially for the lowest dose group having mostly females (63.2% vs 37.3 and 43.3 in other groups). Country and region also had significant imbalance between groups.

As expected, regarding prior and concomitant medication use, most patients used 3 or more AEDs in Pool TSC or OLE TSC. In the All CBD-OS group, the 3 AEDs used by the most patients were valproic acid, vigabatrin, and levetiracetam.

There is a clear treatment and dose related increase in the incidences of TEAEs, TEAEs leading to permanent discontinuation, serious TEAEs, and these groups had same trend for TEAEs being considered treatment related by the investigator. This is concerning as it may signal dose related increase in adverse events and possible unblinding in all groups due to properties of the pharmaceutical product and/or adverse event profile.

After many treatment related events and discontinuations up to the dose of 30 mg/kg/day, there seems to be a very small group of patients remaining who could tolerate these doses without further discontinuation due to TEAEs.

Diarrhoea, decreased appetite, and somnolence were the 3 most frequently occurring TEAEs and showed higher frequency in higher dose group. Pyrexia, constipation, GGT increased, and cough were more common in the 25 mg/kg/day CBD OS group. Liver-related TEAEs also showed a dose-response relationship. In OLE TSC, the 3 most frequently occurring TEAEs in the CBD-OS group were diarrhoea, seizure, and decreased appetite (all reported for > 19% of patients). The most common TEAEs were the same between LGS/DS and TSC populations, although incidence was generally higher in the TSC population. Liver enzyme increases, pyrexia and vomiting had more significant signal and higher incidence in the TSC trial compared to Pool LGS/DS.

Diarrhoea is very common dose related TEAE occurring in up to 43.2% of the population treated with CBD-OS with a potential for leading to discontinuation of treatment, being serious and potential risk for unblinding. Information regarding diarrhoea has been correctly reflected in the SmPC section 4.8.

In Pool TSC, a greater proportion of CBD-OS patients met criteria for decreases in weight from baseline, whereas a greater proportion of placebo patients met criteria for weight increases from baseline, and the relative risk of weight loss was higher in the TSC population than in the LGS/DS population. In OLE TSC,

higher proportions of patients met weight decrease criteria in the > 25 mg/kg/day modal dose group than in the ≤ 25 mg/kg/day dose group. The relevant weight loss/absence of weight gain information is reflected in the SmPC section 4.8 and a warning that continuous weight loss/absence of weight gain should be periodically checked to evaluate if cannabidiol treatment should be continued is added in section 4.4.

Somnolence, fatigue, lethargy, or sedation are very common dose related AE occurring in 27.7% of CBD-OS treated population with a potential for leading to discontinuation of treatment, being serious and potential risk for unblinding in clinical studies. A relationship with clobazam use and enhancement of its effects and side effects could be speculated.

As experienced with LGS/DS, seizure worsening was observed in Pool TSC. 8 patients (10.7%) in the 25 mg/kg/day group, 13 patients (17.8%) in the 50 mg/kg/day group, and 7 patients (9.2%) in the placebo group experienced worsening in seizures showing a dose related pattern. The distinctly increased number of patients who experienced treatment-emergent seizure in the OLE phase was noted in all subgroups. Seizure was added in the SmPC section 4.8 as ADR together with a description of the observations. This is acceptable.

The observations concerning the liver safety of CBD-OS in TSC patients are consistent with observations that have been made in the larger DS and LGS populations and necessary actions are taken by MAH.

Haematological and renal changes observed in TSC patients treated with CBD-OD were similar to findings with LGS/DS patients. Decrease in Hb, Hct and platelets, increase in creatinine are observed.

In Pool TSC, 4 patients (5.3%) in 25 mg/kg/day group, 2 patients (2.7%) in the 50 mg/kg/day group, and no patients in the placebo group had at least 1 AESI of significant cardiovascular disease. 1 patient in the All CBD-OS group had a significant CVD AESI (preferred term: electrocardiogram abnormal) considered related to IMP and permanently discontinued IMP. In the OLE TSC, 15 patients (7.5%) in the All CBD-OS group had at least 1 AESI of significant CVD, 4 patients (2.0%) had events considered related to IMP. Three patients (1.5%) had a severe event, and 3 patients had serious events. No patient permanently discontinued IMP. As such, there is an imbalance in the CVD AESI between CBD groups and placebo in the pivotal trial. TSC population has an intrinsic risk of experiencing cardiac events which might be triggered or worsened by treatment. It is noted that a 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 (results estimated in September 2021). Pending the results of the QTc study and considering the cardiovascular monitoring adopted as standard of care for TSC patients, it is acceptable to add cardiovascular risk evaluation and expected QTc results in the RMP, with regular review in the next PSURs. The SmPC section 4.4 specifies that patients with cardiovascular impairment were not included in the clinical development program.

