EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2019
EMA/458106/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Epidyolex

International non-proprietary name: cannabidiol

Procedure No. EMEA/H/C/004675/0000

Note

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

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Administrative information

Name of the medicinal product:	Epidyolex
Applicant:	GW Pharma (International) B.V. Databankweg 26 3821AL Amersfoort NETHERLANDS
Active substance:	CANNABIDIOL
International Non-proprietary Name/Common Name:	cannabidiol
Pharmaco-therapeutic group (ATC Code):	antiepileptics, other antiepileptics (N03AX)
Therapeutic indications:	Epidyolex is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS), in conjunction with clobazam, for patients 2 years of age and older.
Pharmaceutical form:	Oral solution
Strength:	100 mg/ml
Route of administration:	Oral use
Packaging:	Bottle (glass)
Package sizes:	1 bottle + 2 syringes of 1 ml + 2 syringes of 5 ml + 2 bottle adapters

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List of abbreviations

5-HT	5-hydroxytryptamine
7-COOH-CBD	7-carboxy-CBD
7-OH-CBD	7-hydroxy-CBD
AAC	Abuse adjudication committee
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AED	Antiepileptic drug
AESI	Adverse events of special interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ALZ	Alprazolam
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
AST	Aspartate aminotransferase
AUC	Area under the curve
BAC	Blood alcohol (ethanol) concentration
BCRP	Breast cancer resistance protein
BDS	Botanical Drug Substance
b.i.d.	Twice daily [Latin: *bis in die*]
BMI	Body mass index
BRM	Botanical raw material
CAS	Compassionate access scheme
CB	Cannabinoid
CB1	Cannabinoid receptor type 1
CB2	Cannabinoid receptor type 2
CBD	Cannabidiol (GWP42003-P)
CBDA	Cannabidiolic acid
CBD-OS	Cannabidiol oral solution
CBDV	Cannabidivarin
CDF	Cumulative distribution function
CE	Conformité Européenne
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CLB	Clobazam
Cmax	Maximum measured plasma concentration
CMC	Chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CNS	Central Nervous System
COX	Cyclo-oxygenase
CSR	Clinical study report
CYP450	Cytochrome P450
D1	Dopamine receptor
DA	Dopamine
DDI	Drug-drug interaction
DEA	Drug Enforcement Administration
DRE	Drug-resistant epilepsy

DRESS	Drug reaction with eosinophilia and systemic symptoms
DRO	Dronabinol
DS	Dravet Syndrome
DSMC	Data safety monitoring committee
EAP	Expanded access program
EC	European Commission
ECG	Electrocardiogram
EFD	Embryo fetal development
EMA	European Medicines Agency
EU	European Union
E_{max}	Maximum effect
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GABA	Gamma-aminobutyric acid
GACP	Good Agricultural and Collection Practices
GC	Gas Chromatography
GC-MS	Gas chromatography–mass spectrometry
GGT	Gamma glutamyltransferase
GL	Guideline
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPR	G-protein coupled receptor
G-tube	Gastrostomy tube
GW	GW Research Ltd
HAL	Human abuse liability
HDPE	High Density Polyethylene
HEK	Human Embryonic Kidney
hERG	Human ether-à-go-go-related gene
H-MD	Healthy subjects multiple-dose
HPLC	High performance liquid chromatography
H-SD	Healthy subjects single-dose
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IND	Investigational new drug
i.p.	Intraperitoneal
IPC	In-process control
IR	Infrared
ISS	Integrated Summary of Safety
ITT	Intention to treat
i.v.	Intravenous
IVRS	Interactive voice response system
KF	Karl Fischer titration
LC-MS	Liquid chromatography–mass spectrometry
LDPE	Low density polyethylene
LEV	Levetiracetam
LGS	Lennox–Gastaut Syndrome
LH	Luteinizing Hormone
LPI	L-α-lysophosphatidylinositol
LTG	Lamotrigine

M3	Muscarinic acetylcholine
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MADDERS	Misuse, Abuse, and Diversion Drug Event Reporting System
MATE	Multidrug and toxin extrusion
mEPSC	Miniature excitatory post-synaptic current
MO	Major Objection
mRNA	messenger Ribonucleic acid
N-CLB	*N*-desmethylclobazam
NDA	New drug application
NE	Norepinephrine
NMDA	N-methyl-D-aspartate
NMR	Nuclear Magnetic Resonance
NMRI	Naval Medical Research Institute
NMT	Not more than
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OAT	Organic anion transporters
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporters
OLE	Open-label extension
OR	Odds ratio
OX	Orexin
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamic
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
p.o.	Per os
POPPK	Population pharmacokinetics
PP1-SD	Phase 1 patient (special populations) single-dose
PP	Polypropylene
PPND	Peri-Postnatal developmental
PT	Preferred term
QC	Quality Control
q.s.	*quantum satis*
QTc	The QT interval corrected for heart rate
QTcB	Corrected QT interval with Bazett correction
RCT	Randomized controlled trials
RH	Relative Humidity
SAE	Serious adverse event
S/CGIC	Subject/Caregiver Global Impression of Change
SCN1A	Sodium channel α1 subunit gene
SD	Standard deviation
SE	Status epilepticus
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SOC	System organ class
STP	Stiripentol
SUDEP	Sudden unexpected death in epilepsy
SULT	Sulfotransferases

$T_{1/2}$	Half-life
T3	Triiodothyronine
TBL	Total bilirubin level
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
THC	Δ^9-tetrahydrocannabinol
t_{max}	Time to maximum plasma concentration
TRPV1	Transient receptor potential cation channel subfamily V member 1
TRPV2	Transient receptor potential cation channel subfamily V member 2
TRPA	Transient receptor potential cation channel, subfamily A
TSC	Tuberous sclerosis complex
TSH	Thyroid-Stimulating Hormone
ULN	Upper limit of normal
UPLC	Ultra performance liquid chromatography
USP	United States Pharmacopoeia
USPI	United States Product Information
VNS	Vagus nerve stimulation
VPA	Valproate
vs.	Against [Latin: *versus*]
w/w	Weight by weight

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GW Pharma (International) B.V. submitted on 21 December 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Epidyolex, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2016.

Epidyolex, was designated as an orphan medicinal product EU/3/14/1339 on 15 October 2014 in the following condition: Treatment of Dravet syndrome.

Epidyolex, was designated as an orphan medicinal product EU/3/17/1855 on 20 March 2017 in the following condition: Treatment of Lennox-Gastaut syndrome.

The applicant applied for the following indication: adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients from 2 years of age and older.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0136/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0136/2017 was not yet completed as some measures were deferred.

The PDCO issued an opinion on partial compliance for the PIP P/0136/2017.

Information relating to orphan market exclusivity

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 indications. 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

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal product, Inovelon. However, in the meantime, Inovelon market exclusivity has

expired on 18 January 2019.

New active Substance status

The applicant requested the active substance cannabidiol contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received Protocol assistance from the CHMP on 25 June 2015 and 28 April 2016. The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the starting materials, Drug substance specification, Stability studies;
- Sufficiency of the non-clinical package including juvenile studies;
- General sufficiency of the clinical programme for the characterisation of benefits and risks in the target populations, use of Placebo as comparator, eligibility criteria for the confirmatory studies, definition and relevance of outcomes, statistical plan including handling of missing data.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Mark Ainsworth Co-Rapporteur: Ondřej Slanař

The application was received by the EMA on	21 December 2017
The procedure started on	1 February 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	24 April 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 May 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 May 2018
The CHMP adopted a report on similarity of Epidyolex with Inovelon on (Appendix 1) which becomes no longer applicable as the market exclusivity of Inovelon has expired on 18 January 2019	31 May 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 September 2018
The following GCP inspection(s) were requested by the CHMP and their	

outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 1 analytical laboratory in United Kingdom between 24 – 27 April 2017. The outcome of the inspection carried out was issued on 30 November 2017.	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	25 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 November 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	21 January 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	31 January 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 April 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	24 April 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 April 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 May 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 June 2019
SAG was convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	13 June 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	25 June 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Epidyolex on	25 July 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Epidyolex is proposed for adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients from 2 years of age and older.

Both LGS and DS are early onset encephalopathic epilepsies with a poor prognosis and substantial associated comorbidities. In particular, the affected children tend to exhibit developmental delay and cognitive impairment, often to a severe degree. These conditions have substantial unmet medical needs in the adequate treatment of epileptic seizures associated with LGS and DS, particularly in children. Additionally, cannabidiol (CBD, GWP42003-P) has received orphan drug designations in both indications.

2.1.2. Epidemiology

Lennox-Gastaut Syndrome (LGS): Incidence approximately 1:4,000 births. Prevalence estimates uncertain possibly around 15/100,000. LGS is believed to account for 1-4% of all childhood epilepsies.

Dravet Syndrome (DS): Incidence approximately 1:20,000 births. Prevalence estimates uncertain possibly around 3/100,000. DS is believed to account for approximately 7% of all severe epilepsies starting before the age of 3 years.

2.1.3. Biologic features

Lennox-Gastaut Syndrome (LGS): No single cause has been identified. About two-thirds of cases are considered to be related to an existing neurological condition e.g. abnormal development of the brain cortex (cortical dysplasia), congenital infections, stroke, trauma, reduced oxygen supply that occurs before birth (perinatal hypoxia), or infections of the central nervous system such as encephalitis or meningitis.

Dravet Syndrome (DS): Between 70% and 80% of patients carry sodium channel α1 subunit gene (SCN1A) abnormalities. Truncating mutations account for about 40%. Other SCN1A mutations comprise splice-site and missense mutations, most of which fall into the pore-forming region of the sodium channel. Mutations are randomly distributed across the SCN1A protein. Most mutations are de novo, but familial SCN1A mutations also occur. The aetiology of about 20% of DS patients remains unknown, and additional genes are likely to be implicated.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The onset of Lennox–Gastaut Syndrome (LGS) usually occurs between 3 and 5 years of age and is characterized by the presence of multiple seizure types (predominantly tonic, atonic, and atypical absence seizures), slow electroencephalogram spike-waves with abnormal background activity when awake, and fast polyspikes during sleep. Other seizure types may occur including generalised tonic–clonic, focal, and myoclonic seizures. Seizures often persist into adulthood. All of these seizures types may progress to status epilepticus (SE) which may occur frequently in some patients with LGS, and carries great risks. Drop seizures are common and can lead to physical injury. Cognitive impairment is

apparent in ≥ 75% by 5 years post onset and behavioural and psychiatric comorbidities (including attention deficit/hyperactivity disorder and aggressive behaviour) are common.

Children and adolescents with LGS have an increased risk of death. A population-based study of children with epilepsy showed that all-cause mortality was 14 times greater in LGS than in the general population. Neurological comorbidity including prolonged seizures and SE are correlated with mortality and, in particular, sudden unexpected death in epilepsy (SUDEP).

Dravet Syndrome (DS), also known as severe myoclonic epilepsy in infancy, is characterised by a variety of seizures (febrile and afebrile, generalized and unilateral, clonic or tonic–clonic) that occur in the first year of life. Onset usually occurs between 4 and 8 months of age and is often triggered by fever. In addition to convulsive seizures, other seizure types appear between the ages of 1 and 4 years, including myoclonic seizures, focal seizures, and atypical absences. Status epilepticus (SE) may occur at initial presentation or later in the clinical course. By late childhood, the seizure profile will often have stabilised. Significant developmental delay becomes apparent from the second year onwards and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common. Intellectual impairment affects nearly all patients and is severe in 50% of cases. Dependency in adulthood is a nearly constant feature of DS due to the chronic significant disability. Death during childhood is common and may be due to e.g. SUDEP or other causes.

2.1.5. Management

Felbamate, lamotrigine (LTG), topiramate and rufinamide are approved in the EU as adjunctive therapy for treatment of LGS. Only stiripentol (STP), when taken in conjunction with sodium valproate (VPA) and clobazam (CLB), is currently approved in the EU for the treatment of DS; neither VPA nor CLB are approved for LGS or DS specifically, but both are approved for use in epilepsy in the EU, and widely used in both indications. In both indications, VPA is often used to prevent the initial recurrence of convulsive seizures, and benzodiazepines (e.g., diazepam, midazolam, clonazepam, or CLB) are frequently coadministered to limit the duration of long-lasting seizures. Second-line and later options in DS typically include STP, topiramate, ketogenic diet, levetiracetam (LEV), bromides, and vagus nerve stimulation (VNS), while LTG, rufinamide, lacosamide, and felbamate are also used in LGS. Polytherapy is common in both indications. Of note, patients with DS may be prone to seizure exacerbation with sodium channel modulators such as carbamazepine, oxcarbazepine, LTG, phenytoin, and vigabatrin.

In both indications, sufficient seizure control may be difficult to achieve. Most patients with LGS continue to experience drug-resistant epilepsy (DRE), which has been noted to be as high as 90%. Thus, there is a need for new therapies with a different mode of action.

About the product

Cannabidiol (CBD) exhibits anticonvulsant properties in certain *in vitro* and *in vivo* seizure models. Anticonvulsant activity for the CBD metabolite 7-hydroxy-cannabidiol (7-OH-CBD) has also been demonstrated. Based on these findings as well as preliminary encouraging reports of anticonvulsant effect in humans, larger placebo-controlled trials with CBD oral solution were performed.

A 100 mg/ml CBD oral solution is the intended to-be-marketed formulation. Oral solutions facilitate dosing by volume, meaning dose can be customised for an individual patient's body weight. As CBD is virtually insoluble in water, a lipid-based solvent (sesame oil) has been selected to enable solubility. As it is essential for paediatric medications to be palatable, CBD oral solution (CBD-OS) also contains a sweetener (sucralose) and strawberry flavouring. Sucralose is insoluble in sesame oil; as such, a co-solvent was required. This resulted in a solution containing 10% (v/v), equivalent to 7.9% (w/v) or 79

mg/ml of anhydrous ethanol. In patients aged < 6 years dosing at 20 mg/kg/day, the amount of ethanol may exceed the EMA guidance threshold for ethanol containing medicines. This is adequately reflected in the SmPC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an oral solution containing 100 mg/ml of cannabidiol (CBD) as active substance.

Other ingredients are: sucralose, anhydrous ethanol, refined sesame oil and strawberry flavour.

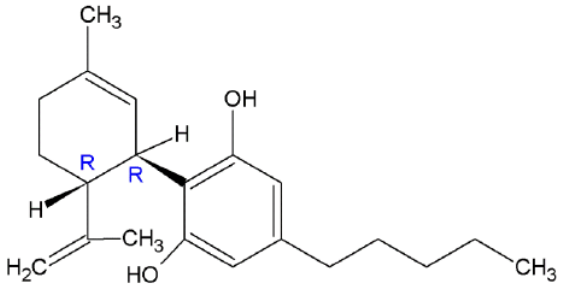
The product is available in amber glass bottles with tamper-evident child-resistant polypropylene (PP) screw caps. As this is a multi-dose bottle, a bottle adaptor and two different-sized graduated oral syringes are provided for accurate administration.

2.2.2. Active substance

General information

The chemical name of cannabidiol is 2-[(1*R*,6*R*)-3-methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol corresponding to the molecular formula $C_{21}H_{30}O_2$. It has a relative molecular mass of 314.5 g/mol and the following structure:

Figure 1 Active substance structure



The chemical structure of cannabidiol was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, mass spectrometry, IR spectroscopy and single crystal x-ray analysis.

The active substance is a white to pale yellow crystalline, non-hygroscopic solid. Cannabidiol is practically insoluble in aqueous media irrespective of pH but freely soluble in some organic solvents, including ethanol, and in oils such as sesame oil. Both ethanol and sesame oil are included in the formulation. It is not photosensitive.

Cannabidiol exhibits stereoisomerism due to the presence of 2 chiral centres. These are introduced specifically within the biosynthetic pathway and are not susceptible to epimerisation during downstream processing.

Manufacture, characterisation and process controls

Cannabidiol is synthesized in a single synthetic step from the milled botanical raw material (milled BRM) which is considered to be the starting material. Four different sites are involved in the production of the active substance.

Cannabis plants produce various different cannabinoids and other organic compounds. The proposed manufacturing process for the active substance leads to isolation of CBD from the other cannabinoids and various other plant related materials.

The starting material, milled BRM, contains cannabinoids present in the leaf and flower of one specific chemotype (3 genotypes) of the plant species, *Cannabis sativa* L. Only the female plants are used. The plants used for the production of the BRM are propagated from cuttings and cultivated in glasshouses under the controlled conditions in accordance with WHO guidelines on Good Agricultural and Collection Practices (GACP). The method of growing, harvesting and primary processing of the plant material has been well described. The decarboxylated BRM is then extracted. The crude extract undergoes winterization to remove plant waxes and other impurities. Pure CBD is crystallized from this refined extract. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Suitable specifications for milled BRM have been provided. In addition, the production of the milled BRM has been described, including controls on growth medium (controls for pesticides and heavy metals), and the quality of water for irrigation (potable or reservoir water is used exclusively). The milled BRM is produced in compliance with GACP.

The initial process was based on extensive prior knowledge gained during commercialisation of a related product. The current process has been optimised during development with improvements to the extraction step, and final crystallisation.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double clear LDPE bags, sealed and stored within HDPE drums. The LDPE bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC), assay (CBD content by HPLC), impurities (HPLC), residual solvents (GC), water content (KF), and residue on ignition (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set, also considering the ability of process to purge them. Other impurities were discussed, including other organic constituents from cannabis, pesticides, elemental impurities, microbial purity, aflatoxins, and residual solvents. The controls are deemed to be sufficient based on the data provided.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data from 104 batches of the active substance were provided, including 29 production scale batches made using the commercial process and batches recrystallized at the commercial recrystallization sites. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 6 production scale batches of active substance (3 from each commercial site) from stored in the intended commercial package for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 12 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The parameters tested are the same as for release. In addition, supportive data on 3 pilot batches from one of the two proposed sites were provided, which were also tested for microbial quality, aflatoxins, melting point and specific optical rotation using compendial methods. No changes were seen to any of the measured parameters under either conditions, and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. The results indicate that CBD is not photosensitive.

Forced degradation studies were carried out under acidic, basic, oxidative, photolytic and thermal conditions. CBD is very stable, and significant degradation was only observed under thermal conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months below 30 ^{o}C in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a multi-dose 100 mg/ml oral solution of CBD dissolved in a mixture of sesame oil and anhydrous ethanol, with sucralose as sweetener and with strawberry flavouring. The product comes in an amber glass bottle with tamper-evident child resistant screw cap. Two graduated 5 ml syringes and two graduated 1 ml syringes are provided for accurate dosing across the posology, along with bottle adaptors for the different syringe sizes, all of which are CE marked.

The product is indicated for chronic diseases for patients aged 2 years old and above, based on body weight. Therefore, a dosage form was sought which allows flexibility in terms of posology and allows easy dosing to paediatric patients. The choice of an oral solution in a multi-dose container, with an administration device able to accurately dose across the posology range fulfils these requirements.

The active substance is practically insoluble in aqueous media, but sufficiently soluble in the proposed commercial vehicle, i.e. a mixture of sesame oil and ethanol.

Palatability of the product has been discussed and justified – sucralose was chosen from an array of sweeteners given its high sweetness intensity and stability in the vehicle at the required concentration. The strawberry flavour is added to further improve palatability. Ethanol is added to ensure that the sweetener, is dissolved in the vehicle. For safety reasons, the content of ethanol was initially questioned, especially as the product is indicated for paediatric use. However, this was justified and reference is made to the clinical safety report addressing this issue. The qualitative/semi-quantitative composition of strawberry flavour was provided to the regulatory authorities, and components were evaluated with respect to safety.

Only benzyl alcohol and propylene glycol are listed in the annex to the EU COM labelling guideline, and the daily dose of propylene glycol is below the threshold. Since benzyl alcohol is a component of the flavouring and has known physiological effects, its quantity is listed in section 2 of the SmPC, along with sesame oil and anhydrous ethanol.

Preservative efficacy testing was performed on the finished product to ensure its antimicrobial effectiveness (Ph. Eur. 5.1.3, Efficacy of Antimicrobial Preservation for oral preparations; USP „51" Antimicrobial Effectiveness) and results comply with acceptance criteria thus the effectiveness of the antimicrobial activity has been sufficiently proven.

The stability of sesame oil was discussed in terms of peroxide value given the risk of rancidity. It has been demonstrated that the precautions to prevent oxygen ingress during manufacture and filling, and the commercial packaging and bottle adaptors provide sufficient protection and no anti-oxidant is needed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The formulation used during clinical studies is the same as that intended for marketing.

Various development data for the packaging components were presented, including a study on extractables and leachables. Toxicological evaluation of the compounds identified was conducted and it has been demonstrated that there is no risk to patients from extractables or leachables. Inclusion of two different syringes in the same pack could be questioned, because of a potential risk of medication errors. On the other hand, the 5 ml syringe cannot be used for the small volume required for paediatric patients due to the presence of a dead space volume 0.15 ml, which could lead to significant overdosing. Therefore, the inclusion of two different syringe sizes in the same pack was accepted, because the need for both has been justified, and because of clear instructions given in the SmPC and packet leaflet. Ph. Eur. 2.9.27 (uniformity of mass of delivered doses for multi-dose containers) was applied to demonstrate reliable dosing accuracy of the syringes. The syringes are reusable and the cleaning procedure is described in the package leaflet.

The manufacturing process is fairly simple and has only had minor modification throughout development and scale up. A risk assessment was conducted in line with ICH Q9 methodology, addressing factors relating to the active substance, process, excipients, container closure system, environment, and analytical aspects and no critical material attributes were identified.

The primary packaging is an amber type III glass bottle, with PP screw cap and LDPE tamper-evident seal. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process, along with the IPCs, consists of six main steps: mixing of some excipients; addition of CBD; mixing with sesame oil followed by filtration under nitrogen blanket; filling and capping; labelling; assembly and secondary packaging. The process is considered to be a standard manufacturing process.

The process has not been formally validated but a protocol has been included and the process will be validated on three consecutive production scale batches of finished product prior to marketing. It has been demonstrated through studies to date that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The IPCs are adequate for this type of

manufacturing process and pharmaceutical form. The lack of an IPC for CBD dissolution has been justified on the basis of experience with the process and the fact that no solid has been seen to date.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance of solution, colour of solution, identification (IR, UPLC), assay (UPLC), degradants (UPLC), ethanol content (GC), water content (KF), uniformity of delivered dose (Ph. Eur.), microbiological quality (Ph. Eur.) and peroxide value (Ph. Eur.).

Overall, the specification is set in agreement with ICH Q6A and the requirements in the European Pharmacopoeia for the pharmaceutical form. Impurities are tested in the active substance, and only degradation products of CBD are tested in the finished product, which is fully acceptable. The three degradation products have been qualified and are not genotoxic. A test for peroxide value was added to the specification at the request of CHMP, with different release and shelf-life limits, to ensure that the oral solution does not become rancid during storage and in-use.

The absence of tests for viscosity, density and extractables/leachables has been adequately justified by the applicant.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The major source of contamination was likely to be the compost used to grow the cannabis plants. Heavy metals are limited in the specification for compost in accordance with the soil association organic standards, as well as in dried BRM (stage before the milled BRM starting material), which complies with compendial requirements for elemental impurities in herbal drugs. No test is deemed necessary in the finished product.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay degradation products testing has been presented.