Generalized maculopapular rash is very common dose related AE occurring in 9.5% of all CBD-OS patients, 4.1% leading to discontinuation of treatment and has a potential risk for unblinding in clinical studies due to no severe events, serious events, or events leading to discontinuation for rash reported in placebo patients. Rash is already identified as risk and followed in PSURs by MAH.

In Pool TSC, 3 patients (4.0%) in the CBD-OS 25 mg/kg/day group, 1 patient (1.4%) in the 50 mg/kg/day group, and no patients in the placebo group had at least 1 event corresponding to individual AESIs relating to DRESS. All considered related to IMP. One patient (0.7%) in the All CBD-OS group had a severe event, which was also serious (PT: rash erythematous). Two patients permanently discontinued IMP due to a DRESS AESI (PTs: eosinophil count increased; rash; rash erythematous).

Aggression, irritability, agitation and psychosis are observed in TSC patients treated with CBD-OD, similar to findings with LGS/DS patients. Suicidality related TEAE was not observed. CBD-OS poses minimal abuse potential and < 2% incidence of abuse liability AESIs.

Across the disease populations, the use of > 4 AEDs was associated with increased incidences of serious TEAEs and AEs leading to discontinuation, as well as with somnolence-related AESIs. Valproic acid (43.9%) and VGB (38.5%) were the most commonly prescribed concomitant AEDs and CLB was used by 24.3% of patients in all CBD-OS group in Pool TSC. A DDI study of CBD-OS and everolimus has been initiated (see also clinical pharmacology section). In the interim, a statement recommending caution when using CBD-OS concomitantly with mTOR inhibitors or calcineurin inhibitors is added in SmPC section 4.5.

Increased number of temporary or permanent dose reductions, discontinuation due to TEAEs, and discontinuations due to treatment related TEAEs were observed with TSC patients, especially in higher dose group compared to LGS/DS experience in clinical trials. In Pool TSC, 10 patients (13.7%) in the 50 mg/kg/day group, 8 patients (10.7%) in the 25 mg/kg/day group, and 2 patients (2.6%) in the placebo group permanently discontinued IMP due to TEAEs. Events leading to discontinuation that occurred in more than 1 patient were ALT increased, somnolence, rash, and urticaria.

2.5.2. Conclusions on clinical safety

Based on the available safety data, the CHMP concludes that the safety profile in the TSC indication, an orphan condition, is acceptable.

The highlighted safety concerns will continue to be managed through the agreed RMP and monitored via the PSURs.

The CHMP noted that a thorough QTc trial in the fed state is scheduled at therapeutic and supra-therapeutic exposures.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan (RMP) version with this application.

The CHMP received the following PRAC Advice on the submitted RMP:

The PRAC considered that the RMP version 2.0 is acceptable.

The CHMP endorsed this advice without changes.

Therefore, the CHMP endorsed the RMP version 2.0 with the following content:

Safety concerns

Important identified risks	• Hepatocellular injury • Somnolence and sedation • Lethargy • Pneumonia • Rash hypersensitivity reactions
Important potential risks	• Suicidality (class effect) • Seizure worsening • Aggression • Euphoria • Impact on cognitive development • Urinary retention
Missing information	• Exposure during pregnancy and lactation • Long-term safety

harmacovigilance Plan

Table 53: Summary table of ongoing and planned additional pharmacovigilance activities in the PV Plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Post-marketing cohort study	Evaluate the long-term safety profile of Epidyolex, and further characterise the safety concerns of Epidyolex, when used under conditions of routine clinical care.	Long term safety Hepatocellular injury Somnolence/sedation Lethargy Pneumonia Rash Suicidality Seizure worsening Aggression Euphoria Impact on cognitive development Urinary retention	Draft study protocol Interim reports Final CSR	Q2 2020 Annually Second half of 2026
Participation in AED pregnancy registry, including: European and international registry of antiepileptic drugs and pregnancy North American antiepileptic	Collect data on pregnancy and lactation	Pregnancy and lactation	Not applicable	Ongoing – it will be discussed in periodic safety update reports (PSURs)