Batch analysis results for 129 bathes are presented, including batches used in the clinical studies and three recent production scale batches. Since the process has not changed throughout development but the specification has evolved, all batches met with the specification in place at the time of testing. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH), up to 12 months under intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Data from a further 3 batches manufactured by an earlier process (which is considered essentially equivalent) and stored in slightly smaller (100 ml vs 105 ml) bottles was also provided, covering up to 24 months under long term and intermediate conditions. These supportive batches are considered to be representative and have been taken into account in the assessment.

Samples were tested for appearance of solution and packaging, CBD content, degradants, density, peroxide value, acid value and microbiological quality. In addition, the primary batches were tested for colour of solution, and water and ethanol content. The analytical procedures used are stability indicating. There was a small increase in total degradants over time, well within specification and the peroxide value increased slightly. All other parameters remained constant with no significant trends observed. In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend in on-going stability studies should be reported to the Rapporteur and EMA.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, confirming that the product is not light sensitive.

A temperature cycling study was conducted to evaluate the impact of any temperature excursions during shipping and storage, including freezing. The changes in temperature had no significant impact on the quality of the product.

An in-use study was conducted on three batches of product, with testing after 4, 8 and 12 weeks. Bottles were stored both vertically and horizontally and opened and sampled daily. There was a slight increase in impurities and peroxide value, reflecting oxygen ingress and reaction with the sesame oil. However, the values remained well below the shelf-life specification. However, the product posology requires twice-daily dosing, so a further in-use study was instigated at the request of CHMP. At the time of opinion, 4 weeks' data was available, with impurity levels and peroxide value more or less in line with the same time-point from the original study. The in-use shelf-life has provisionally been set at 8 weeks.

Based on available stability data, the proposed shelf-life of 24 months and in-use shelf-life of 8 weeks, both without special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It has been demonstrated that the bottle and syringes are suitable for routine use and that doses can be accurately administered. The formulation is sufficiently palatable for paediatric patients.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC and package leaflet. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical data package contains an extensive number of non-clinical studies. The non-clinical testing strategy for purified CBD was in general undertaken in accordance with the guidance documents from the International Council on Harmonisation (ICH) and the Food and Drug Administration (FDA) pertaining to non-clinical safety. Non-clinical studies were conducted with CBD as CBD-OS, purified CBD, or CBD Botanical Drug Substance (BDS).

Non-clinical scientific advices have been received from CHMP, BfArM Germany and Danish Medicines Agency. Recommendations received were followed to some extent.

No novel excipients are used.

Cannabidiol (CBD) molecule contains four stereoisomers but only the (–)-trans isomer occurs naturally or can be isolated as purified CBD. Providing that specific stereoisomeric properties may also influence the efficacy/safety of the molecule, all non-clinical studies were conducted with botanically-derived CBD. Synthetic CBD was not used in any reported non-clinical study.

Based on a MHRA Good Laboratory Practice (GLP) inspection that took place on 4-5 July 2017, a notification of 10 toxicology multisite studies (GWTX: 1578, 1524, 1408, 1454, 1429, 1551, 1412, 1503, 1413, 1579), where the bioanalytical and toxicokinetic phase data is not valid and certain bioanalytical and toxicokinetic data were not in compliance with GLP has been received. The applicant has since made considerable efforts, including initiation of a long range of new studies, to mitigate the consequences of GLP deficiencies in the majority of pivotal toxicity studies, which overall is considered adequate.

All 10 toxicology studies mentioned above are pivotal and represent almost the full data package for cannabidiol. Major deficiencies represent incorrect statements where GLP compliance was being made for study phases when the validation work to support the study activities was not completed. For example, in bioanalytical phases various aspects of the method validation, such as cross interference, long term and some short-term sample storage stability was still on going and incomplete at the time the statements of GLP compliance were made. Furthermore, there were several examples within each compliance statement where the Principal Investigator had stated “that data should be treated with caution”. It is acknowledged that on the basis of the inspection, affected studies cannot be accepted as GLP compliant. Considering that this impacts a large number of pivotal repeat-dose toxicity studies, EFD studies, most critical juvenile toxicity and abuse potential studies, an in-depth assessment has been conducted on bioanalytical reports of these studies (please see section pharmacokinetics) in order to evaluate the scientific value of the non-GLP data.

It can be concluded that the exposure data for CBD seems to be reliable, while exposure of CBD metabolites (including active metabolite 7-OH-CBD and abundant human metabolite 7-COOH-CBD) may have been over- or underestimated. Despite the fact that accuracy of measured values for metabolites remains doubtful due to bioanalytical (GLP) issues, the results from the ten affected toxicokinetic studies are not totally erroneous and give us knowledge about the toxicokinetic profile in rat, mouse and dog into some extent.

Based on the data from study GWTX18001 in juvenile rats, it is evident that original values for metabolite 7-COOH-CBD were overestimated resulting in almost no safety margins (from 3.2 to 1.4, combined for female and male rats) at the amended NOAEL of 150 mg/kg. CBD values were overestimated too, however still resulting in high safety margins ~ 28-fold. There is almost no change

in values for 7-OH-CBD (from 2.75 to 2.4-fold) comparing Cmax exposures from paediatric study GWEP1332.

During the communication with MHRA regarding GLP non-compliance studies, an independent review initiated by the Sponsor was indicated. The external review report was submitted. The review summarized the facts and bioanalytical issues. Conclusions provided in reports (CBD – metabolites) for all affected studies are in line with the initial non-clinical assessment.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamic studies demonstrated antiepileptiform and anticonvulsant activities in *in vitro* and *in vivo* models. In addition, these studies investigated the anticonvulsant mechanism of action of CBD. The observed anticonvulsant activity was achieved in the absence of motor system suppression that was observed with comparator antiepileptic drugs (AED) in the same assays.

Anticonvulsant effect

As CBD is intended for adjunctive therapy, i.e. co-administered with conventional AEDs, studies investigating the effect of CBD co-administered with AEDs were conducted.

The Applicant demonstrated antiepileptiform activity in an *in vitro* model with rat hippocampal slice preparations at 10 µM concentration (3.1 µg/ml). This effect was comparable to those obtained with clinically used AEDs at 100-500 µM (Hill et al, 2010). The applicant investigated the anticonvulsant effect of CBD in several *in vivo* models of seizures (see table 1). Exposure was estimated using the submitted PK studies in mice and rats using i.p. as the route of administration and a similar vehicle. The recommended pharmacological active dose of 20 mg/kg in humans produced mean plasma concentrations in the range of 290-330 ng/ml in children and adults, respectively. Mice seem to be less sensitive to the anticonvulsant effects of CBD. However, the rat showed effects at lower doses in two out of three models (down to 1 mg/kg), all though the highest dose of 100 mg/kg gave the most convincing effects. CBD had a significant effect on welfare scores and survivability after subcutaneous administration (100 mg/kg) in a model of Dravet syndrome (Scn1a-/- mice) as compared to placebo or clobazam (active comparator). Relevant pharmacological effects of CBD were adequately demonstrated, see Overview table below.

Table 1 Overview of the primary pharmacology studies of CBD in seizure animal models and estimated exposure based on submitted PK studies

Study type	End-point	Dose	Exposure (assuming linear kinetics from dose in PK study)	Reference / Study No.
Primary Pharmacology				
In vitro hippocampal slices from rat	Prevention of LPI induced GPR55-mediated increase in mEPSCs frequency	NA	10 µM = 3.1 µg/mL	GWORI1546
Maximal electroshock in mice	Anticonvulsant effect 30 min after CBD adm.	200 mg/kg i.p.	PK: 120 mg/kg i.p. 30 min, mean C_p = 4.7 µg/mL 200 mg/kg, C_p ~ 7.9 µg/mL ~ 25 µM	GWOR0982 (Pharm) GWOR08263 (PK)
Audiogenic seizure model in mice	Anticonvulsant effect 60 min after CBD adm.	100 and 200 mg/kg i.p.	PK: 120 mg/kg i.p. 60 min, mean C_p = 10.5 µg/mL 100 mg/kg, C_p ~ 8.8 µg/mL ~ 28 µM	GWOR11135 (Pharm) GWOR08263 (PK)
PTZ-induced general seizure in rat	Mortality, severity 60 min after CBD adm.	100 mg/kg i.p.	PK: 120 mg/kg i.p. 60 min, mean C_p = 1.6 µg/mL 100 mg/kg, C_p ~ 1.3 µg/mL ~ 4.2 µM	GWOR08168, GWOR08169 (Pharm) GWOR08212 (PK)
Pilocarpine-induced temporal lobe seizure in rat	Anticonvulsant effect 60 min after CBD adm.	1-100 mg/kg i.p.	PK: 120 mg/kg i.p. 60 min, mean C_p = 1.6 µg/mL 100 mg/kg, C_p ~ 1.3 µg/mL ~ 4.2 µM	GWOR08180 (Pharm) GWOR08212 (PK)
Penicillin-induced partial seizure in rat	Anticonvulsant effect 60 min after CBD adm.	1-100 mg/kg i.p.	PK: 120 mg/kg i.p. 60 min, mean C_p = 1.6 µg/mL 100 mg/kg, C_p ~ 1.3 µg/mL ~ 4.2 µM	GWOR08192 (Pharm) GWOR08212 (PK)
Genetically altered mouse model of Dravet syndrome (Nav1.1 knockout on a C129S background)	CBD significantly prolonged survival of Scn1a-/- mice compared to vehicle (P=0.006) or clobazam (P=0.0004).	100 mg/kg s.c. b.i.d. from PND8 until PND25	NA	NA

Mechanism of action

Available literature studies on the mechanism of action of CBD in epilepsy was summarised along with the applicant's proprietary studies. Currently there is an understanding that CBD can elicit its effect by influencing:

- the G-protein coupled receptor GPR55,

CBD might be acting as a GPR55 antagonist with an IC_{50} of 0.5 µM *in vitro*. CBD was shown to be able to antagonize the human GPR55 receptor, as described by inhibition of agonist L-α-lysophosphatidylinositol-stimulated extracellular signal-regulated kinase-1/2 phosphorylation at 1 µM (GWOR1059). CBD was shown to prevent the LPI (GPR55 endogenous ligand) induced GPR55-receptor mediated increase in mEPSCs frequency in hippocampal slice preparations at a concentration of 10 µM. No dose-response studies were presented (GWORI1546). GPR55 mRNA was found in a number of tissues with the highest mRNA levels detected in the adrenals, parts of the gastrointestinal tract, as well as in the CNS. As seen with CB1 receptors, a broad distribution of GPR55 mRNA is found in brain tissue, however the levels were significantly lower than those for CB1.

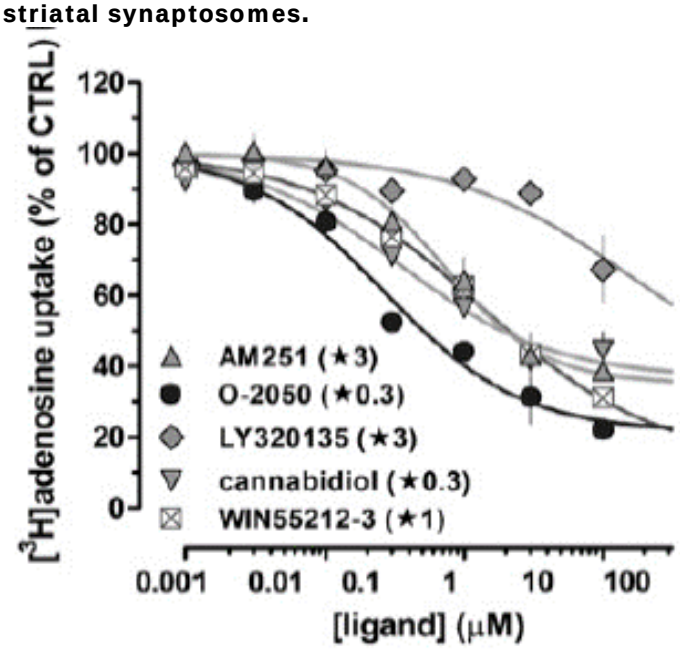
- the transient receptor channel TRPV1

In search for molecular targets, data from using the electrophysiological patch clamp technique revealed that CBD activated, in a concentration-dependent manner, the non-selective cation current mediated by TRPV1, TRPV2 and TRPA1 channels transiently expressed in human embryonic kidney 293 (HEK-293) cells. Moreover, using this approach it was also found that TRPV1, TRPV2 and TRPA1 channels became desensitized upon repeated or prolonged exposure to either CBD or CBDV (GWOR1209). This was substantiated by referring to the study by Petrocellis et al, 2011, showing CBD to desensitize TRPV1 channels for the capsaicin response with an IC_{50} of 0.6 µM (0.2 µg/mL).

- the extracellular levels of adenosine.

CBD inhibits adenosine uptake into macrophages and microglia by the equilibrative nucleoside transporter. CBD also inhibits synaptic uptake of adenosine in rodent striatal neurons, (see Figure 2). Taken together, it is likely that CBD acts through modulation of adenosine-mediated signalling, probably act as a re-uptake inhibitor.

Figure 2 Cannabinoid receptor antagonists/inverse agonists on the uptake of [3H]adenosine in rat striatal synaptosomes.



"Star" indicate the lowest concentration to give statistical significance (0.3 µM for CBD)

The plausible mechanisms of action by CBD in epilepsy was adequately summarised by the Applicant referring to both literature and proprietary data.

Secondary pharmacodynamic studies

Off-target screening studies

The secondary pharmacodynamic profile of CBD was evaluated in a series of *in vitro* radioligand binding and functional screening assays. Additional *in vitro* evaluations were conducted to assess effects within the endocannabinoid system with a specific focus on cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2), endocannabinoid uptake, and inhibition of endocannabinoid metabolic enzymes. Modulation of synaptosomal monoamine transporters, voltage-gated sodium channels (Nav), and cyclo-oxygenase (COX) 1 and COX 2 were also assessed.

It was shown that CBD and 7-OH-CBD are low potency uptake inhibitors of dopamine (DA), norepinephrine (NE), or 5-hydroxytryptamine (5-HT), whereas 7-COOH-CBD does not inhibit monoamine uptake. The applicant concluded that CBD acts as a low potency sodium channel blocker, but this is unlikely to represent a principal and functional anticonvulsant mechanism of action for CBD. This is consistent with recent clinical survey-based investigation of the effect of CBD on intractable paediatric epilepsies; CBD was effective in treating patients with Dravet syndrome, an epilepsy that does not respond to sodium channel blockers. CBD only inhibited COX-1 and COX-2 and endocannabinoid metabolic enzymes at supra-pharmacological concentrations.

CBD was shown to inhibit specific binding of radioligands to several targets to more than 50% at concentration tested (10 µM). For most of these targets, IC_{50} and K_i on binding were then evaluated. Of these targets, the monoamine transporters, the voltage gated sodium channels were further

evaluated as mentioned above. CBD is not a very potent CNS active compound, since plasma concentrations of approximately 2.7 µM should be attained, before significant effect in animal models and clinical studies were shown to be significantly different from vehicle/placebo groups. Hence, it cannot be excluded that some of the targets at which CBD was shown to inhibit radio-ligand binding at low micromolar concentrations might be relevant as targets for CBD in one or more indications.

Abuse potential

The legal status of Epidiolex under the US federal Controlled Substance Act, is currently under schedule V, the least restrictive schedule, defined as those with a proven medical use and low potential for abuse.

CBD has activity within CNS. As a part of the early development, the interaction to known targets involved in drug dependence (e.g. opioid receptors, 5- HT and dopamine transporters and receptors, NMDA, GABA, nicotinic acetylcholine and cannabinoid receptors) were part of the performed screening tests in line with the GL recommendation (EMEA/CHMP/SWP/94227/2004). CBD does not interact with CB receptors on the clinically meaningful concentrations. There was an interaction with opioid receptors (Opioid µ, κ, δ), 5-HT and dopamine transporters and receptors. In functional tests, CBD failed to show any effect on opioid receptors (KOP, MOP) and dopamine receptor (D1). Antagonistic effect was observed on opioid receptor (DOP) and serotonin receptors 5HT2A and 5-HT2B in *in vitro* assay GWTX1562.

The affinity of CBD and its active metabolites were assessed by radioligand binding studies across a panel of 7-transmembrane receptors, ion channels and neurotransmitter transporters. The focus was put on dopamine, nor-epinephrine, 5-HT, GABA, acetylcholine, opioid, glutamate and endocannabinoid systems. If inhibition constant (Ki) was detected below the concentration of 10 µM, the nature of the interaction was further examined – e.g. antagonistic or agonistic effect.

Neither CBD nor its metabolites 7-OH-CBD or 7-COOH-CBD are were agonists or antagonists of cannabinoid receptors. Only antagonistic effect of CBD was observed at 5-HT_{2A} and 5-HT_{2B} receptors, therefore, no adverse effects accompanying the agonists of 5-HT receptors are expected. Similarly, antagonist effect only was observed on δ2 opioid receptor and OX1, M3 receptors for CBD or 7--OH--CBD. No abuse potential is expected from these interactions. No effects were observed for 7--COOH--CBD in functional studies.

As part of the Tetrad Test in NMRI mice, mice were dosed at 0, 1, 10, 50 or 100 mg/kg CBD i.p.. CBD showed decreased the number of rears and decreased rectal temperature of by 5 %. 6-OH-CBD showed no significant effects in the Tetrad test. At 50 and 100 mg/kg 7-OH-CBD showed significantly increased latency to remove forelimbs in the Bar Test (10.1s, $P < 0.05$ and 14.7 s, $P < 0.001$ as compared with vehicle controls) and it decreased the rectal temperature (-1.3 °C and -1.5 °C respectively, $P < 0.05$). The decreased rears for CBD and latency to remove forelimbs for 7-OH-CBD could be linked to side effects of somnolence and fatigue, as mentioned in SmPC.

Safety pharmacology programme

CNS

Potential effects of CBD as CBD BDS on the central nervous system were evaluated on Locomotor Activity and Muscle Strength in Mice and on Locomotor Activity in Rats. In general CBD produced decreased locomotor activity to a slight degree and had no effect on muscle strength.

Cardiovascular system

The effects of CBD as CBD BDS on the cardiovascular system were investigated in *in vitro* studies in HEK-293 cells stably transfected with human ether-à-go-go-related gene (hERG), rabbit isolated cardiac Purkinje fibres, and in an *in vivo* cross-over study in conscious, telemetered Beagle dogs.

In the *in vitro* study in HEK-293 cells, CBD was shown to inhibit hERG tail current at pharmacological relevant concentrations with No Observed Effect Level (NOEL) considered to be the nominal concentration of 150 ng/ml CBD (achieved concentration of 43 ng/ml CBD) as CBD BDS. The achieved concentration in the test chamber is below pharmacological relevant plasma concentrations. This finding was not confirmed by the study in rabbit isolated cardiac Purkinje fibres as no effects were observed in this study. However, due to adsorption in testing chamber, only low concentrations of CBD could be achieved. The data indicated a free plasma NOEL of 22 ng CBD/mL (as CBD BDS) in this test system, which is far below pharmacological relevant plasma concentrations. It should be noted that the clinical QT trial, with documented exposure above pharmacological relevance, showed a lack of effect of CBD-OS on cardiac conduction. Hence, no further non-clinical testing of cardiovascular endpoints are warranted.

The study in four conscious beagle dogs surgically instrumented to measure blood pressure, heart rate, and Lead II ECG parameters showed only benign and small effects of CBD p.o. administration. Each dog received an oral (gavage) dose of 0, 10, 50, and 100 mg/kg CBD as CBD BDS in a Latin square design with an interval of at least 6 days between doses (GWOR10111). Following administration of CBD BDS at dose levels of 50 and 100 mg/kg CBD, the applicant concluded that there were biologically significant decreases in heart rate. A statistically significant dose related decrease ($P<0.01$) in heart rate at 4 hours post dose compared with vehicle treated animals. There was also a statistically significant increase in systolic blood pressure ($P<0.05$) at 5 hours post-dose in animals dosed with 100 mg/kg CBD BDS, along with small apparent dose related increases in systolic blood pressure, but these were not thought to be of biological significance. Statistical analysis also suggested dose-related increases in RR-interval, RH-interval, QRS and QT-interval as well as a statistically significant increase in RR-interval for animals dosed with 100 mg/kg CBD BDS at 4 hours post dose. However, these were also not thought to be of biological significance.

Based upon this information, the NOEL was considered to be 10 mg/kg/day CBD, as CBD BDS. This is supported.

Respiratory safety

Effects on respiratory parameters after oral administration of CBD as CBD-BDS in freely moving conscious rats using whole body plethysmography (0, 10, 50, or 100 mg/kg) was assessed in study GWOR10110. CBD showed no biologically significant effects on respiratory parameters in conscious rats evaluated using whole body plethysmography. The NOEL was 100 mg/kg. However, the time point (30 min) selected for exposure determination in the respiratory safety study in rats was suboptimal. Nonetheless, it is acknowledged that exposure may have been at or above clinically relevant concentrations during the 6 hours assessment period.

Pharmacodynamic drug interactions

The Applicant has not conducted nonclinical studies to specifically evaluate pharmacodynamic drug interactions with CBD. Pharmacodynamic drug interactions of CBD with concomitantly dosed AED were evaluated in clinical studies. This is acceptable.

2.3.3. Pharmacokinetics

The Applicant has performed a battery of absorption, distribution, metabolism and excretion (ADME) studies. Only the data pertaining to CBD and CBD botanical drug substance (BDS) are presented.

Methods of Analysis

The Applicant claimed that the analytical methods were developed and validated for CBD, metabolites and relevant impurities requiring toxicological qualification.

However, a GLP inspection by MHRA performed in July 2017 and a follow up inspection in October 2017 has highlighted inadequacies with respect to the validation of bioanalysis methods used for several of the pivotal studies supporting this MAA.

The Applicant has sponsored an ambitious effort into the bioanalysis of CBD, metabolites and related impurities. Five bioanalytical laboratories were involved in the task and forty bioanalytical validation reports were submitted. Most methods involved a multitude of analytes – up to 7 in some of the methods. Both GC-MS and LC-MS were used for detection and different extraction methods were also used.

Due to extent of the deficiency, bioanalytical phase of affected studies was assessed in-depth to reconsider the scientific value of the data provided in the overall package. A Major Objection (MO) was raised to address the identified limitations in bioanalytical data from pivotal toxicological studies and to obtain a bridge with GLP compliant studies. The applicant made considerable efforts to mitigate the consequences.

A new toxicokinetic study was initiated during the assessment period of the Epidyolex dossier. This includes a repeat of the toxicokinetic cohort of GWTX1408 (10-week juvenile toxicology study of Purified CBD in rat). The final study report has been submitted (GWTX18001). Furthermore, a mouse carcinogenicity study (GWTX1504) with CBD-OS (300 mg/kg/day) commenced in January 2018. This study includes a toxicokinetic cohort wherein exposure on Day 1, Week 13 and Week 26 will be evaluated. Analysis will include CBD, plus its metabolites. Finally, a 13-week (oral gavage) repeat dose study (GWTX18002) commenced dosing in June 2018 and will report in Q2 2019. The applicant is asked to submit these studies when they are finalised.