drug pregnancy registry				

Risk minimisation measures

Table 54: Summary table of PV Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk Minimisation Measure	Pharmacovigilance Activity
Hepatocellular injury	Routine RMMs: • SmPC Section 4.3: Contraindications • SmPC Section 4.4: Special warnings and precautions for use • SmPC Section 4.8: Undesirable effects • Package Leaflet Section 2 • Available by prescription only Additional RMMs: none	Routine activities including: • Specific enhanced pharmacovigilance adverse reaction follow-up and physician to physician follow-up process to follow-up significant transaminase elevation reports. Internal medical review committee for expedited review of important cases. Additional pharmacovigilance activities: • Post-marketing observational cohort study – final CSR - 2H 2026
Somnolence and sedation	Routine RMMs: • SmPC Section 4.4: Special warnings and precautions for use • SmPC Section 4.8: Undesirable effects • Package Leaflet Section 2 • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Lethargy	Routine RMMs: • SmPC Section 4.8: Undesirable effects • Package Leaflet Section 2 • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Pneumonia	Routine RMM: • SmPC Section 4.8: Undesirable effects • Available by prescription only Additional RMM: none	Routine PV activities including: • Specific detailed adverse reaction follow-up for pneumonia reports Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Rash hypersensitivity reactions	Routine RMMs: • SmPC Section 4.8: Undesirable effects	Routine PV activities including: • Specific detailed adverse reaction follow-up for rash hypersensitivity reactions

	• Available by prescription only Additional RMMs: none	Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Suicidality	Routine RMMs: • SmPC Section 4.4: Special warnings and precautions for use • Package Leaflet Section 2 • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Seizure worsening	Routine RMMs: • SmPC Section 4.2: Posology and method of administration • SmPC Section 4.4: Special warnings and precautions for use • SmPC Section 5.1: Pharmacodynamic properties • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Aggression	Routine RMMs: • SmPC Section 4.8: Undesirable effects • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Euphoria	Routine RMMs: • SmPC Section 5.1: Pharmacodynamic properties • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Impact on cognitive development	Routine RMMs: • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026
Urinary retention	Routine RMMs: • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026

Exposure during pregnancy and lactation	Routine RMMs: • SmPC Section 4.6: Fertility, Pregnancy and Lactation • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: Participation in AED pregnancy registry including • European and international registry of antiepileptic drugs and pregnancy And • North American antiepileptic drug pregnancy registry
Long term safety	Routine RMMs: • Available by prescription only Additional RMMs: none	Routine PV activities Additional PV activities: • Post-marketing observational cohort study – final CSR 2H 2026

2.7. Update of the Product information

As a consequence of the extension of indication to TSC, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The MAH also took the opportunity to correct typographic errors and implement editorial updates as well as implement the updated ethanol statement in compliance with the EC Guideline on Excipient. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Sweden.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report referring to Epidyolex. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Tuberous Sclerosis Complex (TSC) is a genetic disorder characterised by the formation of non-malignant tumours (tubers) in multiple organ systems. Mutations in the TSC1 or TSC2 gene may cause tuberous sclerosis complex. The TSC1 and TSC2 genes code for the proteins hamartin and tuberin, respectively.

These proteins normally act as tumour suppressors. The incidence rate is approximately 1:10000 to 1:5000 live births. Prevalence may be underestimated but in Europe is usually given as 1:25000 to 1:5000. TSC is a chronic, life-long condition. Tumours in TSC patients occur primarily in the brain, eyes, heart, kidney, skin, and lungs. Epileptic seizures are the most common neurological manifestation of TSC, affecting more than 70% of patients. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients. The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms. Virtually all TSC patients with infantile spasms and approximately half of all epileptic TSC patients without them develop multiple seizure types, including complex focal seizures (with or without secondary generalization), generalized tonic-clonic seizures, atonic seizures, and atypical absences. Infantile spasms resolve with time, but the frequency and severity of other seizures tend to increase throughout early childhood and nearly two-thirds of TSC patients develop medically intractable epilepsy. Morbidity and mortality are increased in patients with treatment-resistant epilepsies, including TSC. Sudden unexpected death in epilepsy is one of the most common causes of death. Recurrent seizures often lead to intellectual and developmental disabilities and contribute to an increased risk of injury and death.