The CBD-metabolite 7-COOH-CBD was shown to provide human exposure 50 times higher than the parent compound CBD and nonclinical studies in adult animals failed to provide safety margins for this metabolite. The applicant argues that for some studies, the reported data for metabolites was deemed non-compliant due to an anticipated under-representation of exposure. The degree of bias is estimated in the range of 30-50% from the actual value based on comparison of dose-response data with accompanied exposures across studies in the independent review. While it is agreed with the applicant that cross-comparison with the other studies in same species and method of administration is not ideal, the rough estimate of the bias could be done. For safety margin calculations, the applicant adjusted the exposure for 20 mg/kg dose for 24 hours based on the clinical study GWEP1544. No details of data adjustment are provided however it is evident that plasma concentrations correspond to exposures after fasted state. Considering that exposures were 4-5 times higher for AUC and Cmax, respectively, the provided calculations of fold safety margins are even lower. Exposure data from GWTX1454 (embryo-foetal rat) study are considered valid for CBD, 6-OH-CBD, 7-COOH-CBD, THC, 11-OH-THC and 11-COOH-THC. For CBD significant safety margins were reached and again almost no or small margins are reached for CBD metabolites.

The applicant proposes to provide the updated calculation of safety margins intended as a bridge with GLP compliant studies along with the final study reports for the studies GWTX 1504, and 18002 via post-authorization measure. This is acceptable.

Absorption

Pharmacokinetic studies in mouse and rat were conducted by the i.p. and p.o. route of administration. Intravenous administration was only performed in rat. Bioavailability in rats of CBD after i.p. and p.o. administration was calculated based on Cmax values, i.e. AUC was not calculated for i.v. administration, and hence the bioavailability is most likely underestimated. Exposure in mouse after p.o. administration was lower than for rat, i.e. AUC and t½ was not calculable after p.o. administration in mouse and AUC after i.p. was comparable to AUC obtained in rat after p.o. interestingly, the exposure of CBD in rat was higher after p.o. administration than after i.p. administration. The pharmacokinetic study in minipig in 10 different formulations was helpful in developing the optimal formulation for the paediatric population.

Pharmacokinetics (tmax and t½) in brain appeared to be similar to plasma for both mouse and rat, however brain to plasma ratio determined using AUC0-24h obtained after i.p. administration was higher in rat with ratios of 1868/3144 = 0.6 and 5406/1987 = 2.7 in mouse and rat, respectively.

Distribution

CBD was highly protein bound in rat, dog, and human plasma (> 94%), but less so in mouse and rabbit plasma (83% and 65%, respectively). 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD compounds showed high to very high binding in all species, returning values in the 98.8% to > 99.0% bound range.

CBD is highly lipid soluble and distributes widely into tissues with brown fat being the tissue with highest concentration after the liver. After 6 and 12 hours, the ratio of 14C-CBD ng equivalents in brown fat to white fat is 3080/879 = 3.5, 4690/1610 = 2.9, respectively. At 24 hours the radioactivity in brown and white fat is similar. The concentration of CBD in skin of non-pigmented and pigmented rats appeared to be similar and was not accumulating between the first dose and after 3 daily doses of 100 mg/kg.

After 24 hours still, a significant amount of CBD was found in liver indicating a high metabolism rate and distribution to adipose tissue. There was no significantly higher concentration in uveal tract or skin of the pigmented rats, thus CBD does not bind to melanin after single dosing. At 168 hours CBD was still quantified in epididymis and liver. No concentration was quantified 14 days post-dose.

Distribution to adrenal and thyroid gland as well as testis was detected. These were also the target organs of toxicity. In adrenals and thyroid, the effects were considered of adaptive nature and thus not assumed as relevant for safety concern. In liver centrilobular hepatocyte hypertrophy was not associated with significant inflammation or necrosis pathogenesis and thus the effect was also considered of adaptive nature. Final study report (GWTX18002) with characterization of potential risk due to hormonal disturbances will be provided via post-authorization measure.

Testes were target organs for toxicity in PPND study in rats. F1 progeny small testes resulted in impregnation of the mated dam. This was observed at dose-related fashion. Toxicity could be attributed to milk exposure of F1 pups as no effects on fertility were observed in rats directly dosed with CBD. Cause behind the direct/indirect effect remains to be elucidated (see toxicology section).

In consequent study (GWPP10159) with repeated dosing of 100 mg/kg p.o. of purified CBD a significant exposure to dorsal and abdominal skin in comparison to plasma was observed. The most significant accumulation occurred after repeated dosing in abdominal skin (36 825 ng/ml) where exposure was ~8.6 times higher than in plasma and 4 times higher than with single dosing. It is noted that in the study different excipients than the ones used during clinical trials were used. As it was demonstrated in former studies with minipigs, absorption is formulation dependent. Plasma exposure

corresponds to clinically relevant levels and thus accumulation of CBD in skin can be expected. In clinical studies rash was observed as common adverse event (SmPC).

Metabolism

The metabolism of CBD is very complex even after in vitro incubations, especially in hepatocytes. Hepatocyte incubations of CBD showed the highest extent of metabolism in human hepatocytes (93%) followed by dog (66%) and rat (44%) after 4 hours incubation. Several mono- and di-hydroxy metabolites were identified along with glucuronides of CBD and hydroxy-CBD. The major metabolite of CBD was CBD glucuronide in all three species, with human and dog hepatocytes also producing an acid metabolite of CBD (subsequently confirmed to be 7-COOH-CBD). The glucuronide of monohydroxy-CBD was only identified in human hepatocyte incubations. The confirmed 7-OH-CBD was only present in rat hepatocyte incubations.

CBD was shown to be primarily metabolized by CYP3A4 and CYP2C19 by using a standard battery of tests in human liver microsomes and microsomes from recombinant insect cells expressing human CYP450s. It was shown to be likely that CYP3A4 is responsible for the formation of 6-OH-CBD and COOH-CBD, and CYP2C19 for the formation of 7-OH-CBD.

UGT1A7, 1A9 and 2B7 was shown to catalyse the direct glucuronidation of CBD. 7-COOH-CBD in vitro showed the potential of inhibiting UGT 1A1, 1A4 and 1A6. A clinical drug-drug interaction study is being designed and is planned to be completed during 2020. The results will be provided post-authorisation Furthermore the PBPK model will be refined with new UGT IC50 data for 7-COOH-CBD.

7-OH-CBD is one of the major metabolites observed in human plasma with exposure more than half the exposure of CBD (GWEP1544). 7-OH-CBD could, at least to some extent, be the precursor of the major metabolite 7-COOH-CBD.

CBD is an inhibitor of CYP3A4 (IC50 = 1.42 µM) and 2B6, 2C8, 2C9 and 2C19 with IC50s in the range of 2.9 to 3.2 µM. The pharmacological relevant plasma concentration is approximately 1 µM, hence CBD possess the potential to inhibit all these enzymes at pharmacological relevant exposure. CBD was also shown to be a time-dependent inhibitor of CYP1A2 (to some extent) and of CYP3A4 (to large extent). These findings were followed up by performing drug-drug interaction studies of CBD with concomitantly administered AEDs, which are substrates of CYP3A4 and 2C19 in minipigs and human volunteers.

The potential of CBD to induce major CYP450 enzymes was assessed in human hepatocytes. Following exposure to CBD, no marked increases in CYP1A2, 2C9 or 3A4 activity were detected at concentrations up to 1 µM (314 ng/mL). CYP2C19 activity was not evaluated in this study. This enzyme is highly inducible and CBD is a potential substrate. Applicant investigated the potential of CBD for induction of CYP2C19 in human hepatocytes from 3 donors using mRNA expression as the endpoint. There appears to be some induction of CYP2C19. Donor 1 is the only donor not showing a tendency towards induction of CYP2C19. It appears that several measures of mRNA in donor 1 is only recorded in duplicate, whereas donor 2 and donor 3 are reported with triplicate measurements. Donor 3 shows clear signs of concentration dependent induction of CYP2C19. At 20µM both donor 2 and donor 3 show induction at similar level as rifampicin (the positive control). The increases in CYP2C19 mRNA expression levels in human hepatocytes was seen at 20 µM CBD. This is more than 50-fold above clinical exposure and therefore this is not considered clinically relevant.

Excretion

Excretion of radioactivity after p.o. administration of 14C-labelled CBD was studied in rat and dog. Apparently, CBD and its potential metabolites were mainly excreted via faeces, which is expected for a highly lipophilic small molecule. The biliary route was not investigated separately and no metabolite profiling in excreta was presented. The identification of 7-COOH-CBD metabolite as a major metabolite in rat, dog and human and the apparent extensive glucuronidation is leading to a concern for potentially reactive acyl-glucuronides. However, the presence of the acyl-glucuronide of 7-COOH-CBD in human plasma was investigated, and although following administration of CBD-OS an acyl-glucuronide presence of 7-COOH-CBD was observed, it is present only as a very small proportion (estimated <5%) of the total 7-COOH-CBD concentration.

Elimination route in humans is in question as no mass balance study has been conducted and no other data were discussed (see Clinical AR).

CBD is possibly highly excreted to milk. Due to toxicity effects on F1 progeny shown in PPND study in rats, CBD-OS should be contraindicated during breast-feeding.

Pharmacokinetic drug interactions

Drug-drug interaction studies between CBD and AEDs clobazam, stiripentol and sodium valproate were conducted in minipig. CYP3A4 and CYP2C19 are probably the enzyme responsible for clobazam N-desmethylation and therefore highly relevant for this kind of study. Stiripentol is an inhibitor of a broad range of CYPs including 2C19 and 3A4 and is in itself a substrate of CYP1A2, CYP2C19 and CYP3A4 (SPC for Diacomit). Valproic acid is a low potency inhibitor of CYP2C9. Valproate is a first line treatment for a broad range of seizures and a second line treatment for partial seizures and infantile spasms. CBD significantly increased the exposure (4.6 fold) of the major metabolite of clobazam, when administration of clobazam was preceded by 14 days dosing of CBD. This was also observed for clobazam itself; however, the effect was not significant (GWPP1439A; in minipigs, $p > 0.05$). The exposure of stiripentol was also increased when administered after 14 doses of CBD by a factor of 6.5 measured as AUC. No statistical differences were observed when evaluating drug-drug interactions with valproate. The finding of drug-drug interactions of CBD with clobazam was followed up by a clinical study (GWEP1428) and the non-clinical observations were confirmed in humans. When GWP42003-P was combined with stiripentol in healthy volunteers, there was a minor increase (1.55-fold increase in AUCtau), which was deemed unlikely to be clinically relevant (GWEP1543).

CBD and its three major metabolites were tested for interactions with a broad range of transporters. The main conclusions from these studies were that CBD and 6-OH-CBD were not interacting with any of the tested transporters at pharmacological relevant concentrations. The in vitro transporter inhibition study results suggested that there is a potential for 7-COOH-CBD to interact with BCRP, OATP1B3 and OAT3 in vivo, however, no further in vivo study has been conducted. Since among the likely concomitant medicines in the indicated patient population there is no known substrate for BCRP, OATP1B3 or OAT3 (except valproic acid, in which clinically relevant interaction was not observed) and since the results of *in vivo* interaction studies with other drugs are not easily extrapolated to further drugs, the *in vivo* interaction study is not deemed necessary. The Applicant´s justification that the clinically important interactions appear low is accepted. The SmPC contains satisfactory information about *in vitro* observations.

The risk of CBD interaction with P-gp was assessed by a calculated Ki. The estimated CBD Ki is lower than the calculated concentration, which indicates that in vivo CBD inhibition of intestinal P-gp-mediated efflux cannot be excluded. The applicant discussed that this result could be overestimated due to CBD solubility and stability limits in the assay matrix for study GWOR1251. However, it is impossible to accurately evaluate the impact of observed limits on the results and their clinical relevance. The final formulation of CBD-OS contains the excipients that provide enhanced solubility.

Due to the fact that the *in vivo* inhibition of intestinally expressed P-gp by CBD cannot be excluded, this information has been reflected in the SmPC.

2.3.4. Toxicology

An extensive toxicology package in mice, rats, rabbits, dogs, monkeys and juvenile rats and juvenile dogs with CBD-OS and/or purified CBD and/or CBD as BDS was provided. Yet, only factual description of study results with a brief discussion of toxicity findings was provided. Most of the studies included also toxicokinetic analysis of all major metabolites identified in human and these data were also neglected in discussions.

Except for three repeat-dose toxicity studies with CBD as BDS and carcinogenicity study in rats (with insufficient exposure to CBD via diet), all pivotal in vivo studies including all juvenile toxicity studies in rats and dogs, self-administration study in rats are considered as non-GLP compliant based on recent inspection conducted by MHRA. Major deficiencies were found on the bioanalytical phase of the studies but toxicology data are not affected. Reliability of the toxicokinetic results is questioned mostly on metabolites for CBD.

Moreover, for CBD, safety margins calculations of NOAELs from pivotal toxicology studies were compared to much lower plasma exposures than were quantified in clinical studies with corresponding posology (multiple dose, fed study).

Single dose toxicity

No single dose toxicity studies for CBD-OS, Purified CBD, or CBD as CBD BDS were conducted by the Applicant. CBD has low acute i.v. toxicity with lethal dose for 50% of the exposed population values of 50, 242, > 254, or 212 mg/kg in mice, rats, dogs, and monkeys, respectively.

This is considered acceptable as these studies have limited value in this context and literature studies are available.

Repeat dose toxicity

The toxicity profile of CBD-OS, formulated in ethanol, sucralose, strawberry flavouring, and sesame oil (clinical formulation), was evaluated in *GLP-compliant* repeated dose general toxicity studies in mice, rats, and dogs via oral administration. Studies were conducted for up to 13, 26, or 39 weeks for each species, respectively. Furthermore, rats and dogs were dosed for up to 28 days via i.v. administration.

It should be noted, that for all these pivotal toxicity studies, no GLP compliance was claimed for bioanalysis and this also includes the toxicokinetics phase. In order to be able to provide a meaningful assessment of the general toxicity studies submitted to date, the exposure of parent drug CBD was used, but exposure to all other analytes (metabolites and potential impurities) were not taken into account in this assessment, see above comment. The studies submitted currently can be viewed as supportive, and exposure measurements can be utilised, if the results from the new planned studies are within the same ranges. Furthermore, a number of repeat dose toxicity studies conducted with CBD BDS was also submitted along with a carcinogenicity study. These will only be briefly mentioned under section carcinogenicity, due to the difficulty in dissecting out effects of CBD with concomitant administration of other cannabinoids etc. THC was typically present and could therefore have elicited effects, when dosed at such high doses as used in toxicity studies (up to 225 mg/kg/day).

Table 2 Overview of pivotal toxicity studies conducted with CBD-OS (clinical formulation) or purified CBD

Study ID	Species/Sex/Number/Group	Dose/Route	Duration	NOEL/NOAEL (mg/kg/day)	Major findings
GWTX1503 BioA not GLP	CD-1 mice/12	100, 150, 300 mg/kg CBD-OS *p.o.*	13 weeks	300 mg/kg	Liver centrilobular hypertrophy in some animals given 100 or 150 mg/kg/day and all animals given 300 mg/kg/day
GWTX1412 BioA not GLP	Wistar/10 or 15	15, 50, 150 mg/kg CBD-OS *p.o.*	26 weeks + 4 weeks recovery	150 mg/kg	Liver centrilo-bular hyper-trophy at ≥ 50 mg/kg/day Doses ≥ 50 mg/kg/day CBD: Thyroid hypertrophy in both sexes and increased adrenocortical vacuolation in males. Pale foci in lungs, increase in pulmonary foamy macrophages
GWTX1413 BioA not GLP	Beagle dog/4-6	10, 50, 100 mg/kg CBD-OS *p.o.*	39 weeks + 4 weeks recovery	100 mg/kg/day	Hepatocyte hypertrophy at ≥ 10 mg/kg/day associated with increased liver weight
GWTX1578 BioA not GLP	Wistar/10	30, 35, 50 mg/kg purified CBD *i.v.* 10 min infusion	14 days	50 mg/kg/day	Post-dose observations were low gait, staggering, and underactivity in animals given ≥ 35 mg/kg/day; and tremors, slow deliberate movements, subdued/slug-gish at 50 mg/kg/day
GWTX1579 BioA not GLP	Beagle dog/3	3, 6, 9, 15 mg/kg purified CBD by i.v. bolus	14 days	15 mg/kg	Post-dose observations at all dose levels were associated with an "anaphylactoid-type" response to the vehicle. Diffuse hepatocellular vacuolation at ≥ 6 mg/kg/day

Mouse study GWTX1503, 13week oral toxicity

In mice, the target organs of toxicity in the 13-week study were the liver and the kidneys.

The key findings in this study were indicative of changes in the liver. Mean alanine amino transaminase/alanine aminotransferase (ALT) levels were higher than controls during Week 7 and 13 in males given ≥ 150 mg/kg/day (by approximately 65% and 40%, respectively) and during Week 7 for females given 150 or 300 mg/kg/day (by 259% or 83%, respectively). Microscopic centrilobular hepatocyte hypertrophy in all animals given 300 mg/kg/day and in some animals given 100 or 150 mg/kg/day was associated with increased liver weight in all groups and macroscopic enlargement at ≥ 150 mg/kg/day.

In conclusion, the no observed adverse effect level (NOAEL) was 300 mg/kg/day CBD-OS, corresponding to the respective Week 13 maximum measured plasma concentration (C_{max}) and area under the concentration-time curve calculated to the last observable concentration at time t ($AUC_{(0-t)}$) values of 9810 ng/mL and 44300 ng h/mL in males and 5770 ng/mL and 46400 ng·h/mL in females.

Several signs of liver toxicity were observed (increased ALT/AST, dose-dependent increased liver weight in all groups correlated with both macroscopic (mottled) and microscopic findings (hepatocyte hypertrophy) in higher dose-groups. At the low dose only minimal findings were observed, however increased liver weight was significant (p = 0.01). It should also be noted, in this context, that not all animals in the mid and low dose were subjected to microscopic evaluation and findings of mottled livers were present in mid dose. Based on macroscopic and microscopic evaluation, no adverse effects were deemed present as the impact on livers were ascribed to a reaction to large doses of a xenobiotic and not to an effect of CBD per se. Applicant has adequately explained the missing histopathological evaluation of livers in mid and low dose in this study. However, incidence of liver impact in patients treated with CBD is high and measures have been taken to follow up on a group of patients to assess the potential for chronic liver injury for up to 5 years as part of post approval requirements for the FDA. This is adequate.

Rat GWTX1412, 26-week oral toxicity study with 4-week recovery

In rats, the target organs for toxicities were liver, thyroid, and adrenals presented by change in organ weight.

Microscopically these were specified by liver centrilobular hypertrophy and thyroid follicular cell hypertrophy in both sexes along with increased adrenocortical vacuolation in males and minor ovarian interstitial cell hyperplasia in females. In liver, an organ enlargement was also associated with increased mean plasma ALT and alkaline phosphatase (ALP) activities at the highest dose tested. Effects in liver and thyroid were considered by Expert as non-adverse and representative of adaptive changes due to microsomal hepatic induction.

The applicant summarise the liver findings as follows: *The centrilobular hypertrophy in the liver of animals given ≥ 50 mg/kg/day, the main finding in this study, was associated with increased liver weight, macroscopic enlargement, and, in animals given 150 mg/kg/day, increases in ALP and ALT activities. Thyroid follicular hypertrophy in both sexes, correlated with increased thyroid weights and macroscopic enlargement in males, was considered an indirect effect of treatment due to its recognized relationship with liver hypertrophy*.

Group Mean Plasma Toxicokinetic Parameters for CBD (GWTX1412)

		Day 1			Week 13		
Dose mg/kg/day		C_{max} ng/mL	t_{max} hour	$AUC_{(0-t)}$ ng·h/mL	C_{max} ng/mL	t_{max} hour	$AUC_{(0-t)}$ ng·h/mL
15	M	388	2.0	1140	908	4.0	5370
	F	408	2.0	1380	1460	2.0	6110
50	M	2180	2.0	8750	4480	2.0	29900
	F	2380	2.0	11900	5590	2.0	36200
150	M	2570	4.0	29700	8710	4.0	65400
	F	2480	2.0	30200	7290	2.0	82800

Group Mean Plasma Toxicokinetic Parameters for CBD (GWTX1412)							
Dose mg/kg/day		C_{max} ng/mL	t_{max} hour	$AUC_{(0-t)}$ ng·h/mL	C_{max} ng/mL	t_{max} hour	$AUC_{(0-t)}$ ng·h/mL
		Week 20			Week 26		
15	M	1160	2.0	4510	1400	4.0	8700
	F	2230	2.0	5460	2070	2.0	10800
50	M	5580	4.0	26200	5240	2.0	36700
	F	6130	4.0	25500	3750	2.0	39000
150	M	8140	2.0	39600	6160	6.0	60000
	F	10400	2.0	36200	7530	4.0	67500

Levels of thyroid hormones, luteinizing hormone (LH) follicle stimulating hormone (FSH) and/or prolactin were not examined in the rodent studies and thus mode of action of the findings and their relevance to humans are not clear. The underlying cause of the adrenal gland toxicity was only commented by fact that adrenocortical vacuolation is also a recognized common phenomenon which occurs under a variety of conditions including the administration of a xenobiotic. However, these effects are also known for studies with drugs especially those that interfere with normal steroidogenesis in the adrenal cortex and/or perturb the hypothalamic-pituitary-adrenal hormonal axis.

Some further effects of hormonal dysregulation were observed across the studies with cannabidiol or impurities (structurally very similar to CBD) such as small testes with unsuccessful impregnation of the dam (PPND study in rats at the high dose), interstitial cell hyperplasia of ovary in rats (26-week study in rats with CBD-OS), or an increased incidence of the dioestrus/metoestrus phases of cycle. In addition, triiodothyronine (T3), T4 and thyroid-stimulating hormone (TSH) endpoints in this repeat dose study, was provided as draft results to address the underlying effects causing discrepancies in hormonal pathways. Dose-dependent decrease in T4 and increase in TSH has been noted mostly in male rats and in individual female rats. In general, rodents are more sensitive than humans to thyroid perturbation effects. It is however agreed with the applicant that monitoring for potential hormonal disturbance via clinical and pharmacovigilance activities should be initiated, if the final non-clinical and/or available clinical data demonstrates a cause for concern regarding endocrine parameters. Final study report (GWTX18002) with characterization of potential risk due to hormonal disturbances is awaited via post-authorization measure commitment.

Toxicity effects were observed in lungs with dose-related increase in incidence and severity of pulmonary foamy macrophages observed across studies in rat with cannabidiol. These of findings are deemed toxicologically insignificant and not relevant to humans. No associations to other pulmonary adverse effects in non-clinical or clinical studies have been detected.

39-Week Oral (Gavage) Toxicity with 4-Week Recovery in Dogs (GWTX1413)

Beagle dogs (4/sex/main groups) received CBD-OS at 0 (vehicle), 10, 50, or 100 mg/kg/day once daily for 39 weeks. Reversibility of changes was evaluated following a 4-week recovery phase (2/sex/control and high dose groups).

In dogs, the target organ for toxicity was liver with hepatocyte hypertrophy, macroscopic enlargement and increased liver weight. No increase in bilirubin, necrosis or significant inflammation and/or proliferation suggests that effects observed in rats and dogs might be reflections of adaptive changes due to microsomal hepatic induction. However, due to absence of hormonal examinations and some other effects of hormonal misbalance observed in the studies these effects need to be further substantiated via post-authorisation measure.

Genotoxicity

CBD, purified CBD and CBD as BDS were evaluated in a range of *in vitro* and *in vivo* standard genotoxicity assays. Only studies performed with purified CBD and CBS-OS are summarised.

Table 3 Overview of genotoxicity studies performed with purified CBD or CBD-OS

Type of test / study ID / GLP	Test system	Concentration range / Metabolising system / dose	Results Positive / negative / equivocal
Gene mutations in bacteria (GWOR0910/GLP)	Salmonella strains TA98, TA100, TA1535, TA1537, and TA102	1.6 – 320 µg purified CBD/plate +/- S9	Negative
Chromosomal aberrations *in vivo* (GWOR0903/GLP)	Rat, micronuclei in bone marrow	125, 250, 500 mg/kg p.o. CBD-OS	Negative
DNA damage *in vivo* (GWTX1510/GLP)	Rat Alkaline COMET Assay	125, 250, 500 mg/kg p.o. purified CBD	Negative

The genotoxic potential of CBD has been evaluated in a standard test battery of *in vitro* and *in vivo* assays according to ICH S2(R1). All tests concluded CBD to be negative for genotoxic potential.

A genotoxicity assessment of 7-COOH-CBD using non-GLP test material in an Ames Test (GWTX18016) was provided. Results from this study showed that 7-COOH-CBD did not induce mutation in 5 *Salmonella typhimurium* strains (TA98, TA100, TA102, TA1535 and TA1537) under the conditions selected for this study. However, test item output from the scaled-up manufacture will produce appropriately characterised material to conduct genotoxicity GLP studies planned with both 7-OH-CBD and 7-COOH-CBD. GLP genotoxicity studies are awaited via post-authorization measure commitment.

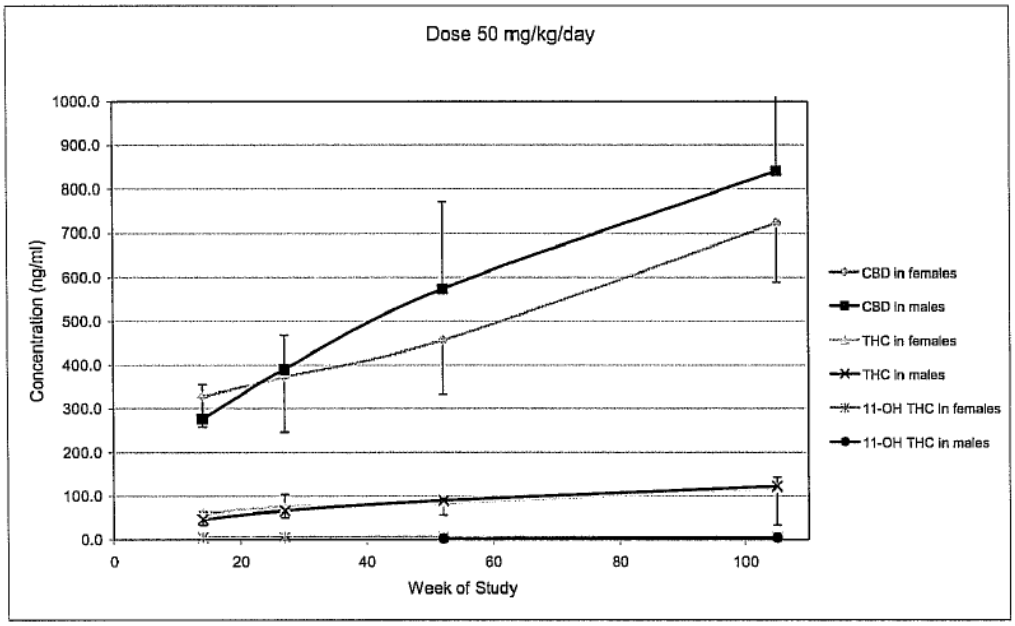
Carcinogenicity

A 104 weeks carcinogenicity study was conducted in rats with CBD as CBD BDS by the oral dietary route of administration at doses 5, 15, or 50 mg/kg/day. Overall, no concerns of tumour findings were found. Interestingly, at 50 mg/kg/day CBD there was a reduced incidence of tumours generally associated with hormonally-mediated neoplasia in aging animals. The clinical relevance of this finding is uncertain.

Exposure was adequate to provide safety margin to clinical exposure at the high dose, see Figure 3. However, was very low in comparison to clinically achievable exposures and standard safety margins for carcinogenicity studies.

What is remarkable for this study is the increase in exposure of CBD over time. This trend was also observed in the 26 weeks repeat dose toxicity study in rat, especially from week 20 to 26.

Figure 3 Mean data curve for the plasma samples taken 08:00. Dose 50 mg/kg/day of CBD



Some overlap with the liver findings in the repeat dose toxicity studies were observed, e.g. dose-related agonal vacuolation and centrilobular vacuolation. The low dose in this study (5 mg/kg/day) seem to be devoid of any significant findings in liver.

The carcinogenic potential of CBD has been adequately evaluated to be negative and the liver findings of the repeat dose toxicity studies was confirmed at lower doses in rat at life-time exposure.

In mice, carcinogenicity study (GWTX1504) with CBD-OS (300 mg/kg/day) commenced in January 2018. This study includes a toxicokinetic cohort wherein exposure on Day 1, Week 13 and Week 26 will be evaluated. Analysis will include CBD, plus its metabolites. Results of the study will be provided post-authorisation and reflected in SmPC as relevant.

Table 4 Insert from statistical report. List of non-neoplastic lesions

104 Week Oral (Dietary) Carcinogenicity Study in the Rat

[redacted]

List of non-neoplastic lesions for terminal kills
Organs examined routinely in all groups

		Sex x Group								
		Male				Female				
DOSE (MG/KG/DAY)		0	5	15	50	0	5	15	50	Trend
Liver: centrilobular vacuolation										
	n	2	1	0	1					
	N	37	34	41	39					
Liver: agonal vacuolation										
	n	3	7	19	15	0	0	0	1	
	N	37	34	41	39	35	26	40	34	
	KW P		N.S.	+++	++					++
	KWExP		N.S.	+++	++					
Liver: centrilobuilar hypertrophy										
	n	0	0	6	19	0	0	0	9	
	N	37	34	41	39	35	26	40	34	
	KW P		N.S.	+	+++					+++
	KWExP		N.S.	+	+++					
	KW P						N.S.	N.S.	++	+++
	KWExP						N.S.	N.S.	++	

Reproduction Toxicity

Pivotal fertility, embryo-foetal developmental, and prenatal/postnatal development toxicity studies were performed with Purified CBD that was formulated in sesame oil and given p.o. by gavage. Preliminary (DRF) embryo-foetal and prenatal/postnatal development toxicity studies in rats and rabbits were performed to enable the selection of suitable doses for the pivotal studies.

Table 5 Preliminary (DRF) embryo-foetal and prenatal/postnatal development toxicity studies in rats and rabbits

Study type/ Study ID / GLP	Species; Number/ group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg)
Male fertility GWTX1456/GLP	Wistar rat/20	75, 150, 250 mg/kg/day	2 weeks prior to pairing up to review of female pregnancy data	No effects on male reproductive organ weights	250 mg/kg/day
Female fertility GWTX1456/GLP	Wistar rat/20	75, 150, 250 mg/kg/day	2 weeks prior to pairing up to GD 6	No effect on female reproductive indices, female oestrus cycling or pregnancy parameters	250 mg/kg/day
Embryo-fœtal development GWTX1455/non-GLP	Wistar/6 DRF study	150, 250, 300 mg/kg/day	GD6 to 17	300 mg/kg/day: One dead rat, weight loss of 32% of controls. Increased pre-implantation loss at 300 mg/kg/day. No adverse effects at lower doses	F0: 250 mg/kg/day F1: 250 mg/kg/day
Embryo-fœtal development GWTX1454/GLP *Bioanalysis & TK: non-GLP*	Wistar/20	75, 150, 250 mg/kg/day	GD6 to 17	Complete litter loss of 2/20 dams at 250 mg/kg/day	F0: 150 mg/kg/day F1: 150 mg/kg/day
Embryo-fœtal development DRF GWTX1453/ Non-GLP	Rabbit/6	50, 80, 125 mg/kg/day	GD7 to 19	Body weight loss compared to controls	DRF study NA
Embryo-fœtal development DRF GWTX1452/ GLP	Rabbit/22	50, 80, 125 mg/kg/day	GD7 to 19	Unossified metacarpal, bulging eyes, and nonerupted incisors) were considered to be secondary to the reduced fetal weights at 125 mg/kg/day.	F0: 80 mg/kg/day F1: 80 mg/kg/day
Pre & postnatal development GWTX1532/GLP	Rat/22	75, 150, 250 mg/kg/day	GD6 to LD21	F1 males: Small testes F1 female: Reduced fertility indices	F0: 250 mg/kg/day F1: 75 mg/kg/day

Fertility and early embryonic development

In a fertility and early embryonic development toxicity study, Han Wistar rats (20/sex/group) were given 0, 75, 150, or 250 mg/kg/day for 2 weeks prior to pairing until the day prior to necropsy for males and up to gestation day (GD) 6 for females (GWTX1456). There were no treatment-related deaths and no adverse clinical or post-dosing observations. During the post-pairing phase, there was a treatment-related reduction in the overall body weight gain of males given ≥ 150 mg/kg/day. There were no treatment-related necropsy observations in either sex and no test article-related effects on male or female reproductive indices, male reproductive organ weights, female estrus cycling, or any caesarean-section parameters at doses up to 250 mg/kg/day Purified CBD, which was determined to be the NOAEL. Evaluation of CBD effects on male and female reproductive performance is considered adequate and it is agreed that no significant negative effects were observed in rat. A Safety margin of 60 fold were calculated for inclusion in the SmPC section 5.3 based on exposure measurements from the rat embryofetal study (GWTX1454) at 250 mg/kg/day dose level on Day GD17. Adjusted human $AUC_{(0-24h)}$ 2790 ng·h/ml was used for calculation.

Embryo-foetal development

Embryo-foetal development was evaluated in rat and rabbit. Rabbit seemed to be more sensitive to effects of CBD compared to rat. This was evident by the observed dose-dependent body weight loss compared to controls in rabbit. Embryo-foetal development in rat was insensitive to high CBD exposure (C_{max} up to 12800 ng/ml). The NOAEL for maternal toxicity was amended to 150mg/kg/day due to 100% loss of pregnancy in 2 dams at the high dose of 250 mg/kg/day. NOAEL for effects on embryo-foetal development in rabbit was 80 mg/kg/day. Foetal variations observed at 125 mg/kg/day CBD (e.g., unossified metacarpal, bulging eyes, and nonerupted incisors) were considered to be secondary to the reduced foetal weights. Maternal exposure at 80 mg/kg/day Purified CBD corresponded to GD 19 C_{max} and $AUC_{(0-t)}$ values of 220 ng/mL and 2030 ng·h/ml, respectively. C_{max} of this dose was lower than pharmacological relevant exposure in children and adults (approximately 290 ng/ml and 320 ng/ml, respectively). However, protein binding is lower in rabbit compared to rats and humans with 65% bound in rabbit and 95% and 94% in rat and humans, respectively. The non-existing safety margins for the rabbit study are reflected in SmPC section 5.3. and the rat NOAEL of 150 mg/kg/day is reflected to result in a safety margin of 50 fold.

Prenatal and postnatal development, including maternal function

The effects of CBD on pre- and postnatal development including maternal function were evaluated in rat. There were no Purified CBD- related clinical or post dosing observations for the maternal animals (F0). Endpoints in F1 generation included body weight, developmental landmarks including sexual development, learning and memory, fertility and macroscopic examination at necropsy. NOAEL was lower for F1 generation (75 mg/kg/day) than for the parental generation (250 mg/kg/day) due to small testes in males and reduced fertility index in females of F1 generation. Dosing of the maternal animals at MD and HD in PPND study in rats (GWTX1532) had a direct effect on progeny exposed to the drug via placenta prenatally or postnatally via milk. In F1 generation physical, sexual and developmental delay with effects on neurobehavioral functions (pupillary response) were observed. Cannabidiol is a lipophilic compound with long elimination half-life and thus is expected to be excreted significantly to milk. No data on CBD analysis in milk was provided. However, published data on CBD and Sativex indicate very high milk to plasma ratio. Breast-feeding is not recommended during treatment and due to severity of the proposed indications discontinuation of the therapy during lactation is out of question. Thus, breast-feeding should be discontinued during treatment. A Safety margin of 9 was calculated for this study, based on exposure data from Study GWTX1454, at 75 mg/kg/day, on GD6. Adjusted human $AUC_{(0-24h)}$ 2790 ng·h/ml was used for calculation of the safety margin.

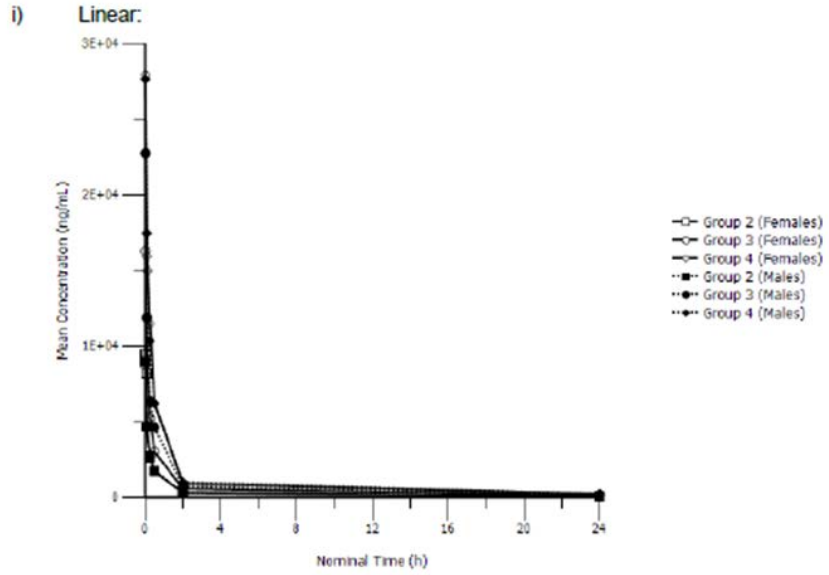
Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

The Applicant sponsored three pivotal neonatal and juvenile toxicity studies. One study in rat with s.c./p.o. administration, one study in rat with s.c./i.v administration and one study in dog with i.v. administration. It should be noted, that this MAA does not include an intravenous formulation. In the 10-week main neonatal/juvenile toxicity study with 6 weeks recovery, Han Wistar rats were given an s.c. dose of 0 or 15 mg/kg/day Purified CBD on PND 4 to 6 followed by p.o. (gavage) doses of 0, 100, 150, or 250 mg/kg/day CBD-OS from PND 7 to 77 (GWTX1408). CBD effects on fertility (i.e., sexual maturity), behavioural endpoints, Dual-energy X-ray absorptiometry, macroscopic and microscopic evaluation were assessed.

In juvenile rats, no new organs for toxicity were identified in comparison to adult rats. No neurological effects (Morris water maze, motor activity, learning and memory and auditory startle assays) or effect on long bone (femur) 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. Safety margins and exposures for metabolites are being re-examined, as the bioanalysis method first used was not GLP compliant and has been shown to overestimate the exposure of the metabolites compared to reanalysis performed and submitted in an interim report. The NOAEL (15/250) was amended to 15/150 mg/kg/day since there were three inconclusive pup deaths at this dose level.

Two studies were conducted using the intravenous route of administration. Exposure obtained in these studies was lower based on AUC compared to the study using the oral route of administration. It is anticipated that most findings are effects of continuous exposure to CBD and not pharmacokinetic peaks of very high plasma concentrations. Using the dog as an illustrative example, C_{max} was higher than AUC_{0-t}, indicating a very fast half-life in juvenile dogs after i.v. administration, see figure below. C_{max} and $AUC_{(0-t)}$ values of 27700 ng/ml and 25600 ng·h/ml in males and 27900 ng/ml and 24700 ng·h/ml in females.

Figure 4 Mean (composition) CBD dog plasma concentration vs time profiles, D34 34 pp



Toxicokinetic data

PK profiles in juvenile dog (GWTX1556)

In juvenile dogs, no adverse effect upon body weight, growth measurements, physical development (development of testes descent and vaginal opening) or extended assessments such as ophthalmology (indirect ophthalmoscopy and biomicroscopic (slit lamp) examinations), neurological examination (general attitude and behaviour, spinal and cranial nerves, postural reactions /qualitative observational battery or ECG (HR and/or RR interval, PR and QT intervals, calculation of the QTc (using Van de Water's formula) as well as QRS complex duration) were seen up to highest dose tested. Dose-related effects which were not considered by study director as relevant included transient effect of decreased activity in some males at high dose and statistically significant but transient decrease in length growth. Effect of bone growth was compensated at the end of the study. Bone density was not measured. Liver enzyme levels or plasma calcium levels were not affected.

The rat study (GWTX1524) employed much lower doses than the oral study and obtained lower exposure as well: C_{max} and $AUC_{(0-t)}$ values of 1310 ng/mL and 5980 ng·h/ml in males and 2160 ng/ml and 10800 ng·h/ml in females. In this study, no organ weight changes, macroscopic or microscopic findings considered to be related to treatment with CBD was found. This is reassuring, since exposure was determined to be higher than C_{max} in children of 290 ng/ml.

Local Tolerance

No stand-alone local tolerance studies were performed. This is acceptable as the route of administration is p.o. and this route has been used in most of the pivotal toxicity studies.

Other toxicity studies

Antigenicity

No stand-alone antigenicity studies were performed. This is acceptable as antigenicity may be observed in repeat-dose toxicity studies if arising.

Immunotoxicity

No stand-alone immunotoxicity studies were performed. This is acceptable as CBD is not suspected to immuno-toxic and signs of potential immunotoxicity may be observed in repeat-dose toxicity studies.

Dependence

Based on preclinical and clinical studies, purified CBD appears to have low abuse potential, therefore Epidiolex is currently a Schedule V substance in the USA (DEA, Schedules of Controlled Substances: Placement in Schedule V of Certain FDA-Approved Drugs Containing Cannabidiol, 83 Fed. Reg. 48950 Sept. 28, 2018). Abuse potential studies were performed with CBD-OS (or an appropriate i.v. formulation for i.v. self-administration studies) in accordance with contemporaneous FDA and EU guidelines. *In vitro* studies pertaining to abuse potential of CBD were also conducted as was an *in vivo* Tetrad test in the mouse.

The abuse potential of CBD-OS and/or Purified CBD was investigated in models of abuse potential using:

• Drug Discrimination Procedure to evaluate CBD against THC and Midazolam.

• Non-precipitated Withdrawal Procedure compared to diazepam and morphine.

• Self-Administration Procedure in the heroin and cocaine trained rat and midazolam-trained rhesus macaque.

In non-clinical models of abuse, only minor, signals predictive of abuse potential were observed with CBD at doses producing systemic exposures equal to, or in excess of, those measured following therapeutic doing in man.

Rats trained to THC dosed with CBD showed partial, non dose-dependent generalization to THC at 75 and 150 mg/kg. Rats trained to midazolam generalised CBD-OS to saline cue at all doses.

Evaluation of CBD in the non-precipitated withdrawal test in the juvenile and adult rats showed some withdrawal effects. There are apparent differences in sensitivity to withdrawal effects after morphine treatment between male and female rats, with males showing withdrawal symptoms of increased severity. Female rats still show withdrawal symptoms similar to that described in the literature. It is agreed that behavioural withdrawal effects of positive controls diazepam and morphine were reported for male adult and juvenile rat (GWTX1555). The vehicle group did show few and mild symptoms of withdrawal similar to the low dose group treated with CBD-OS (slight increase in body temperature and increase in food consumption). The high dose group showed slight decrease in temperature upon withdrawal of CBD similar to an effect observed after withdrawal of morphine and diazepam. Upon withdrawal of diazepam and morphine, a decrease in food consumption was observed. This was not seen with CBD-OS or vehicle. Hence, if the effects observed are due to withdrawal of CBD/ethanol, the effects are mild.

Female juvenile rats seemed to be the most sensitive to withdrawal effects while toxicity effect (body weight loss) to CBD treatment was pronounced in adult rats.

No positive reinforcement was observed with CBD in midazolam-trained rhesus macaque up to 5.6 mg/kg/infusion (GWTX1664).

In cocaine-trained rats up to 1.5 mg/kg/infusion (GWTX1551), no reinforcing effects were observed, however in the heroin-trained rat (GWTX1663), a non-dose dependent weak positive reinforcement was observed (at only the intermediate dose (0.1 mg/kg/infusion), which was significantly lower than positive reinforcement observed with heroin.

At high doses the same or higher than therapeutic exposures were reached.

Excipients

The single dose with amount of ethanol 7.9 mg/kg (at doses of 20 mg/kg/day CBD-OS) exceeds the limit (6 mg/kg) which corresponds also to marginally crossed limit (0.01g/l) for BAC as well in 2-6 years old children up to 20 kg. Moreover, the drug product will be used in epileptics, a group of patients very sensitive to alcohol adverse effects. This is acceptable and adequately reflected in the SmPC.

Studies on impurities

The applicant has submitted adequate information to document that the four impurities of CBD drug product identified to above qualification limits according to ICHQ3 A/B (R2) are not likely to impose further risk to the patients than CBD alone. The four impurities did not show potential for genotoxicity. The applicant conducted studies to define pharmacological activity of impurities. A panel of 70 targets comprising of 7-TM receptors, ion channels, transporters and enzymes was used in radioligand binding study (GWPP17035). Furthermore, functional activity study for COX1 and COX2 enzymes was examined. No concentration dependence was observed in range of tested conditions 10nM, 100 nM up to 1 µM. At concentration of 10 µM several molecular targets were engaged. This is, however,

appreciable above the clinical plasma concentrations potentially reached based on proposed specifications for impurities.

As mentioned above, all impurities above qualification level are considered as toxicologically qualified. Pharmacological profile of one impurity was evaluated in pharmacological studies and described in scientific literature. This impurity can engage with a range of molecular targets at micro-molar concentrations. The content of CBDV is up to 1.0 % (w/w) in the to-be-marketed formulation. No involvement of targets studied is expected. The content of Δ^9-THC is up to 0.10% (w/w) in the to-be marketed product.

24 month supportive stability data demonstrated that there has been no significant change in levels of these compounds over the period tested for the long term and accelerated stability.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant argues that Phase II Environmental Risk Assessment is not necessary for CBD, since it is present in the environment already due to the increasing production of hemp for purposes other than in the pharmaceutical industry. Nevertheless, the applicant rightly calculated a refined Fpen to be used for determination of PECsurfacewater for CBD in EU to be 0.15 µg/l, and has sponsored a toxicity pilot screen in zebrafish as summarised below.

An *in vitro* toxicity pilot screen (GWP002) of Purified CBD was performed in zebrafish (Danio rerio) to determine acute toxicity, hepatotoxicity, cardiotoxicity, and embryotoxicity at doses ranging from 0.01 µM to 500 µM.

Purified CBD produced acute toxicity at body burdens > 1.8 ng/larva. Hepatotoxicity occurred at a high body burden of 116.1 ng/larva and cardiotoxicity, characterized by bradycardia, occurred from 50 µM (15700 ng/ml). In the embryotoxicity screen, all Purified CBD doses up to 1 µM (314 ng/ml = 314 µg/l) were considered nontoxic was the no observed effect concentration [NOEC]). The lowest observed effect concentration (LOEC) was 5 µM (1570 ng/ml).

This study may predict that no risk for aquatic organism is present as PECsurfacewater for CBD in EU is 0.15 µg/l.