3.1.2. Available therapies and unmet medical need

Most patients with TSC take between 3 and 5 AEDs. However, such treatment regimens rarely provide sufficient seizure control and are often accompanied by intolerable side effects.

The only approved therapy for TSC-associated seizures in the EU is the mTOR inhibitor everolimus. Everolimus was originally approved in the EU in 2011 (as Votubia) to treat tumours in TSC patients aged 3 years and older, and the indication was subsequently extended in 2017 to include adjunctive treatment of adult and paediatric patients aged 2 years and older with TSC-associated partial-onset seizures. Everolimus is an immunosuppressant agent initially developed to prevent transplant rejection and for oncology indications. As such, everolimus is associated with a safety and tolerability burden, including non-infectious pneumonitis, increased infection risk, hypersensitivity reactions, stomatitis, renal failure, impaired wound healing, myelosuppression and metabolic disorders.

Vigabatrin (VGB) was first licensed as an antiepileptic agent (in the UK and the Republic of Ireland) in 1989 (as Sabril) and was most recently approved in the EU in 2018 (as Kigabeq) to treat infantile spasms, and is often used for treatment of infantile spasms secondary to TSC. Vigabatrin is typically recommended as a first-line treatment for TSC-related spasms or focal seizures in children < 1 year of age in Europe.

Corticotropin (ACTH) or other corticosteroids have been demonstrated as effective in the treatment of infantile spasms. ACTH treatment is associated with serious AEs, including fulminant infections secondary to immunosuppression, hypertension, glucosuria and metabolic abnormalities and may contribute to enlargement of cardiac rhabdomyoma in TSC patients. Thus, corticosteroid therapy is generally short-term (approximately 2 weeks followed by taper), and close monitoring is required in TSC patients with cardiac rhabdomyoma.

Utilisation of Clobazam (CLB) is estimated to be limited to < 20% of the 46,000 patients with TSC in the EU. Benzodiazepines such as CLB are not commonly used for treating seizures associated with TSC, and guidelines do not support utilisation. Data on effectiveness of CLB on focal seizures are limited, and there are no dosing recommendations to guide initiation, titration, and target dosing of CLB for the treatment of seizures associated with TSC in children aged < 6 years old. While CLB may be a useful add-on medication for some with refractory epilepsy, its clinical use may be limited by the side effects on behaviour (severe aggressive outbursts, hyperactivity, insomnia, and depression with suicidal ideation),

which are important comorbidities in some patients with TSC. Additionally, CLB is associated with adverse reactions including somnolence, sedation, cognitive impairment, respiratory depression, tolerance, and dependence.

There is therefore an unmet medical need for new efficacious and safe pharmaceutical treatments for refractory seizures in TSC. Despite the currently available treatment options, many patients with TSC-associated epilepsy continue to have seizures: more than 60% of patients do not achieve seizure control despite the availability of multiple AEDs and non-pharmacological interventions. Current AEDs are often associated with side effects, which can be worsened by polypharmacy. As with any refractory epilepsy, physicians typically try several AEDs in order to gain epilepsy control. However, such polypharmacy often leads to a high burden of adverse events (AEs), and the appropriate balance of tolerability and efficacy is critical to achieving seizure control.

3.1.3. Main clinical studies

The clinical development program supporting the efficacy of CBD-OS in TSC comprises a single, Phase III, randomised, placebo-controlled trial (GWEP1521) that investigated 25 mg/kg/day and 50 mg/kg/day CBD-OS for the treatment of TSC-associated seizures. The trial design was similar to that used for the CBD-OS trials in other indications. The GWEP1521 trial consisted of a 4-week baseline period, followed by a 16-week treatment period comprising a 4-week titration (dose escalation) period and a 12-week maintenance (stable dosing) period. Patients who completed the double-blind phase could transition to the OLE phase of the trial where all patients were titrated to 25 mg/kg/day CBD-OS; the dose could then be increased up to 50 mg/kg/day if required for better seizure control or decreased if the patient experienced intolerance.