Log Kow was determined to be >5. This triggers that CBD should be screened in a stepwise procedure, for persistence, bioaccumulation and toxicity according to EU Technical Guidance Document.

However since;

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.

2.3.6. Discussion on non-clinical aspects

Pharmacology

In general CBD showed anticonvulsant effect in several relevant animal seizure models.

A considerable effort was put into the elucidation of the CBD mechanism of action. The proposed targets are as an antagonist on the GPR55 receptor, a TRPV1 agonist inducing desensitization and a

reuptake inhibitor of adenosine. These targets seem to be showing activity in relevant concentrations. A number of other CNS targets were also investigated as part of the off target screening.

With regard to secondary pharmacology, a great effort was performed to characterise CBD and selected impurities and metabolites.

Safety pharmacology was evaluated in separate studies in rat and dog. The rat studies (CNS and respiratory) were negative, however were not supported with adequate exposure. Cardiovascular safety was evaluated in vitro in sub-pharmacological relevant concentrations. The GLP in vivo study performed in dogs demonstrated a decreased in heart rate (≥ 50 mg/kg, biologically relevant), increased systolic blood pressure (≥100 mg/kg), and increased R-R (statistically significant), R-H, QRS, and QT intervals (at 100 mg/kg). In lower doses, dose-related increases occurred which was however considered as not biologically relevant. The NOEL was found to be 10 mg/kg CBD as CBD BDS. The changes observed following dosing at 50 or 100 mg CBD/kg/day were considered not adverse but related to the pharmacodynamic activity of CBD by the study director.

Pharmacokinetics

The applicant sponsored an overly complicated and ambitious bioanalytical program. A GLP inspection performed by MHRA, revealed several concerns of flawed bioanalytical reliability. Considerable efforts were made to mitigate the consequences of GLP-deficient bioanalysis in the majority of pivotal toxicity studies, which overall is considered adequate.

Single dose pharmacokinetic studies were conducted in rodents; however, the study evaluating the i.v. route of administration presented no pharmacokinetic calculations. Pharmacokinetics (tmax and t½) in brain appeared to be similar to plasma for both mouse and rat, however brain to plasma ratio determined using AUC0-24h obtained after i.p. administration was higher in rat with ratios of 0.6 and 2.7 in mouse and rat, respectively. This may explain the lower sensitivity of mice compared to rats in the pharmacological rodent models. A pharmacokinetic study in minipig in 10 different formulations was helpful in developing the optimal formulation for the paediatric population.

The metabolism of CBD is very complex and was investigated in hepatocytes, microsomes and plasma of dosed animals and human volunteers. Metabolites in excreta were not investigated.

The potential of CBD to inhibit and/or induce CYP450 and UGTs was investigated in a series of studies. CBD is a substrate, a time dependent inhibitor (potential irreversible) and a potential inducer of CYP3A4. CBD is also a substrate and an inhibitor of CYP2C19, which is polymorphic and can also be induced. The data generated in these studies indicate that CBD and 7-COOH-CBD are likely to induce CYP450 enzymes at clinically relevant concentrations via PXR, CAR and AhR. Therefore, it can be assumed that CYP450 induction is a contributing factor to the enlarged livers observed in the rats in studies conducted. Drug interaction studies with concomitant treated antiepileptic drugs were conducted in minipigs and again in humans.

Toxicology

The toxicity profile of CBD-OS, formulated in ethanol, sucralose, strawberry flavouring, and sesame oil (clinical formulation), was evaluated in GLP-compliant repeated dose general toxicity studies in mice, rats, and dogs via oral administration. Studies were conducted for up to 13, 26, or 39 weeks for each species, respectively. Consistently, CBD induced liver toxicity, which was dose dependent. The applicant considered all findings in toxicity studies as non-adverse, as there was an absence of inflammation and necrosis, and a tendency for reversal was observed after end of treatment, therefore the highest dose levels were consistently selected as NOAEL. Levels of thyroid hormones, luteinizing hormone (LH) follicle stimulating hormone (FSH) and/or prolactin were not examined in the studies and thus mode of action and its relevance to humans is not clear. Some further effects of hormonal

dysregulation (e.g., small testes, interstitial cell hyperplasia of ovary, increased incidence of the dioestrus/metoestrus phases of cycle etc.) were observed across the studies with cannabidiol or impurities (a structurally very similar to CBD). It is expected that comprehensive table with safety margins updates showing original and new value will be provided along with final reports post-authorisation. Monitoring for potential hormonal disturbance via clinical and pharmacovigilance activities should be initiated and the final study report (GWTX18002) with characterization of potential risk due to hormonal disturbances should be submitted as a post-authorization measure.

CBD showed no genotoxic potential. Genotoxic potential for active metabolite 7-OH-CBD or abundant human metabolite 7-COOH-CBD is currently under investigation and should be submitted as a post-authorization measure.

A carcinogenicity study in mice revealed some overlap with the liver findings in the repeat dose toxicity studies, e.g. dose-related agonal vacuolation and centrilobular vacuolation. The low dose in this study (5 mg/kg/day) seems to be devoid of any significant findings in liver. No increases in tumour findings were identified.

The applicant sponsored a battery of reproductive and developmental toxicity studies. Rats (F0) were insensitive to reproductive toxicity. However, the F1 generation was more sensitive than the parental generation due to small testes in males and reduced fertility index in females. The rabbit did show adverse effects in an embryo-foetal development study at plasma concentrations in the same range as relevant in patients. However, protein binding is lower in rabbit compared to rats and humans with 65% bound in rabbit and 95% and 94% in rat and humans, respectively. Hence, if protein binding is taken into account, adequate safety margins to human plasma concentrations would be anticipated for the rabbit findings.

Effects of CBD in juvenile animals were evaluated in rat and dog. The liver findings observed in adult animals were confirmed in juvenile rats as well. Statistically significant occurrence of variations of a supernumerary liver lobe in foetuses was above historical control data. The applicant, however, failed to provide discussion on human relevancy of the observed effect. It is claimed that human data on supernumerary liver is limited and that possible causes can be drug or congenitally related. Potential for occurrence under maternal treatment with CBD during pregnancy thus cannot be excluded. It is however acknowledged that CBD-OS should not be used during the pregnancy. Furthermore, in view of severity of the indications, the concern is not further pursued.

The applicant sponsored studies to determine the rewarding properties, the similarity of physiological effect compared to known drugs of abuse, and potential for dependence/withdrawal of CBD. While marginal signals were observed in some studies, CBD does not possess rewarding properties, is not similar in affect to THC and midazolam and dose not induce a withdrawal syndrome.

2.3.7. Conclusion on the non-clinical aspects

From a nonclinical point of view, the application is considered approvable. However, the applicant is recommended to submit the following nonclinical studies post-authorisation:

a. Purified CBD: 13 Week Oral (Gavage) Administration Toxicity Study in the Rat

b. Purified CBD: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Mouse

c. An embryofetal development study of 7-COOH-cannabidiol in rat

d. A pre- and postnatal development study of 7-COOH-cannabidiol in rat

e. A juvenile animal toxicology study of 7-COOH-cannabidiol in rat

f. A 2-year carcinogenicity study of cannabidiol and 7-COOH-cannabidiol, both directly administered, in rat

g. GLP genotoxicity studies with both 7-OH-CBD and 7-COOH-CBD

A comprehensive table with safety margins updates showing original and new value should be provided along with the final reports

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

A national GLP inspection (MHRA) has questioned the validity and reliability of the bioanalytical data in the preclinical studies. As similar analytical methods were used throughout the clinical pharmacology studies, the results of these studies were questioned. An EMA GCP inspection was triggered concerning 6 clinical studies.

Consequently, a request for GCP inspection has been adopted for the following clinical studies:

GWEP1544, GWEP1428, GWEP1543, GWEP1332, GWEP1423, GWEP1414. At the inspection of the analytical laboratory, 6 major and 8 minor findings were observed. After evaluation of the response two of these findings were upgraded to critical. Four Major and 2 Critical findings were reported in the final GCP report, which were of concern. However, based on the GCP report and the responses from the applicant, the PK/PD data included in MA Application are overall considered valid.

2.4.2. Pharmacokinetics

A total of 15 clinical pharmacology and patient trials with a PK component were completed as part of the CBD-OS clinical development program. The application includes 10 completed trials in healthy subjects (GWEP1544, GWEP1431, GWEP1541, GWEP1543, GWEP17028, GWEP17075, GWEP17077, and GWEP1446 [trials with a PK element], and the 2 supporting trials, looking at the effects of CBD-OS on sleep [GWEP1448] and withdrawal symptoms [GWEP1542]), 2 trials in specific populations (renal-impaired [GWEP1540], hepatic-impaired [GWEP1539]), and 5 trials in patients with epilepsy (efficacy: 2 in DS [GWEP1332 and GWEP1424], 2 in LGS [GWEP1414 and GWEP1423]; clinical pharmacology: 1 in epilepsy [GWEP1428]); interim data was also included from an ongoing DS and LGS patient open-label extension (OLE) trial (GWEP1415), and an ongoing clinical pharmacology trial in epilepsy patients (GWEP1447).

Additionally, population PK and exposure-response analyses were conducted based on the data collected during the CBD-OS clinical development program.

A PK-pharmacodynamic (PD) analysis looking at QTc was conducted as part of the TQT trial.

Absorption

The PK of Cannabidiol (CBD) has been studied in healthy volunteers, patients and in special populations.

Bioavailability of CBD was approximately 6.5 % following oral administration in fasting conditions. Due to significant food effect observed the bioavailability following administration with food can be expected around 14-25%. The effect of a high fat meal on the PK of a single 1500 mg CBD OS dose in healthy male and female subjects was studied in a randomized 2 period crossover period, incorporating 12 randomly selected subjects (mean age 25 years) from the SAD arm. There was a 10-day washout between periods. The results for Cmax and AUC of CBD are tabulated below:

Table 6 Summary of Food Effect

		geometric LS means		Ratio Test/Reference			p value	
		Test	Reference		90% CI			
Analyte	Parameter	(fed)	(fasted)	Estimate	[lower,upper]	Treatment	period	sequence
CBD	Cmax	1588	327	4.85	[4.01, 5.87]	<.0001	0.0067	0.3863
	AUC0-t	8337	1985	4.20	[3.63, 4.85]	<.0001	0.0079	0.3971
	AUC0-inf	8670	2198	3.94	[3.45, 4.51]	<.0001	0.0177	0.3843
	AUC0-inf *	8670	2198	3.94	[3.45, 4.51]	<.0001	0.0177	0.3843
6-OH-CBD	Cmax	27.1	9.68	2.80	[2.32, 3.36]	<.0001	0.1162	0.3175
	AUC0-t	250	94.7	2.64	[2.14, 3.25]	<.0001	0.2210	0.3341
	AUC0-inf	274	106	2.59	[2.06, 3.26]	<.0001	0.4910	0.3460
	AUC0-inf *	274	106	2.59	[2.06, 3.26]	<.0001	0.4910	0.3460
7-COOH-CBD	Cmax	4585	2205	2.08	[1.64, 2.64]	0.0002	0.4271	0.4876
	AUC0-t	123735	51202	2.42	[2.05, 2.85]	<.0001	0.1273	0.1448
	AUC0-inf	140311	59613	2.35	[2.02, 2.74]	<.0001	0.1024	0.1294
	AUC0-inf *	140311	59613	2.35	[2.02, 2.74]	<.0001	0.1024	0.1294
7-OH-CBD	Cmax	378	130	2.91	[2.43, 3.48]	<.0001	0.0523	0.5088
	AUC0-t	3218	1018	3.16	[2.64, 3.78]	<.0001	0.0929	0.2922
	AUC0-inf	3337	1030	3.24	[2.72, 3.87]	<.0001	0.1875	0.2233
	AUC0-inf *	3337	1030	3.24	[2.72, 3.87]	<.0001	0.1875	0.2233

Note: Food effect was explored using a mixed effect (ANOVA) model with treatment, period and sequence as fixed factors, and subject within sequence as a random factor.
**: with values based on %AUCextra>30 excluded.*
There was a significant period effect for CBD parent compound (period 2 has higher values than period 3)

CBD Tmax ranged from 2-5 h with maximal plasma levels mostly observed at 4-5 hours following single oral dose. At steady state Tmax of CBD is approximately 3 hours (range 2.5-5 h). Significant food effect was observed in the conducted fed study and both Cmax and AUC was 4-5-times increased following administration of study drug with standard high fat meal. Tmax was not significantly affected by administration with food.

Study GWEP1424 has been presented with the applicant's responses to the D180 List of Outstanding Issues. A secondary objective was to determine (PK) of CBD and its major metabolites following single and multiple doses of GWP42003-P and to assess the presence of THC and its major metabolites in plasma and the presence of THC, CBD and their major metabolites in urine after multiple doses of CBD. Subjects < 20 kg were not included due to limitation in the volume of blood samples required. Furthermore, urinary PK was not conducted as there were only a few patients who consented but were unable to provide samples. Thus, PK data from GWEP1424 are limited. PK results reported are consistent with previously reported results.

Distribution and Elimination

Plasma concentrations appear to follow a biphasic pattern suggesting a distribution into peripheral compartments. Apparent volume of distribution ranged in healthy volunteers for single doses of between 200 and 6000 mg CBD-OS from 2820 to 42849 L. A radiolabelled (ADME) study was not conducted. Literature data submitted by the applicant suggest that only about 8% of the total dose of IV administered CBD is present in plasma at the peak of radioactivity and the rest is redistributed in tissues. In the absence of an ADME study, it is important to clarify the metabolic routes for oral CBD-OS. Study GWEP17075 evaluated the impact of selective inhibitors on the clearance of CBD and exposure to the major metabolites. It showed that itraconazole (potent CYP3A4 inhibitor) did not affect CBD exposure and caused only minor increases in 7-hydroxy-cannabidiol (7-OH-CBD) (17%) and

7-carboxy-cannabidiol (7-COOH-CBD) (12%) exposure (AUC_{0-t}). Fluconazole (a potent CYP2C19 inhibitor) had only a minor effect on CBD exposure (approximately 20% increase) and caused small decreases in 7-OH-CBD (29%) and 7-COOH-CBD (34%) exposure (AUC_{0-t}). From in vitro studies, plasma protein binding – mainly to albumin – is high, about 92-99%. Free fractions were studied in relation to studies in subject with hepatic impairment.

In a human study (GWEP1540) using titrated CBD, CBD and 7-OH-CBD were present in very low quantities whilst 7-COOH-CBD metabolite was detected in all subjects with normal renal function, however levels of urinary elimination of conjugated products were not evaluated. About 16% of the total dose was excreted in urine within 72 hours, indicating that renal excretion is a minor route of excretion for CBD. A large proportion of CBD was excreted unchanged in faeces. In humans, hepatic clearance is a major route of CBD metabolism. The mean CL/F of CBD in healthy subjects ranged between 375 and 1909 L/h (fasted after a single CBD-OS dose of between 200-6000 mg).

In healthy subjects, the terminal t½ was approximately 60 hours after multiple b.i.d. dosing, although using 2 compartmental modelling (population PK) in healthy volunteers and in LGS patient data suggested there may be a longer terminal slope with t½ estimates of between 85 hours and 202 hours. The population PK estimate of CBD CL/F after oral administration was 35.5 L/h, assuming a typical body weight of 70 kg from the population PK analysis.

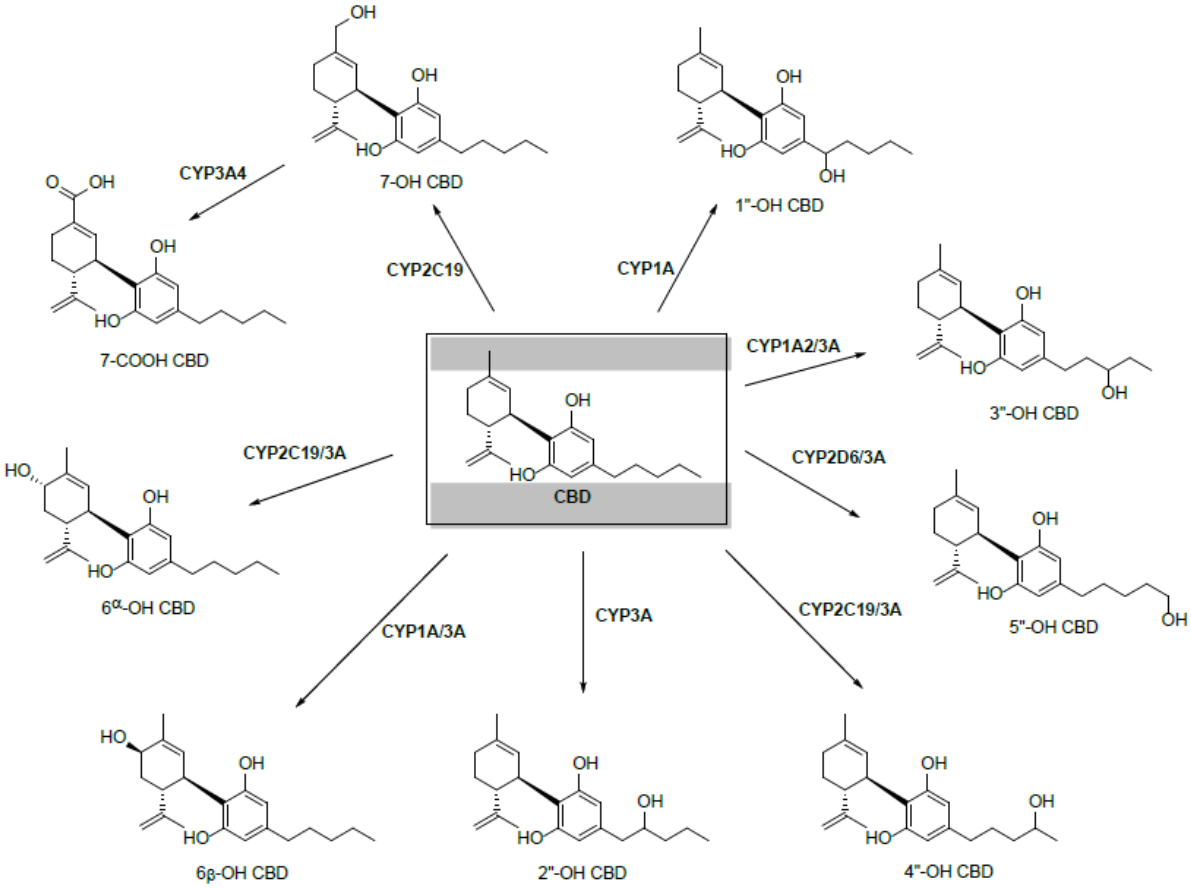
CBD is extensively metabolized *in vivo*, likely following first pass effect by gut and liver metabolism.

The main isoforms responsible for phase I metabolism of CBD are CYP2C19 and to a lesser extent CYP3A4. Phase II metabolism is mediated by uridine 5' diphospho glucuronosyltransferase (UGT) subtype 2B7 (UGT2B7), UGT1A7, and UGT1A9. The major CBD metabolites identified in human hepatocytes were 7 carboxy cannabidiol (7-COOH-CBD) and 7-hydroxy cannabidiol (7-OH-CBD). CYP2C19 is likely to be the major enzyme *in vitro* responsible for the hydroxylation of CBD to 7-OH-CBD. CYP3A4 is likely to be the major enzyme responsible for the further oxidation of 7-OH-CBD to 7-COOH-CBD. 6-hydroxy cannabidiol (6-OH-CBD) was identified as a CBD metabolite in HLMs, and CYP3A4 is likely responsible for its production. The most abundant metabolite was 7-COOH-CBD which was identified as having little or no intrinsic anticonvulsant efficacy. The exposure was 29-46 times higher than the mother compound. 7-OH-CBD was identified as an active metabolite with similar activity to CBD was present in lower concentrations than CBD, at approximately 40-60% of parent drug exposure.

The metabolite to parent ratios for 7-OH-CBD and 6-OH-CBD in healthy subjects were comparable with values observed in both patient populations, for 7-COOH-CBD there was very high variability among trials however significant difference between healthy subjects and patient population was not observed.

Based on *in vitro* data and the literature, the major metabolic pathways of CBD in human tissue are shown in the figure below.

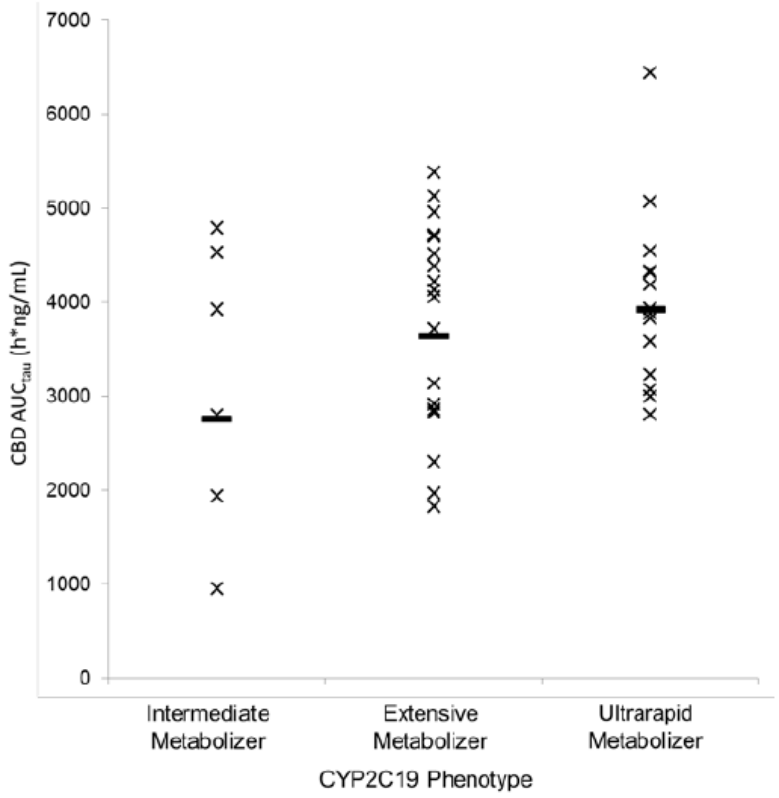
Figure 5 Metabolic Pathways of CBD in Human Liver Microsomes and Primary Human Hepatocytes



The PK of metabolites are reported and assessed in relation to the parent drug throughout the assessment report.

The applicant presents post-hoc analysis of PK data as related to polymorphisms on CYP2C19 and CYP3A4. The main inferential results pertaining to the CYP2C19 data are illustrated below:

Figure 6 Relationship between CBD AUCtau and CYP2C19 Phenotypes in Subjects from Group 2, 4 and 6, Period 1, CBD-OS Alone

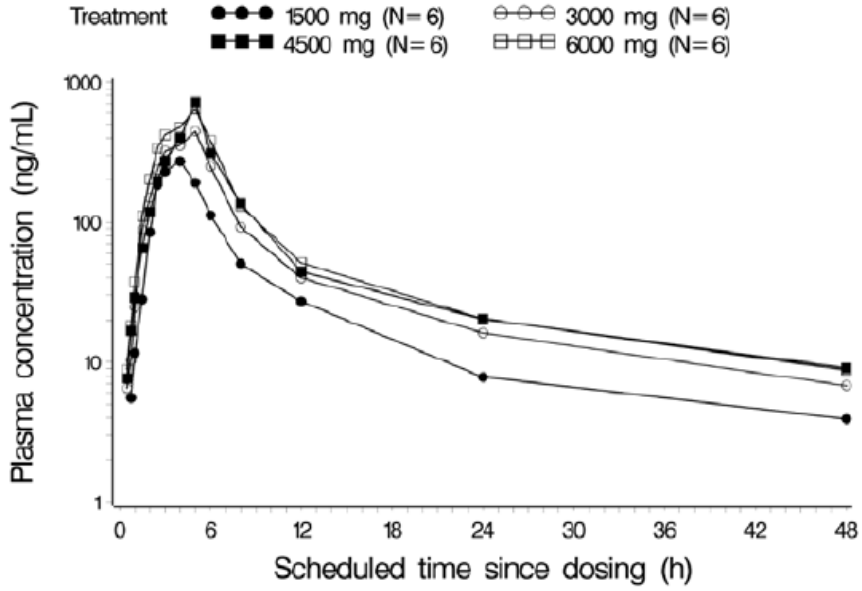


The frequencies of the CYP2C19 phenotypes were EM (34/77) > UM (27/77) > IM (11/77) > PM (1/77); 4 subjects were undetermined metabolizers. In Group 1, in the 1 subject with a CYP2C19 IM phenotype, steady-state exposure to N-CLB was consistent with their phenotype (highest Cmax and AUCtau values in Group 1). Apart from 1 CYP2C19 UM subject with very low steady-state N-CLB exposure in the absence of GWP42003P and the highest treatment ratio of all subjects, there were no other notable differences between N-CLB exposures in EMs vs. UMs. Across Groups 2, 4 and 6, exposure to steady-state CBD tended to be higher in subjects with CYP2C19 UM phenotypes and lowest in subjects with CYP2C19 IM phenotype. So far data are too limited to draw conclusions of the effect of genotype on the CBD pharmacokinetics.

Dose proportionality and time dependencies

From study GWEP1544, the time-concentration profile of CBD at different oral single doses is illustrated below in children and adults:

Figure 7 Geometric Mean Plasma Concentrations of CBD Over Time after Administration of Single Doses of CBD-OS during Fasted Conditions, Semilogarithmic Scale (PK Set)



The following observations were made:

• CBD appeared rapidly in plasma following single doses.

• The plasma concentration-by-time profiles for the CBD metabolites were similar. Cmax was followed by multiphasic decline.

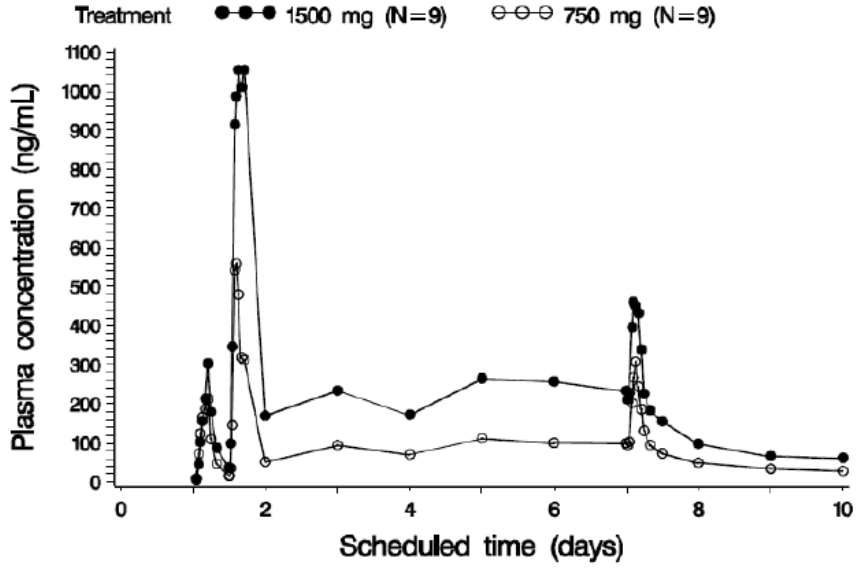
• CBD and its metabolites were detectable in plasma at 48 hours post dose at all dose levels.

Time dependency

From study GWEP1544, the following summary data on repeated dose PK of CBD at two different doses are reported.

Mean plasma concentrations are illustrated below:

Figure 8 Mean Plasma Concentrations (Day 1 am/pm and Day 7 am with Ctrough on Intermediate Days) of CBD Over Time After Administration of Multiple Doses of CBD-OS During Fasted Conditions (PK Set)



Steady state for CBD (based on trough values) was observed after 2-3 days. At steady state, there was a near doubling in exposure (Cmax and AUC) for a doubling in CBD-OS dose (750 and 1500 mg). Following repeated dose administration there was moderate accumulation (Rac = 1.8) after 7 days of multiple b.i.d. dosing, the extent of which was similar for CBD metabolites except for 7-COOH-CBD, which had a Rac of 4.5.

Pharmacokinetics in target population

The pharmacokinetics of CBD and major metabolites was characterized in both the LGS and DS patient population. The applicant characterized PK at two (10 and 20 mg/kg/day) respectively three (5, 10, 20 mg/kg/day) dose levels and the final dose was applied following titration phase. Summary PK from study GWEP1332 in children, DS, (mean age 7.6 years) observations from 5, 10 or 20 mg/kg/day doses are tabulated below:

Table 7 - Summary of CBD-OS Pharmacokinetics from study GWEP1332

Population No. Subjects (Male/Femal	**Treatments Route, Dose, Dosage Form**	**Pharmacokinetic Parameters**				
DS Patients 34 (16/18) 4.0-10.9 years	CBD-OS and matched placebo 5, 10 or 20 mg/kg/day MD Note: both 25and 100 mg/mL CBD-OS formulations were used for this trial	**CBD and Metabolite Plasma Concentrations**				
		CBD				
		CBD-OS Dose (mg/kg/day) and PK Day	**Cobs** ng/mL **(0h)**a	**Cobs** ng/mL **(2.5h)**[a]	**Cobs** ng/mL **(5h)**a	**AUC** ng.h/mL **(0-t)**
		5 (n=10) D1	0	37.56	10.02	70.61
		5 (n=10) D22	23.04	130.0	72.07	240.8
		10 (n=8) D1	0	34.42	11.27	66.35
		10 (n=8) D22	62.14	241.8	287.6	721.8
		20 (n=9) D1	0e	29.29	25.32	73.69
		20 (n=9) D22	120.7	380.0	307.5	962.6
		6-OH-CBD				
		CBD-OS Dose (mg/kg/day) and PK Day	**Cobs(0h)**a	**Cobs(2.5h)**[a]	**Cobs(5h)**a	**AUC(0-t)**
		5 (n=10) D1	0	0.960 (142)b	0.233 (158)d	3.27
		5 (n=10) D22	1.53 (47.5)	4.18 (76.4)	3.01 (62.3)e	9.33 (119)e
		10 (n=8) D1	0	0.993 (92.6)	0.243 (91.3)	2.79 (87.7)c
		10 (n=8) D22	4.10 (55.6)d	8.05 (55.4)d	9.49 (84.7)d	26.3 (82.9)d
		20 (n=9) D1	0d	1.43 (95.2)d	1.04 (136)	5.16 (57.2)c
		20 (n=9) D22	9.88 (81.8)h	20.2 (72.6)g	18.4 (79.5)g	58.6 (90.1)g

		7-COOH-CBD				
		CBD-OS Dose (mg/kg/day) and PK Day	**Cobs (0h)**a	**Cobs(2.5h)** a	**Cobs(5h)**a	**AUC(0-t)**
		5 (n=10) D1	0d	157 (96.1)b	103 (63.2)d	297 (97.3)g
		5 (n=10) D22	1150 (67.6)	1180 (64.5)b	1200 (69.8)b	4190 (81.2)b
		10 (n=8) D1	0d	207 (114)d	120 (94.7)g	125 (1750)g
		10 (n=8) D22	3440 (101)g	3550 (104)g	3630 (121)c	9220 (178)c
		20 (n=9) D1	0g	159 (108)d	131.0 (108)e	195 (573)g
		20 (n=9) D22	5630 (69.0)g	6090 (67.5)g	4920 (64.5)g	15500
		7-OH-CBD				
		CBD-OS Dose (mg/kg/day) and PK Day	**Cobs(0h)**a	**Cobs(2.5h)** a	**Cobs(5h)**a	**AUC(0-t)**
		5 (n=10) D1	0	10.9 (124)b	4.17 (55.6)d	21.9 (57.0)c
		5 (n=10) D22	21.4 (59.3)	47.6 (76.3)	40.0 (53.9)e	131 (107)e
		10 (n=8) D1	0	12.5 (107)	5.38 (92.9)	18.4
		10 (n=8) D22	36.1 (85.6)d	112 (119)d	81.7 (76.6)d	244 (120.0)d
		20 (n=9) D1	0e	12.9 (85.2)e	11.6 (102)b	30.2
		20 (n=9) D22	123 (116)d	224 (74.8)d	158 (122)g	508 (96.0)g

Values are geometric mean (geometric CV%) with the exceptions below.
NC, not calculable.
a Arithmetic mean (CV%).
*b n=9, c n=5, d n=7, e n=8, f n=3, g n=6, h n=34, i n=37, j n=32, k n=28, l n=30, m n=31, n n=26, o n=24, p n=18, q n=27,r n=39, s n=36, t n=25, u n=42, v n=38, w n=19, x n=21, y n=20, z n=22, ♣ n=23, $ n=2, £ n=14, # n=15, % n=17, & n=11, * n=41,^ n=35, ♦ n=33, ♥ n=40, ♠ n=16, ◊ n=29, ■ n=1, □ n=4, † n=10, ‡ n=12, § n=13.*
†† Median and range

Based on the above results, it can be concluded that exposure to CBD and its metabolites increases in a dose-related manner (over the dose range of 5, 10 and 20 mg/kg/day), with no major deviation from dose proportionality.

Study GWEP1423, double-blind 14-week treatment period efficacy trial in 171 LGS patients (mean age 15.42 years) investigated the PK of CBD and its major metabolites following single and MDs of 20 mg/kg/day CBD-OS (or placebo [1:1 ratio]), as well as the effects of CBD-OS on CLB (and N-CLB), and other AEDs if taken as concomitant medications. Summary PK observations are tabulated below, for 20mg/kg/day dose:

Table 8 Summary of CBD-OS Pharmacokinetics from study GWEP1423

Population No. Subjects (Male/Femal	**Treatments Route, Dose, Dosage Form**	**Pharmacokinetic Parameters**
LGS Patients	CBD-OS	**CBD and Metabolite Plasma Concentrations**
		2-17 year olds

171 (88/83) 2.7-45.1 years	20 mg/kg/day MD	**CBD**				
		PK Day	**Cobs(0h)**	**Cobs(2.5h)**	**Cobs(5h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	16.0 (131.3)h	9.51 (102.5)i	50.5 (91.5)j
		Visit 8 (Day 99)	128 (57.8)k	377 (140.5)l	273 (83.9)m	1250 (106.4)l
		6-OH-CBD				
		PK Day	**Cobs(0h)**	**Cobs(2.5h)**	**Cobs(5h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	0.907 (69.4)n	0.496 (51.7)o	2.68 (65.7)p
		Visit 8 (Day 99)	5.16 (95.2)k	11.5 (114.2)k	9.81 (93.6)l	40.1 (97.4)q
		7-OH-CBD				
		PK Day	**Cobs(0h)**	**Cobs(2.5h)**	**Cobs(5h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	4.84 (192.6)i	3.99 (126.4)r	17.6 (114.0)s
		Visit 8 (Day 99)	60.0 (87.8)k	119 (100.1)n	104 (83.2)k	423 (85.7)t
		7-COOH-CBD				
		PK Day	**Cobs(0h)**	**Cobs(2.5h)**	**Cobs(5h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	454 (28.7)b	387 (34.7) ‡	1350 (20.0)g
		Visit 8 (Day 99)	6620	7680	7510	29900

		18-55 year olds						
		CBD						
		PK Day	**Cobs (0h)**	**Cobs (0.5h)**	**Cobs (1h)**	**Cobs (2h)**	**Cobs (4h)**	**Cobs (6h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	10.9 (51.8)g	16.6 (192.0)	32.5 (144.3)	18.9 (128.0)n	15.8 (174.8)	127 (102.6)k
		Visit 8 (Day 99)	198 (76.7)♣	229 (79.9)p	315 (73.6)y	418 (76.5)x	463 (76.9)y	404 (65.3)x	2320 (80.9)z
		6-OH-CBD						
		PK Day	**Cobs (0h)**	**Cobs (0.5h)**	**Cobs (1h)**	**Cobs (2h)**	**Cobs (4h)**	**Cobs (6h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	0.923 (12.8)$	1.23 (63.3)£	1.28 (62.7)#	0.816 (67.6)v	0.635 (78.3)%	4.74 (60.9)x
		Visit 8 (Day 99)	6.86 (80.4)♣	7.46 (54.7)%	9.01 (51.7)p	11.6 (58.8)z	12.0 (61.3)y	11.3 (56.4)x	66.6 (53.0)z
		7-OH-CBD						
		PK Day	**Cobs (0h)**	**Cobs (0.5h)**	**Cobs (1h)**	**Cobs (2h)**	**Cobs (4h)**	**Cobs (6h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	1.91 (264.9)g	5.31 (333.0)	6.87 (288.0)x	7.53 (147.4)t	8.47 (145.9)y	44.4 (124.8)k
		Visit 8 (Day 99)	81.1 (60.0)z	90.7 (47.5)♠	110 (48.8)	126 (56.5)w	149 (47.1)w	139 (42.7)y	771 (39.1)x
		7-COOH-CBD						
		PK Day	**Cobs (0h)**	**Cobs (0.5h)**	**Cobs (1h)**	**Cobs (2h)**	**Cobs (4h)**	**Cobs (6h)**	**AUC(0-t)**
		Visit 2 (Day 1)	BLQ (NC)	BLQ (NC)	695 (49.7)f	500 (44.0)	595 (53.0) ‡	543 (41.9) ‡	2500 (50.3)&
		Visit 8 (Day 99)	10800 (80.4)p	10600 (94.1)£	10500 (77.7)£	12100 (98.1)%	11000 (70.5)♠	12900 (79.9)p	73300 (86.3)p

Values are geometric mean (geometric CV%) with the exceptions below.
NC, not calculable.
a Arithmetic mean (CV%).
*b n=9, c n=5, d n=7, e n=8, f n=3, g n=6, h n=34, i n=37, j n=32, k n=28, l n=30, m n=31, n n=26, o n=24, p n=18, q n=27,r n=39, s n=36, t n=25, u n=42, v n=38, w n=19, x n=21, y n=20, z n=22, ♣ n=23, $ n=2, £ n=14, # n=15, % n=17, & n=11, * n=41,^ n=35, ♦ n=33, ♥ n=40, ♠ n=16, ◊ n=29, ■ n=1, □ n=4, † n=10, ‡ n=12, § n=13.*
†† Median and range.

Based on the results reported from GWEP1423 and GWEP1332 studies, the CHMP considered that the PK in the target populations compare well to those achieved in healthy volunteers.

Special populations

<u>Population PK analysis</u>

The Applicant presents three different PoP-PK models: healthy volunteer data; LGS adults, and children with DS. The single- and multiple-dose arms of a healthy subject trial (GWEP1544) was used for the construction of a POPPK model which was then applied to the pivotal trials in adults and children with LGS, and to a lesser extent in children with DS. A detailed assessment evaluation of all three individual models is not performed as they were developed in a similar setup and model evaluation performances were comparable. The LGS model was evaluated in detail.

LGS model:

The population PK analysis was performed using Non-Linear Mixed Effect modelling analysis in NONMEM.

The population PK model previously developed in healthy adult subjects was transposed to the current patient population with LGS.

Covariate Models for Parent Drug and Metabolites

Selection of Potential Covariates and Rationale for Selection

Given the scope of the present project, potential covariates were the following: age, sex, baseline drop seizure, race, WT, unit dose of CBD, ketogenic diet, concomitant AEDs, CYP2C19 inhibitors, CYP3A4 inhibitors and inducers. The baseline WT was included upfront as a structural covariate as a part of the patient population is paediatric. Owing to the short trial duration and the available data, only the baseline WT was considered.

Base model structure

The structure of the base model includes 2-compartments with linear disposition for CBD. Apparent central volumes of distribution were set to 1 L for both metabolites to prevent structural identifiability issues. Apparent clearances and volumes of distribution were independent on baseline WT.

CBD absorption followed zero-order absorption kinetics without lag time with a constant duration (D1).

Base Model Parameters

Parameter estimates are tabulated below:

Table 9 Parameter Estimates of the Base Model After Conversion to a Normal Scale

Description	Unit	Estimate on normal	95%CI
D1	h	2.25	1.94-2.61
CL10	L/h	35.52	23.0– 54.8
VP1	L	6836	4505 -10373
Q12	L/h	159.2	17.4 -1458
VP2	L	4629	0.08 – 281319052
CLF-7-OH-CBD	L/h	0.0009	0.0006 – 0.001
CLF-7-COOH-CBD	L/h	15.03	13.5 - 16.7
CLE-7-COOH-CBD	L/h	0.194	0.174 -0.216
Dose50	mg	134.3	75.9 - 237
RUVCBD	%	0.444	0.424 – 0.464

RUV7-OH-CBD	%	0.154 FIX	
RUV7-COOH-CBD	%	0.496	0.473 – 0.519
Common RUVCBD-7-OH- CBD -7-COOH-CBD	µM	0.738	0.703 – 0.773

CI: Confidence interval; CL10: Apparent CBD clearance not forming 7-OH-CBD; CLE-7-COOH-CBD: Apparent elimination clearance of 7-COOH-CBD; CLF-7-COOH-CBD: Apparent formation clearance of 7-COOH-CBD; CLF-7-OH-CBD: Apparent formation clearance of 7-OH-CBD; Common RUV7-OH-CBD -
7-COOH-CBD: Absolute residual unexplained variability common to the 3 analytes; D1: Minimum absorption duration; Dose50: Potency of the dose effect on bioavailability; Food effect on F1:Food-effect on bioavailability (fractional change from nonfed conditions); Q12: Apparent intercompartmental clearance of CBD; RUV7-COOH-CBD: Percent residual unexplained variability on 7-COOH-CBD; RUV7-OH-CBD: Percent residual unexplained variability on 7-OH-CBD; RUVCBD:
Percent residual unexplained variability on CBD; VP1: Apparent central volume of distribution of CBD; VP2: Apparent peripheral volume of distribution of CBD.

Covariate selection

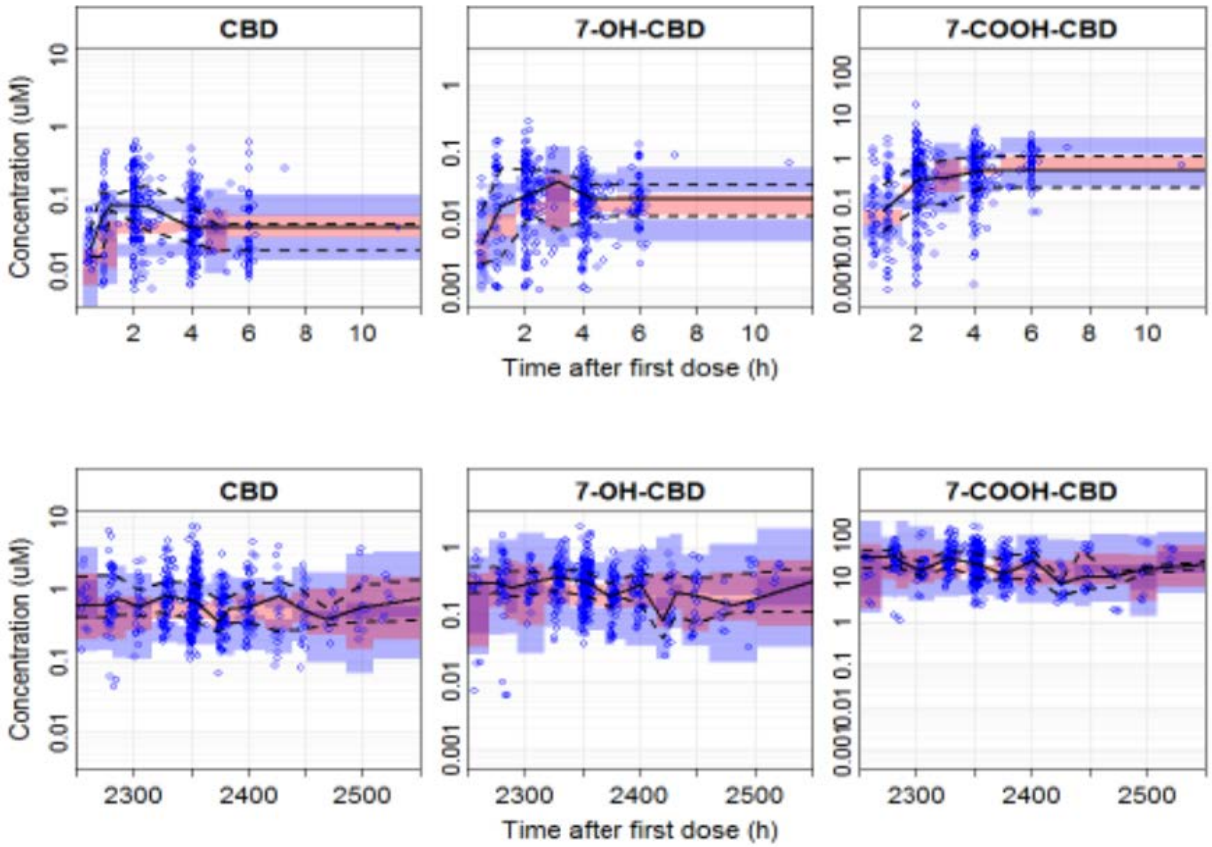
Potential covariates were the following: age, sex, baseline drop seizure, race, WT, unit dose of CBD, ketogenic diet, concomitant AEDs, CYP2C19 inhibitors, CYP3A4 inhibitors and inducers. The baseline WT was included upfront as a structural covariate as a part of the patient population is paediatric.

Model validation

The GOF plots showed that CBD, 7-OH-CBD and 7-COOH-CBD observations were in good agreement with their respective population and individual predictions. No trends were observed on the CWRES plots versus time or versus population predictions demonstrating the adequacy of the model structure to describe the time course of CBD, 7-OH-CBD and 7-COOH-CBD concentrations.

The final model pcVPC is illustrated below:

Figure 9 Prediction-Corrected Visual Predictive Check of the Final Population Pharmacokinetic Model versus Time, Stratified by Visit (Top Panel: VISIT A2; Bottom Panel: VISIT A8)



NOTE: The blue areas are the 95% predictions intervals of the first and third quartiles. The pink areas are the 95% predictions intervals of the median. The lower and upper dotted lines are the first and third quartiles of observations, respectively. The solid lines are the median observations.

Exploratory Covariate Screening and Covariate Analysis

None of the covariates were included in the final population PK model, which was therefore identical to the base model.