3.2. Favourable effects

The primary analysis demonstrated greater reduction in TSC-associated seizures in the active treatment groups as compared with the placebo group. The median change in number of TSC-associated seizures during the treatment period for 25 mg/kg/day, 50 mg/kg/day, and placebo were -43.36, -36.55, and -20.08, respectively. Thus, the percent decrease in TSC-associated seizure frequency was 48.6% in the 25 mg/kg/day group and 26.5% in the placebo group compared to their baseline. The primary endpoint (change from baseline in TSC-associated seizures for the 25 mg/kg/day dosage group) was statistically significant (treatment ratio 0.699, 95% CI: 0.567, 0.861; p=0.0009), demonstrating the efficacy of Epidyolex in patients with TSC. A similar pattern was seen for the percent decrease in total seizures for patients who received CBD-OS compared to placebo (treatment ratio 0.709, 95% CI: 0.576-0.873; p=0.0013). The proportion of patients with any improvement in overall condition on Global Impression of Change Score (slightly improved, much improved, or very much improved) at their last visit for patients with caregiver and/or subject data available was higher in the 25 mg/kg/day GWP42003-P group (68.6%) and 50 mg/kg/day GWP42003-P group (62.3%) compared with the placebo group (39.5%).

The change from baseline in TSC-associated seizure free days per 28 days was greater in both the 25 mg/kg/day and 50 mg/kg/day GWP42003-P groups compared to placebo.

To account for differences in sample size with increasing time, maintenance of efficacy was assessed in patients treated for > 52 weeks in the Interim Expanded Access Program. The median percentage reduction in convulsive seizure frequency from Week 15 onwards was 43.9%, which was maintained to Week 53 onwards (median 52.5% reduction).

3.3. Uncertainties and limitations about favourable effects

The primary efficacy endpoint is not fully in line with recommendation given in the EU Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders, according to which "Two important variables should be specified in the protocol. The primary endpoint should be responders/non-responders, where responders are patients who obtained at least a certain pre-defined percentage reduction of seizure frequency (e.g. a 50% reduction is commonly used). The other variable should be some parameterisation using the actual change in seizure frequency." Nonetheless, the use of 50% responder rate as a key secondary endpoint instead of primary endpoint was accepted by PDCO and included in the agreed PIP.

The efficacy of the 50 mg/kg/day dose was found to be similar to that of the 25 mg/kg/day dose; however, the safety and tolerability burden is greater with the 50 mg/kg/day dose. Only the 25 mg/kg/day dose of Epidyolex has been submitted for approval.

There is no evidence of efficacy available for the lower dose level of 10 mg/kg/day and the similar efficacy profile of 50 mg/kg/day dose to 25 mg/kg/day dose is precluding establishment of a dose-response relationship or low or high doses to be approved or used for treatment of TSC.

As also observed with studies in other indications, the treatment ratio in the subgroup of patients on clobazam was 0.534 (95% CI 0.356, 0.800) suggesting a treatment effect twice as large in patients on clobazam in comparison to 0.753 (0.589-0.963) in the subgroup of patients not on clobazam in the subgroup analysis of primary endpoint. Concomitant administration of cannabidiol and CLB causes an approximate 3-fold elevation in the active metabolite N-CLB with little or no increase in CLB likely mediated by CYP2C19 inhibition. Literature indicate that both pharmacodynamic and pharmacokinetic interactions between CBD and clobazam that may contribute to its efficacy in Dravet syndrome.

Nevertheless, in study GWEP1521, 73% of patients did not receive CLB (in contrast to 36% in clinical trials with Dravet syndrome) and the results from this subgroup still reached nominal statistical significance. Thus, the apparent clinical efficacy observed in the primary analysis does not appear only to be driven by interaction with clobazam although it is a factor.

Clinical efficacy of the 25 mg/kg/day dose was not fully supported by the most important key secondary analysis, the 50% responder analysis, where the OR for achieving a ≥ 50% reduction in TSC-associated seizure frequency did not reach statistical significance for the 25 mg/kg/day group (P=0.0692). This is still considered supportive as these results are in accordance with the European Medicines Agency (EMA) Guideline on Multiplicity Issues in Clinical Trials (EMA/CHMP/44762/2017): "In a situation in which the primary endpoint establishes a statistically significant effect, "the results of the 'responder' analysis need not be statistically significant, but the difference in the proportions of responders should support a statement that the investigated treatment induces clinically relevant effects." Actually, 16.0% of patients in the 25 mg/kg/day Epidyolex group achieved the ≥ 75% response level, compared to no patients in the placebo group (nominal p=0.0003).