Table 10 Influence of Extrinsic Factors on CBD Exposure Endpoint Ratios of Geometric Means

Extrinsic Factor	N	GMR $AUC_{CBD\ v8\ 24h}$	GMR $AUC_{CBD\ v8\ 24h\ 5\%}$	GMR $AUC_{CBD\ v8\ 24h\ 95\%}$	GMR CmaxssCBD	GMR CmaxssCBD 5%	GMR CmaxssCBD 95%
Total	199						
Female/Males	95/104	0.970	0.971	0.968	0.980	0.983	0.978
Black African American / White	8/172	1.001	0.788	1.272	0.995	0.796	1.245
Asian / White	5/172	1.226	0.645	2.330	1.174	0.616	2.237
Other / White	14/172	1.036	0.873	1.228	1.027	0.859	1.227
[Age 2-5 yrs] / [Age >18 yrs]	16/65	0.568	0.548	0.588	0.565	0.544	0.587
[Age 6-11 yrs] / [Age >18 yrs]	65/65	0.661	0.661	0.662	0.673	0.675	0.671
[Age 12-18 yrs] / [Age >18 yrs]	53/65	0.707	0.683	0.731	0.712	0.688	0.737
[WT < 60] / [WT 60-90 kg]	155/35	0.628	0.681	0.579	0.621	0.673	0.573
[WT>90] / [WT 60-90 kg]	9/35	1.029	0.932	1.137	1.027	0.940	1.121
Ketogenic diet[1] (With/Without)	13/184	0.721	0.624	0.834	0.733	0.632	0.851
Clobazam (With/Without)	100/99	1.061	1.060	1.062	1.061	1.062	1.060
Levetiracetam (With/Without)	62/137	1.028	0.981	1.078	1.029	0.980	1.080
Topiramate (With/Without)	28/171	0.659	0.590	0.737	0.651	0.582	0.728
Valproate (With/Without)	49/150	1.268	1.185	1.357	1.290	1.204	1.383
Paracetamol (With/Without)	6/193	0.898	0.835	0.966	0.877	0.808	0.952
Rufinamide (With/Without)	63/136	0.837	0.818	0.857	0.844	0.827	0.861
Lamotrigine (With/Without)	66/133	1.174	1.107	1.245	1.159	1.092	1.230
CYP3A4 inhibitors[2] (With/Without)	13/186	0.939	0.626	1.410	0.943	0.631	1.409
CYP3A4 inducers[3] (With/Without)	71/128	0.839	0.829	0.849	0.841	0.834	0.849
CYP2C19 inhibitors[4] (With/Without)	44/155	1.012	0.956	1.070	1.024	0.974	1.077

[1] *Two patients had their ketogenic diet status unknown.*
[2] *Examples of CYP3A4 inhibitors: ketoconazole, grapefruit juice, clarithromycin and posaconazole.*
[3] *Examples of CYP3A4 inducers: carbamazepine, St John's wort, efavirenz and rifampin.*
[4] *Examples of CYP2C19 inhibitors: ketoconazole, fluconazole, carbamazepine and omeprazole.*

Simulation of exposure in children

Children aged 2-17 years:

The trial design used for simulation of CBD plasma concentration-time profiles following oral *administration in children aged 2-17 years, was based on the studies GWEP1414 and GWEP1423*

Children aged 1-24 months:

A series of simulations were run using the paediatric CBD-OS PBPK model to predict the concentration time-profiles of CBD in children aged 1 to 24 months. Application of the adult CBD-OS PBPK model within the paediatric simulator failed to adequately predict the observed paediatric plasma CBD concentration-time profiles and an increase in the fa to 0.45 for the paediatric model was required. This could be related to the intake of food in the patients, however, protocols for studies GWEP1414 and GWEP1423 did not contain any information regarding the prandial state of the patients, nor is

there any information regarding the impact of food on CBD PK in paediatric populations to support this assumption. Furthermore, the limited number of individuals less than 6 years old restricted the comparison at the most sensitive age group studied.

Predicted plasma concentrations of CBD on Day 14 of multiple oral dosing with CBD OS (10 mg/kg b.i.d.) to children aged 1-24 months, 2-5 years, 6-11 years, and 12-17 years were simulated. Predicted mean plasma Cmax and AUC(0-24h) values for each age group are tabulated below.

Table 11 Day 14 Mean Predicted Cmax and AUC(0-24h) for CBD Following MD CBD-OS Administration (10 mg/kg b.i.d.) in Pediatric Populations Using Ontogeny Models

Age group	Ontogeny model A		Ontogeny model B	
	C_{max}	AUC_{0-24h}	C_{max}	AUC_{0-24h}
	(ng/mL)	(ng/mL.h)	(ng/mL)	(ng/mL.h)
1 month	508.3	2641	622.4	3383
2 months	487.6	2476	614.0	3266
3 months	477.7	2396	602.1	3156
4 months	471.1	2343	588.4	3044
5 months	466.0	2308	575.3	2949
6 months	464.3	2293	565.8	2885
7 months	462.8	2282	557.8	2833
8 months	461.0	2275	549.9	2787
9 months	456.3	2247	539.8	2725
10 months	454.5	2240	533.5	2692
11 months	452.7	2230	527.8	2659
12-14 months	450.7	2223	519.9	2618
15-17 months	449.6	2223	512.9	2585
18-20 months	449.3	2224	508.6	2564
21-23 months	450.3	2239	506.9	2566
2-5 years	445.9	2280	489.3	2543
6-11 years	451.7	2426	467.5	2529
12-17 years	489.0	2853	486.5	2834

Impaired renal function

The effect of reduced renal function was studied in study GWEP1540 in subjects with mild (CLCR 50 to 80 ml/min), moderate (CLCR 30 to < 50 ml/min), and severe (CLCR < 30 ml/min) renal impairment compared with subjects with normal renal function (CLCR > 80 ml/min). Patients with end-stage renal disease have not been specifically studied in the CBD-OS development programme.

Time concentration profiles for CBD are tabulated below:

Table 12 PK Parameters for CBD (Excluding Subjects with %AUC Extrapolation Obs > 30)

Renal Function Group	C_{max} (ng/mL)[a] n=8	t_{max} (h)[b] n=8	$t_{1/2}$(h)[c] n=8	$AUC_{(0-t)}$ (ng*h/mL)[a] n=8	$AUC_{(0-\infty)}$ (ng*h/mL)[a] n=8	$\%AUC_{extra}$[c] n=8	CL/F (L/h)[c] n=8	V_z/F (L)[c] n=8
Group 1 Mild RI	199.669 (42.69)	2.5 (1.5-5.0)	15.508[d] (64.45)	670.588 (40.88)	600.165[e] (49.99)	7.498[e] (72.95)	364.502[e] (52.27)	6660.57[e] (55.48)
Group 2 Moderate RI	171.653 (85.29)	2 (2.0-3.0)	14.603[d] (46.62)	529.623 (74.42)	522.483[d] (63.56)	7.986[d] (55.45)	433.809[d] (50.37)	7778.06[d] (57.95)
Group 3 Severe RI	155.372 (40.62)	2.5 (1.5-7.0)	13.092[d] (41.48)	531.958 (32.73)	601.135[d] (35.89)	8.634[d] (31.31)	350.711[d] (37.31)	6015.80[d] (39.89)
Group 4 Normal RF	152.832 (74.70)	2.5 (2.0-3.0)	11.164 (47.22)	464.291 (77.62)	499.457 (76.58)	6.806 (27.35)	509.664 (87.58)	5799.54 (29.22)

RF, renal function; RI, renal impairment.
a Geometric mean (CV%).
b Median and range.
c Arithmetic mean (CV%).
d n=6.
e n=4.

For the main metabolites, 6- and 7-OH-CBD and 7-COOH-CBD, similar patterns are documented: no differences were apparent. These data do not signify any difference between groups pertaining to renal excretion of CBD and its metabolites.

Urine concentrations of CBD and metabolites were below the limit of quantification (< 2 ng/ml) for most subjects at most time points, or detectable only at trace concentrations.

Impaired hepatic function

The effect of impaired hepatic function was studied in study GWEP1539 in subjects with mild (Child-Pugh Grade A, Score: 5–6), moderate (Child-Pugh Grade B, Score: 7–9), or severe (Child Pugh Grade C, Score: 10–15) hepatic impairment compared with subjects with normal hepatic function.

The main results for CBD PK are presented below:

Table 13 CBD Pharmacokinetic Parameters (PK Set)

Parameter	Geometric mean (Geometric CV%)[a]			
	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)	Normal Hepatic Function (n=8)
C_{max} (ng/mL)	233.08 (70.51)	354.15 (42.33)	380.94 (52.22)	148.00 (64.97)
$AUC_{(0-\infty)}$ (h*ng/mL)[c]	699.48 (44.18)	1162.70 (39.88)	2438.53 (29.54)[b]	473.68 (73.83)
$AUC_{(0-t)}$ (h*ng/mL)	648.09 (44.24)	1054.15 (38.90)	1855.10 (51.99)	449.08 (73.50)
CL/F (L/h)	285.93 (44.18)	172.01 (39.88)	82.02 (29.54)[b]	422.23 (73.83)
V_z/F (L)	5302.44 (60.06)	4668.44 (40.13)	2437.09 (70.52)[b]	4105.49 (37.50)
t_{max} (h)	2.8 (1.5-5.0)	2.0 (1.5-3.0)	2.5 (2.0-5.0)	2.3 (1.5-5.0)
$t_{½}$ (h)[d]	15.68 (58.31)	20.47 (39.19)	22.05 (44.94)[b]	8.58 (68.38)
$C_{max(u)}$ (ng/mL)	10.42 (83.24)	27.51 (119.04)	36.96 (120.60)	9.99 (63.41)
$AUC_{(0-\infty)(u)}$ (h*ng/mL)[c]	31.27 (58.48)	90.32 (118.21)	269.56 (89.72)	31.98 (76.73)
$AUC_{(0-t)(u)}$ (h*ng/mL)	28.98 (58.34)	81.89 (119.29)	180.01 (126.70)	30.32 (76.71)
$CL_{(u)/F}$ (L/h)	12.78 (79.62)	13.36 (64.47)	9.07 (71.55)[b]	28.51 (87.94)
$V_{z(u)}/F$ (L)	237.08 (85.25)	362.65 (58.71)	269.40 (128.11)[b]	277.18 (42.83)

[a]*Except for tmax where median and range are shown and t½ where arithmetic mean and %CV are shown.*
[b]*n=5.*
[c]*Percent extrapolation ≤ 30% was required to retain AUC(0-∞) for unbound and total fractions; subjects that did not satisfy this criterion were excluded from the analysis.*
[d]*Percent extrapolation ≤ 30% and r2> 0.80 was required to retain t½; subjects that did not satisfy these criteria were excluded from the analysis.*

For CBD and 7-OH-CBD, there were consistently > 2-fold increases in both total and unbound Cmax, AUC (0-∞) and AUC(0-t) in the moderate and severe hepatic impairment groups, compared with subjects with normal hepatic function, with the following exceptions:

7-OH-CBD: the increase approached 2-fold (was 1.92-fold) for AUC (0 t) in the moderate hepatic impairment group compared with subjects with normal hepatic function.

For 7-COOH-CBD, both total and unbound Cmax were unchanged in moderate/normal, reduced slightly in mild/normal and greatly reduced in severe/normal (ratio of geometric least squared means was approximately 0.3 and the upper and lower 90% CI were less than 1.0). The ratios for total and unbound 7-COOH-CBD AUC (0-∞) and AUC (0-t) showed some fluctuations with hepatic impairment relative to normal hepatic function; however, except for AUC (0-t) in the severe hepatic impairment group, the 90% CI all included 1.

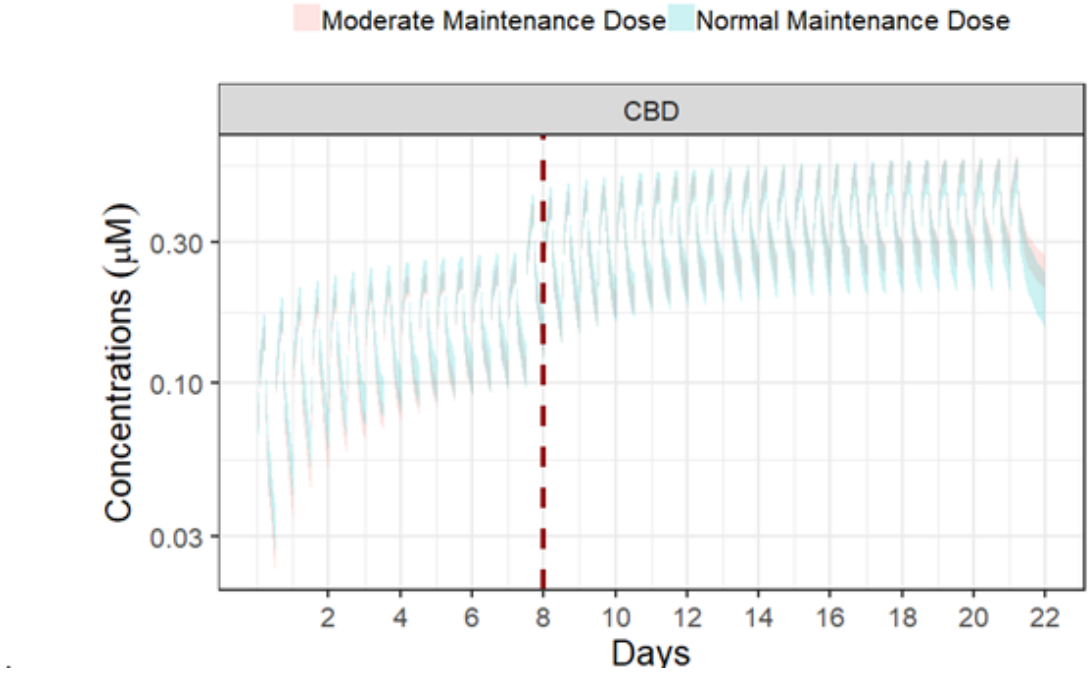
The ratio of geometric LS means comparing CBD CL/F between hepatic impairment groups and the normal hepatic function group was reduced in all cases (upper and lower limits of 90%CI were < 1.0 in all cases except for total CL/F in the mild hepatic impairment group relative to normal hepatic function [upper limit was 1.11]), and was lowest in the severe hepatic impairment.

Simulated exposures for the proposed dose adjustment in hepatic impaired patients are displayed below. Simulated exposures achieved in patients with moderate hepatic impairment were similar to

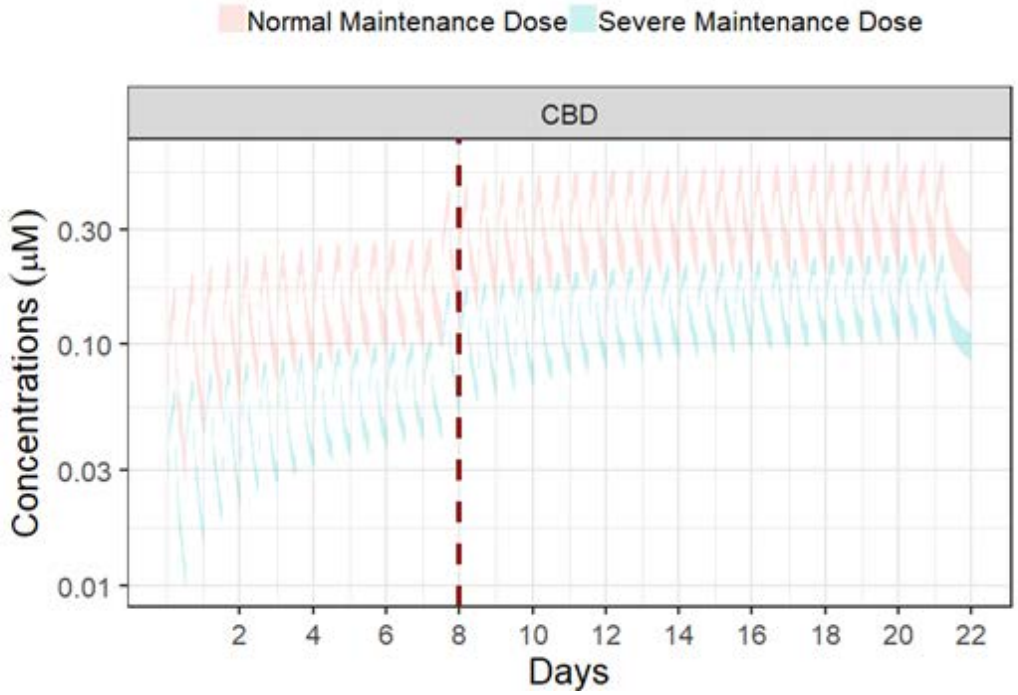
exposures in subjects with normal hepatic function when the dosing recommendations provided in the SmPC were applied. However, simulated exposures for subjects with severe hepatic impairment were approximately half those for subjects with normal hepatic function. In the SmPC the applicant has adequately addressed that CBD efficacy may be reduced in patients with severe hepatic impairment.

Figure 10 Pharmacokinetic Simulation for the Proposed Dose Adjustment in Hepatically Impaired Patients

A) Moderate Hepatic impairment



B) Severe Hepatic Impairment



Gender

A slight increase in CBD (but not of the major metabolites) clearance among female patients is noticed.

Race

Data were insufficient for a specific analysis. Please refer to PoP-PK analysis.

Weight

No specific analysis of weight on the PK of CBD from individual studies has been made. The PoP-PK analysis suggest some difference in exposure in subjects weighing less than 60 kg:

During initial model development, body weight was included allometric through relationships on clearance and volume parameters as part of the structural population PK model for CBD, 7-OH-CBD and 7-COOH-CBD (GWPP17004). When estimating the allometric coefficients, they converged to 0, indicating no effect of body weight on these parameters.

Consistent with this, no effects of body weight on any of the PK parameters were found in LGS patients as part of covariate analyses. The proposed mg/kg dose for CBD OS therefore results in somewhat lower exposures in the lowest weight (paediatric) subjects.

The details of the complete datasets from trials GWEP1414 and GWEP1423 that were used as source data included in the POPPK model were not specifically included in the GWPP17004 PK report. These details are now detailed in the table below. Only 20/216 subjects had a baseline body weight < 20 kg.

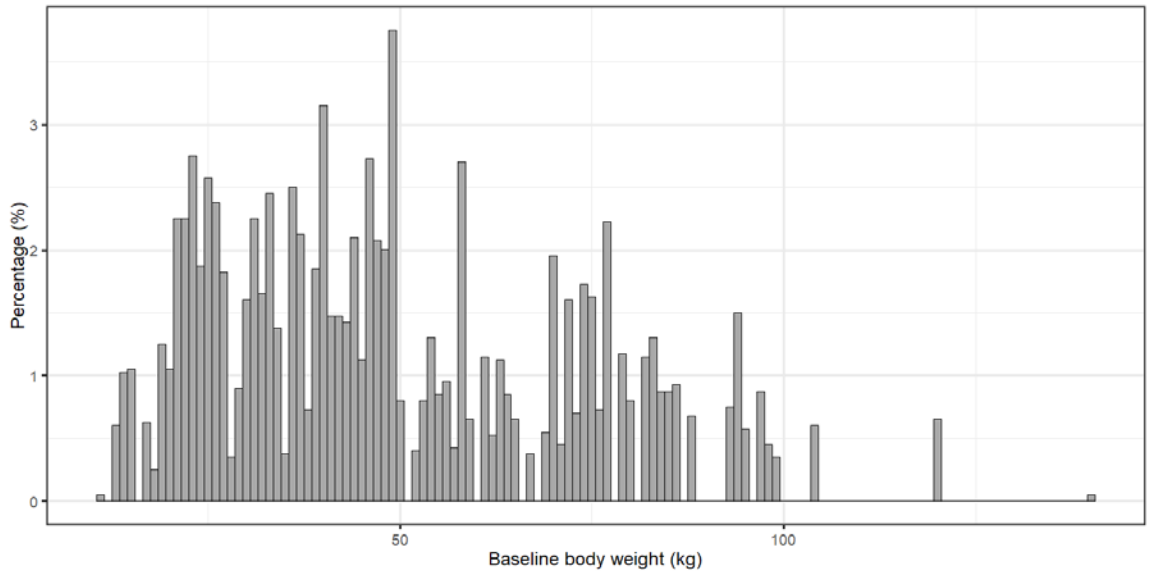
Table 14 Analyses Dataset Included in Study GWPP17004 Presented by Age and Baseline Body Weight

	Patients Included in the Analysis Dataset						
		2-17 years n (%)			≥ 18 years n (%)		
Trial Treatment Arm	Total n (%)	All n (%)	BSLWT < 20 kg n (%)	BSLWT ≥ 20 kg n (%)	All n (%)	BSLWT < 20 kg n (%)	BSLWT ≥ 20 kg n (%)
GWEP1414							
10 mg/kg CBD-OS	64 (100)	46 (71.9)	7 (10.9)	39 (60.9)	18 (28.1)	0	18 (28.1)
20 mg/kg CBD-OS	74 (100)	51 (68.9)	6 (8.1)	45 (60.8)	23 (31.1)	0	23 (31.1)
Total Active Groups	**138 (100)**	**97 (70.3)**	**13 (9.4)**	**84 (60.9)**	**41 (29.7)**	**0**	**41 (29.7)**
GWEP1423							
20 mg/kg CBD-OS	78 (100)	45 (57.7)	7 (9.0)	38 (48.7)	33 (42.3)	0	33 (42.3)
Total Active Groups	**78 (100)**	**45 (57.7)**	**7 (9.0)**	**38 (48.7)**	**33 (42.3)**	**0**	**33 (42.3)**

BSLWT, Baseline body weight.
Note: Two patients (1 in GWEP1414 and 1 in GWEP1423) were excluded from the analysis for GWPP17004 based on graphical diagnostics and the modelling process.
Note: Analysis dataset includes the patients with evaluable PK data included in the model.

The GWEP1414 protocol was amended to exclude collection of blood samples from patients < 20 kg. The figure 12 below shows the distribution of weight data within the PK analysis sets from both GWEP1414 and GWEP1423 and there was no truncation in baseline weight data.

Figure 11 Distribution of Weight Data from Trials GWEP1414 and GWEP1423, Excluding Patients < 20 kg.



Elderly

Not applicable; no patient above the age of 55 was included.

Children

There were changes in CBD and metabolite exposure with age in LGS patients (exposures were higher in older [18 to 55-year old] patients compared with younger [2 to 17 year old] patients) at both trial visits where PK were investigated. Exposure simulations from the PoP-PK model did not recover these findings in that age did not have a significant effect on the PK of CBD at the given weight-based posology. However, age was evaluated as a covariate of the POPPK model in patients with LGS only.

Pharmacokinetic interaction studies

In Vitro

In vitro data suggest that clinically relevant DDIs between CBD and other drugs may be relevant for a number of enzymes and transporters involved.

CYP and UGT inhibition and induction

CBD is a direct reversible inhibitor of major hepatic CYP450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP3A4. Typical IC50 values were < 10 µM [except CYP2C9, CYP2E1, and CYP2D6 with IC50 > 10 µM]). The most potent reversible inhibition was observed with CYP3A4. CBD is also a time dependent inhibitor of CYP3A4 and CYP1A2 in vitro. CBD shows a positive inductive effect on CYP1A2, CYP2B6, and CYP3A4. CBD shows potent inhibition of UGT1A9 and UGT2B7. 7-OH-CBD and 7-COOH-CBD inhibited the major UGT isoenzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) with IC50 values ranging from 5 to 70 µM.