In addition, data to support PK, efficacy and safety in children below 2 years of age are limited. The indication is therefore for children age 2 years and older.

3.4. Unfavourable effects

There is a dose related increase in the incidences of TEAEs, TEAEs leading to permanent discontinuation, serious TEAEs, and these groups had same trend for TEAEs being considered treatment related by the investigator. Diarrhoea, decreased appetite, and somnolence were the 3 most frequently occurring TEAEs

and showed higher frequency in higher dose group. Pyrexia, constipation, GGT increased, and cough were more common in the 25 mg/kg/day CBD OS group. Liver enzyme increases, pyrexia and vomiting had more significant signal and higher incidence in the TSC trial compared to Pool LGS/DS.

Treatment-emergent AEs of diarrhoea were far more common in the TSC population than in the LGS/DS population (CBD-OS treated 30.7%-56.2 vs. 12.9%-21.2%, placebo 25.0% vs 9.6 %).

In Pool TSC, a greater proportion of CBD-OS patients met criteria for decreases in weight from baseline, whereas a greater proportion of placebo patients met criteria for weight increases from baseline, and the relative risk of weight loss was higher in the TSC population than in the LGS/DS population.

Somnolence, fatigue, lethargy, or sedation are very common dose related AE occurring in 27.7% of CBD-OS treated population in comparison to 13 patients (17.1%) in the placebo group, with more patients in the All CBD-OS group, having an AESI of somnolence, fatigue, lethargy, or sedation considered related to treatment, a serious TEAE; and 2 a TEAE leading to discontinuation.

A comparison of the safety profiles in patients treated with or without concomitant CLB reveals that there is an increased risk for certain AEs and SAEs in the patient population treated with CLB, including somnolence, sedation, lethargy, and pneumonia.

CBD-OS caused dose-dependent elevations in serum ALT-AST in TSC patients, including some elevations meeting the consensus criteria for drug-induced liver injury. There was no clear increased risk associated with concomitant use of AEDs other than VPA.

Generalized maculopapular rash is very common dose related AE occurring in 9.5% of all CBD-OS patients, some leading to discontinuation of treatment. Increased number of temporary or permanent dose reductions, discontinuation due to TEAEs, and discontinuations due to treatment related TEAEs were observed with TSC patients, especially in higher dose group compared to LGS/DS experience in clinical trials.

3.5. Uncertainties and limitations about unfavourable effects

The number of all TSC patients exposed to 25 mg/kg/day (targeted treatment dose) for 16 weeks in the clinical program is 75 while there are no patients exposed to 10 mg/kg/day dose. The number of patients followed up in the OLE TSC is 199 patients, 156 of these patients were on 25 mg/kg/day.

Across the disease populations, the use of > 4 AEDs was associated with increased incidences of serious TEAEs and AEs leading to discontinuation, as well as with somnolence-related AESIs. Valproic acid and VGB were the most commonly prescribed concomitant AEDs. Interaction of CBD-OS with everolimus, the only therapy approved for TSC, is unknown.

Only patients in Pool TSC had at least 1 AESI of significant cardiovascular disease, including severe and serious events. Relationship of significant cardiovascular disease to CBD-OD treatment in TSC patients is uncertain.

The higher incidence of SAEs was reported in 25 mg/kg/day group (21,3%) than in 50 mg/kg/group (13,7%), which is unexpected. The SOC with the most frequently reported SAEs included Investigations, Infections and infestations and Nervous system disorders, which is in line with the results obtained from previous studies.

3.6. Effects Table

Table 55: Effects Table for Epidyolex and TSC indication

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects 25 mg/kg/day						
Seizure reduction	Change in TSC-associated seizures	%	-43	-20	46.6% reduction or treatment ratio 0.534 (p=0.0025) when used with concomitant clobazam treatment, in comparison to 24.7% reduction or treatment ratio 0.753 (p=0.0242) without CLB	
Responders	Pts with ≥ 50% reduction in TSC-associated seizures	%	36	22	NS	
Unfavourable Effects 25 mg/kg/day						
Diarrhoea	Diarrhoea TEAE	%	30.7	25	41 patients (56.2%) for 50 mg/kg/day. Dose-related pattern	
Decreased appetite	Decreased appetite TEAE	%	20	11.8	23.3% in the 50 mg/kg/day group. Dose related pattern	
Weight decrease	≥ 5% decrease in weight from baseline	%	30.7	7.9	42.1% of (32) patients receiving placebo had a weight **increase** of ≥ 5% from baseline	
Somnolence -related TEAE	Somnolence, fatigue, lethargy, or sedation TEAE	%	21.3	17.1	34.2% in the 50 mg/kg/day group. Dose related pattern. Clobazam has been identified as a risk factor	
Seizure worsening	Seizure worsening	%	10.7	9.2	17.8% in the 50 mg/kg/day group. Dose related pattern	
Abnormal Liver tests	TE ALT or AST ≥ 3 × ULN	%	12	0	Dose related pattern. Increased risk associated with concomitant use of VPA	
	TE ALT or AST ≥ 5 × ULN	%	6.7	0		
Rash	Rash, generalized maculopapular rash	%	6.7	3.9	12.3%) in the 50 mg/kg/day group. Dose related pattern	
Significant CVD	Significant Cardiovascular Disease. Preferred term: electrocardiogram abnormal	%	5.3	0		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is a significant unmet medical need for new therapies in TSC and the patients randomised in Study GWEP1521 are representative of the highly refractory patient population.

In the single pivotal study submitted to support the application, CBD-OS 25 mg/kg/day reduced TCS-associated seizures by 40 % compared to 20 % in the placebo group. The key secondary endpoint (≥ 50 % reduction in TSC associated seizures) narrowly missed statistical significance (p=0.0692) but nevertheless supports a conclusion of efficacy of CBD-OS. In TSC, the proposed maximum recommended dose is 25 mg/kg/day, compared to 20 mg/kg/day for other indications, and no dose-response relationship has been established.

CBD-OS is proposed to be indicated as adjunctive treatment in TSC and has been investigated on top of other AEDs. A higher efficacy is seen with concomitant clobazam treatment, which can be explained by the known pharmacokinetic interaction between CBD and clobazam resulting in an increase in the active metabolite N-desmethylclobazam as also observed in studies in other indications. However, albeit less robust, the treatment effect of CBD-OS was still statistically significant and is considered clinically relevant without concomitant clobazam therapy in this difficult-to-treat TSC patient population. Clobazam use in TSC is limited. Utilisation of CLB is estimated to be < 20% of the 46,000 patients with TSC in the EU and only 27% of the patients in Study GWEP1521 were treated with clobazam. Data on effectiveness of CLB on focal seizures are limited, and there are no dosing recommendations to guide initiation, titration, and target dosing of CLB for the treatment of seizures associated with TSC in children aged < 6 years old. Its clinical use may also be limited by the side effects on behaviour (severe aggressive outbursts, hyperactivity, insomnia, and depression with suicidal ideation), which are important comorbidities in some patients with TSC. Additionally, CLB is associated with adverse reactions including somnolence, sedation, cognitive impairment, respiratory depression, tolerance and dependence. A comparison of the safety profiles in patients treated with or without concomitant CLB in Study GWEP1521 reveals that there is an increased risk for certain AEs and SAEs like somnolence, sedation, lethargy, and pneumonia in the patient population treated with CLB.

In addition, if such a 'heterogeneity' is observed between subgroups, the requirement is that the magnitude of the estimated effects must be set in the context of a benefit-risk consideration for the subgroups (EMA/CHMP/539146/2013).

The CHMP therefore agrees that the decision to combine cannabidiol with CLB in patients with TSC associated seizures should be left to the treating physician.

Considering that the data to support PK, efficacy and safety in children below 2 years of age are limited, the indication is agreed for children age 2 years and older.

3.7.2. Balance of benefits and risks

The benefit of CBD-OS in TSC is demonstrated with the proposed dose level of up to 25 mg/kg/day and is reasonably supported by the key secondary endpoint.

3.7.3. Additional considerations on the benefit-risk balance

NA

3.8. Conclusions

The overall B/R of Epidyolex is positive for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. The updated RMP version 2.0 is agreed.
The MAH also took the opportunity to correct typographic errors and implement editorial updates as well as implement the updated ethanol statement in compliance with the EC Guideline on Excipient. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Sweden.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0047/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Epidyolex is not similar to Votubia within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 2

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-0005'

Appendices

1. CHMP AR on similarity dated 25 February 2021
2. CHMP AR on the significant clinical benefit in comparison with existing therapies