CBD as substrate inhibitor or inductor of transporters

In vitro, CBD does not appear to be a substrate of or inhibitor of major transporters including p-glycoprotein, OATP1B2, OATP2B1:

CBD is not a substrate for P-glycoprotein (P-gp) multidrug resistance protein 1. CBD is not a substrate or inhibitor of brain transporters organic anion transporter polypeptide (OATP) 1A2 or OATP2B1. 7-OH-CBD and 7-COOH-CBD are not substrates of BCRP, OATP1B1, OATP1B3, or OCT1.

CBD and 7-OH-CBD do not inhibit the major renal or hepatic uptake transporters.

7-OH-CBD does not inhibit OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, OCT1, or multidrug and toxin extrusion (MATE)2-K; at other transporters 7-OH-CBD is a weak inhibitor.

7-COOH-CBD does not inhibit OCT2, OCT1, MATE1, or MATE2 K; 7-COOH-CBD weakly inhibits P-gp, OAT1, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, OAT3, and bile salt export pump.

Based on plasma exposures, there is a potential for 7-COOH-CBD to interact with BCRP, OAT3 and OATP1B3 in vivo.

In silico

The final adult PBPK model for CBD-OS was based on both in vitro and in vivo data. Predicted geometric mean AUC(0-24h) and Cmax ratios for various test CYP450 and UGT substrates in the absence and presence of CBD OS (750 mg b.i.d. for 7 days), administered to subjects of various ages are presented in table below. Data are based on simulated results of 100 subjects over 10 trials. Results are tabulated below:

Table 15 Geometric Mean AUC(0-24h) and Cmax ratios for Test CYP450 and UGT Substrates in the Absence and Presence of CBD OS (750 mg b.i.d. for 7 days) Administered to Subjects of Various Ages

Population	$AUC_{(0-24h)}$ Ratio		C_{max} Ratio	
	GMR	90% CI	GMR	90% CI
Bupropion (150 mg, single oral dose): sensitive CYP2B6 substrate				
Adults (18+ years)	1.08	1.07, 1.09	1.07	1.06, 1.08
Adolescents (12-17 years)	1.11	1.10, 1.12	1.09	1.08, 1.10
Children (2-11 years)	1.11	1.09, 1.13	1.09	1.07, 1.10
Rosiglitazone (4 mg, single oral dose): sensitive CYP2C8 substrate				
Adults (18+ years)	1.01	1.01, 1.02	1.00	1.00, 1.00
Adolescents (12-17 years)	1.03	1.02, 1.03	1.00	1.00, 1.00
Children (2-11 years)	1.02	1.02, 1.02	1.00	1.00, 1.00
Repaglinide (0.25 mg, single oral dose): sensitive CYP2C8 substrate				
Adults (18+ years)	1.72	1.63, 1.81	1.41	1.37, 1.45
Adolescents (12-17 years)	1.80	1.71, 1.89	1.44	1.40, 1.47
Children (2-11 years)	1.94	1.83, 2.06	1.45	1.42, 1.49
S-warfarin (10 mg, single oral dose): sensitive CYP2C9 substrate				
Adults (18+ years)	1.01	1.01, 1.01	1.00	1.00, 1.00
Adolescents	1.02	1.02, 1.02	1.01	1.01, 1.01

Population	$AUC_{(0-24h)}$ Ratio		C_{max} Ratio	
	GMR	90% CI	GMR	90% CI
(12-17 years)				
Children (2-11 years)	1.02	1.02, 1.02	1.01	1.01, 1.01
Tolbutamide (500 mg, single oral dose): sensitive CYP2C9 substrate				
Adults (18+ years)	1.02	1.02, 1.02	1.01	1.01, 1.01
Adolescents (12-17 years)	1.03	1.03, 1.03	1.02	1.01, 1.02
Children (2-11 years)	1.02	1.02, 1.02	1.01	1.01, 1.01
Midazolam (5 mg, single oral dose): sensitive CYP3A4 substrate				
Adults (18+ years)	8.87	7.81, 10.1	2.81	2.65, 2.97
Adolescents (12-17 years)	9.44	8.25, 10.8	2.70	2.57, 2.84
Children (2-11 years)	11.5	10.0, 13.1	2.82	2.69, 2.96
Simvastatin (40 mg, single oral dose): sensitive CYP3A4 substrate				
Adults (18+ years)	26.7	24.5, 29.1	11.7	10.8, 12.6
Adolescents (12-17 years)	29.1	26.8, 31.7	11.7	10.9, 12.6
Children (2-11 years)	28.1	25.8, 30.6	10.7	9.97, 11.5
Propofol (2 mg/kg i.v.,single dose): sensitive UGT1A9 substrate				
Adults (18+ years)	1.21	1.18, 1.25	NC	NC
Adolescents (12-17 years)	1.43	1.38, 1.48	NC	NC
Children (2-11 years)	1.41	1.36, 1.46	NC	NC
Lorazepam (2 mg, single oral dose): sensitive UGT2B7 substrate				
Adults (18+ years)	1.34	1.32, 1.36	1.22	1.20, 1.23
Adolescents (12-17 years)	1.40	1.38, 1.43	1.25	1.23, 1.26
Children (2-11 years)	1.31	1.29, 1.33	1.21	1.19, 1.23
Zidovudine (200 mg, single oral dose): sensitive UGT2B7 substrate				
Adults (18+ years)	1.44	1.40, 1.48	1.13	1.11, 1.15
Adolescents (12-17 years)	1.59	1.55, 1.64	1.15	1.13, 1.17
Children (2-11 years)	1.37	1.34, 1.40	1.08	1.06, 1.09

The influence of concomitant administration of several drugs, CLB, LEV, TPM, VPA, paracetamol and lamotrigine on CBD has been evaluated as part of a population PK model in LGS patients. Dedicated Clinical DDIs studies have been conducted in patients (clobazam) and in healthy volunteers (clobazam, stiripentol and valproate).

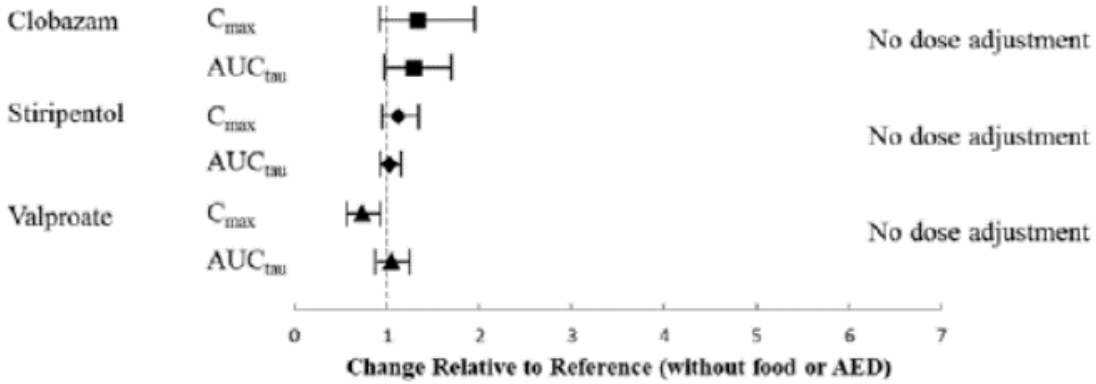
In vivo

Stiripentol, clobazam and valproate in healthy volunteers.

Study GWEP1543 was a clinical DDI open-label, fixed sequence DDI trial determined whether steady state CBD-OS (750 mg b.i.d. or placebo) affected the PK profiles of steady state antiepileptics, CLB (5 mg), STP (750 mg) or VPA (300-500 mg), and vice versa (effect of AEDs on CBD-PK). It was designed as 6 parallel groups of 12 healthy subjects (except in Groups 2 [CBD OS and CLB] and 6 [CBD OS and VPA], which recruited 15 and 14 subjects, respectively). In all DDI studies, all investigational drugs were administered 30 minutes after a non-standardized meal.

The main inferential PK analyses are illustrated and tabulated below.

Figure 12 Effect of selected AEDs on CBD PK



For exposure of CBD metabolites, the data pertaining to clobazam is tabulated below.

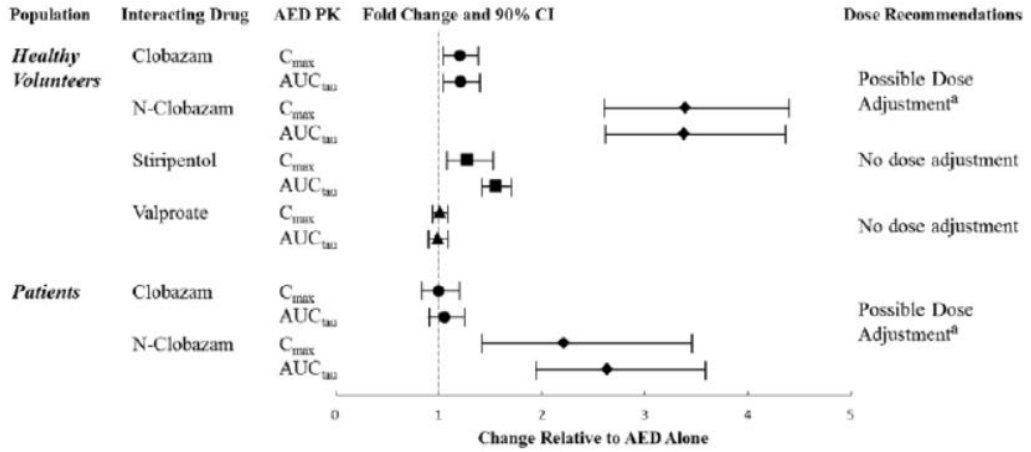
Table 16 Summary of PK Parameters For CBD, 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD

Trial Day	Treatment	PK Parameter	CBD	6-OH-CBD	7-OH-CBD	7-COOH-CBD
Group 1: CLB + GWP42003-P						
Day 23	750 mg GWP42003-P (n=3)	C_{max} (ng/mL) [a]	865 (65.2)	9.63 (18.6)	224 (7.3)	2670 (14.6)
		AUC_{tau} (h*ng/mL) [a]	2390 (32.3)	38.4 (18.2)	854 (29.4)	18400 (18.4)
		t_{max} (hours) [b]	5.00 (5.00-5.00)	5.00 (5.00-6.00)	5.00 (5.00-6.00)	6.00 (5.00-12.00)
	250 mg GWP42003-P (n=9)	C_{max} (ng/mL) [a]	256 (42.6)	5.00 (30.9)	62.7 (31.7)	952 (30.2)
		AUC_{tau} (h*ng/mL) [a]	802 (17.7)	17.6 (15.4)	259 (24.2)	6850 (27.7)
		t_{max} (hours) [b]	5.00 (2.50-6.00)	3.00 (3.00-5.00)	3.00 (3.00-6.00)	6.00 (4.00-12.00)
Day 29/36	750 mg b.i.d. GWP42003-P + 5 mg CLB (n=12)	C_{max} (ng/mL) [a]	950 (63.1)	15.5 (47.9)	276 (54.9)	11200 (48.4)
		AUC_{tau} (h*ng/mL) [a]	3730 (37.0)	97.9 (46.1)	1620 (39.9)	116000 (46.6)
		t_{max} (hours) [b]	5.00 (2.00-6.00)	5.00 (2.00-6.00)	5.00 (2.00-6.00)	5.00 (0.00-12.00)

NC, not calculable.
aGeometric mean (intra + intersubject CV%)

bMedian (range)

Figure 13 Effect of CBD on AEDs



[a] Caution should be taken and dose modification may be necessary when coadministering CBD-OS with CLB in patients.

Concomitant administration of clobazam and CBD resulted in noticeable DDIs: a 2-4-fold increase in the active N-clobazam exposure and while no or minor effect of clobazam on CBD, and increase in exposure to the main active metabolites -7-OH-CBD of about 30 to 70%.

A minor effect on stiripentol exposure was found with exposure increases in stiripentol AUC of about 55% and Cmax of about 28%.

For main inferential result, please refer to the figure 12. Concomitant administration of CBD and clobazam resulted in a 2-3-fold exposure to the main active metabolite of clobazam, N-clobazam. This result is, while of a lesser order of magnitude, consistent with the findings in healthy volunteers.

The applicant is in the process of re-evaluating the DDI potential for CBD by updating the PBPK model. The new model will include influences of the metabolites on various enzyme systems. In addition, a number of DDI studies have either been completed, are ongoing, or planned. Data from these studies will also be used to inform the improved PBPK DDI predictions.

Exposure relevant for safety evaluation

Potential for confounding of efficacy attributable to either CBD-OS, CLB or STP during concomitant use was investigated.

The relationships between the exposures of CBD, 7-OH-CBD and 7-COOH-CBD, and safety as characterized by the occurrence of selected AEs were investigated in LGS patients through exploratory logistic regression analyses. The following AEs were included in the exploratory analyses: alkaline phosphatase (ALP) > 2 × ULN, ALT > 2 × ULN, AST > 2 × ULN, bilirubin > 2 × ULN, diarrhoea, fatigue, GGT > 2 × ULN, loss of appetite, maculopapular rash, nausea, rash, and somnolence.

An overview of statistically significant associations is tabulated below.

Table 17 Overview of statistically significant correlations in exploratory logistic regression of adverse events and the exposure (AUC) of the 3 analytes

AE	AUC CBD	AUC 7-OH-CBD	AUC 7-COOH-CBD	Yes	No
ALP > 2 × ULN				11	349
ALT > 2 × ULN	++	++	+	44	316
AST > 2 × ULN	++	++		23	337
Bilirubin > 2 × ULN				0	360
Diarrhoea	+			43	317
Fatigue	+	+	+	20	340
GGT > 2 × ULN	+			107	253
Loss of appetite	++	++	++	44	316
Maculopapular rash				5	355
Nausea				9	351
Rash	+	+	+	19	341
Somnolence	++	++	++	56	304

Note: ++, p<0.01 and positive correlation; +, p<0.05 and positive correlation. Yes and No columns indicate the numbers of subjects with at least 1 of the given AE (Yes) or not (No).

Consistent, highly statistically significant correlations were observed across the 3 analytes (p<0.01 for CBD and 7-OH-CBD; p<0.05 for 7-COOH-CBD) for ALT > 2 × ULN, AST > 2 × ULN (except 7-COOH-CBD), loss of appetite, and somnolence; increasing exposure to CBD and its metabolites appeared to be associated with an increased frequency of these types of AEs. There was a correlation between the AUCs of CBD and the metabolites, so it was not possible to distinguish between the effect of CBD and the metabolites on response endpoints, nor was this analysis intended to conclude on the activity of the metabolites.

Pharmacokinetics using human biomaterials

2.4.3. Pharmacodynamics

Mechanism of action

The exact mechanism of action of CBD is not completely elucidated. CBD is a cannabinoid but shares none of the pharmacologic features of the archetypal cannabinoid, Δ9-tetrahydrocannabinol (THC). CBD has negligible affinity or activity at either the cannabinoid (CB1 or CB2) receptors *in vitro*, and is negative in the tetrad test, an accepted bioassay for CB1 agonism.

However, the main mechanisms which contribute to the CBD activity are modulation of intracellular Ca2+ levels and adenosine re-uptake inhibition. Modulation of intracellular Ca2+ is influenced through inhibition of GPR55 (G-protein coupled receptor) and TRPV1 (Transient receptor potential vanilloid). GPR55 is a trans-membrane receptor which increases the intracellular Ca2+ levels via release of IP3-gated intracellular stores. CBD acts as a GPR55 antagonist and doing so prevents from increase in the intracellular Ca2+levels, thus excitatory neurotransmission. The other possible GPR55 activity is regulation of neuro-inflammatory processes. As neuro-inflammation participates in development and maintenance of epilepsy, potential to attenuate inflammatory activity could contribute to the anticonvulsant effects.

TRPV1 channel is a non-selective ion channel. Its activation results in desensitisation and consequent decrease in Ca2+ influx. Therefore, modulation of the activity of this channel also contributes to the decrease in the neuronal excitability.

The other involved mechanism is inhibition of adenosine re-uptake leading to increase in an adenosine extracellular concentration. Adenosine acts via A1 and A2A receptors as an anticonvulsant and anti-

inflammatory agent. Increasing of the extracellular adenosine level makes adenosine available for the activation of these receptors.

Primary and Secondary pharmacology

Human abuse liability

GWEP1431 was a randomized, double-blind, double-dummy, placebo- and active-controlled crossover trial evaluated the abuse potential of single doses of 750, 1500, and 4500 mg CBD OS compared with alprazolam (2 mg), dronabinol (10 and 30 mg) and placebo in 95 healthy recreational polydrug users (mean age 37.7 years). Plasma concentrations of CBD, its main metabolites, THC and its main metabolites were measured. Primary pharmacodynamic outcome was scored in Drug Liking VAS (E max).

Summary of the main PD outcome analysis using Drug Liking VAS scale is tabulated below.

Table 18 Summary of Drug Liking VAS Parameters – Primary and Secondary Endpoints (Completer Population)

			DRO		GWP42003-P		
	Placebo (N=35)	ALP 2 mg (N=35)	10 mg (N=35)	30 mg (N=35)	750 mg (N=35)	1500 mg (N=35)	4500 mg (N=35)
	Mean (SD) Median						
E_{max}	54.6 (11.14) 50.0	79.1 (15.66) 79.0	73.5 (19.18) 72.0	86.7 (14.82) 90.0	56.8 (13.81) 51.0	61.1 (16.52) 51.0	64.1 (17.14) 56.0
E_{maxD}	54.6 (11.14) 50.0	79.1 (15.66) 79.0	88.9 (13.28) 96.0		67.6 (18.35) 64.0		
E_{min}	44.9 (12.91) 50.0	39.5 (17.36) 50.0	45.0 (11.51) 50.0	44.0 (14.11) 50.0	46.1 (11.87) 50.0	45.0 (12.89) 50.0	42.7 (15.31) 50.0
TA AUE	51.0 (4.65) 50.0	63.6 (14.03) 58.8	58.5 (10.97) 55.4	66.0 (13.43) 63.2	50.7 (3.98) 50.0	52.5 (7.81) 50.1	51.7 (9.04) 50.3

ALP = alprazolam; DRO = dronabinol; Emax = maximum effect; EmaxD = maximum effect at any dose level; Emin = minimum effect; SD = standard deviation; TA_AUE = time-averaged area under the effect curve; VAS = visual analogue scale.
Drug Liking VAS item: "At this moment, my liking for this drug is", where responses range from 0 (Strong disliking) to 50 (Neither like nor dislike) to 100 (Strong liking).

While mean Drug Liking VAS Emax values for GWP42003-P were only slightly greater than those of placebo at the 2 higher dose levels, mean Emax with alprazolam 2 mg and dronabinol 30 mg were markedly higher (≥ 15 points compared to placebo and all doses of GWP42003-P), with an intermediate value observed for dronabinol 10 mg. Median Drug Liking VAS Emax values for GWP42003-P doses were even lower, while median scores with alprazolam 2 mg and dronabinol 10 mg doses were similar to mean scores, or in the case of dronabinol 30 mg, slightly higher. While alprazolam and GWP42003-P 4500 mg were associated with the lowest mean Drug Liking VAS Emin values, mean values for all active treatments were relatively similar to placebo and median scores for all treatments were 50.0, indicating little or no disliking.

Main results from the pharmacodynamic inference analysis is tabulated below:

Table 19 Comparison of Drug Liking VAS Emax – Primary Endpoint (Completer Population)

Contrasts	LS Mean (SE)[a]	95% CI	P-value
Positive Controls *vs* Placebo (Trial Validity)			
ALPZ 2 mg - Placebo	24.2 (3.06)	18.2, 30.3	**<0.0001**
DRO 10 mg - Placebo	18.6 (3.07)	12.6, 24.7	**<0.0001**
DRO 30 mg - Placebo	32.3 (3.06)	26.2, 38.3	**<0.0001**
CBD-OS *vs* Placebo (Absolute Abuse Potential)			
CBD-OS 750 mg - Placebo	2.0 (3.07)	-4.0, 8.1	0.5059
CBD-OS 1500 mg - Placebo	6.4 (3.05)	0.3, 12.4	**0.0389**
CBD-OS 4500 mg - Placebo	9.5 (3.05)	3.4, 15.5	**0.0022**
CBD-OS *vs* Positive Controls (Relative Abuse Potential)			
CBD-OS 750 mg - ALPZ 2 mg	-22.2 (3.05)	-28.2, -16.1	**<0.0001**
CBD-OS 1500 mg - ALPZ 2 mg	-17.9 (3.06)	-23.9, -11.8	**<0.0001**
CBD-OS 4500 mg - ALPZ 2 mg	-14.8 (3.07)	-20.8, -8.7	**<0.0001**
CBD-OS 750 mg - DRO 10 mg	-16.6 (3.06)	-22.6, -10.5	**<0.0001**
CBD-OS 1500 mg - DRO 10 mg	-12.3 (3.06)	-18.3, -6.2	**<0.0001**
CBD-OS 4500 mg - DRO 10 mg	-9.2 (3.08)	-15.2, -3.1	**0.0033**
CBD-OS 750 mg - DRO 30 mg	-30.2 (3.08)	-36.3, -24.1	**<0.0001**
CBD-OS 1500 mg - DRO 30 mg	-25.9 (3.06)	-32.0, -19.9	**<0.0001**
CBD-OS 4500 mg - DRO 30 mg	-22.8 (3.06)	-28.8, -16.8	**<0.0001**

ALPZ, alprazolam; DRO, dronabinol; Emax, maximum effect; LS, least squares; SE, standard error. Drug Liking VAS item: "At this moment, my liking for this drug is", where responses range from 0 (strong disliking) to 50 (neither like nor dislike) to 100 (strong liking).

LS means were estimated from a mixed-effects model having treatment, period, treatment sequence as fixed effects, sex as a covariate, and subject nested within sequence as a random effect. Treatment effect was significant (p<0.0001), whilst period (p=0.2243), treatment sequence (p=0.4552) and sex (p=0.8615) were not significant; carryover effect was not significant at the 25% level and dropped from the model.

Plasma concentrations of THC and/or its metabolites were present in 14/40 subjects predose in Period 1, indicating a degree of carryover from previous Cannabis use. In all CBD-OS dose groups, there were subjects with THC plasma concentrations BLQ at all postdose time points (12/26, 4/35 and 12/28 in the 750, 1500 and 4500 mg CBD-OS groups, respectively).

With CBD-OS treatment, THC plasma concentrations were low, consistent with levels of the impurity in the product, and were much lower than those detected with dronabinol. The therapeutic 750 mg CBD-OS dose showed little significant and no consistent abuse potential. Higher (high therapeutic and supratherapeutic) CBD-OS doses (1500 and 4500 mg, respectively) were associated with detectable subjective effects that were significantly lower than those of the positive controls, alprazolam and dronabinol, and not indicative of clinically important abuse potential. These results suggest that CBD-OS is associated with a minimal signal for abuse potential.

Study GWEP1542 was a randomized, double-blind trial, using a single-blind baseline, to assess withdrawal symptoms after prolonged treatment with CBD-OS. Reported scores on the Cannabis Withdrawal Scale (CWS) and Penn Physician Withdrawal Checklist (PWC-20) were low throughout the trial and no increases were seen after the abrupt discontinuation of CBD-OS. No scores were of clinical concern during the trial. Based on these results it can be concluded an abrupt discontinuation of CBD at steady state does not appear to induce withdrawal symptoms.

The results of GWEP1448 study showed no significant effect of CBD-OS on total sleep time (TST). It can be concluded that CBD does not appear to affect sleeping quality in healthy adult volunteers. Somnolence was a frequent adverse event in the clinical studies in children.

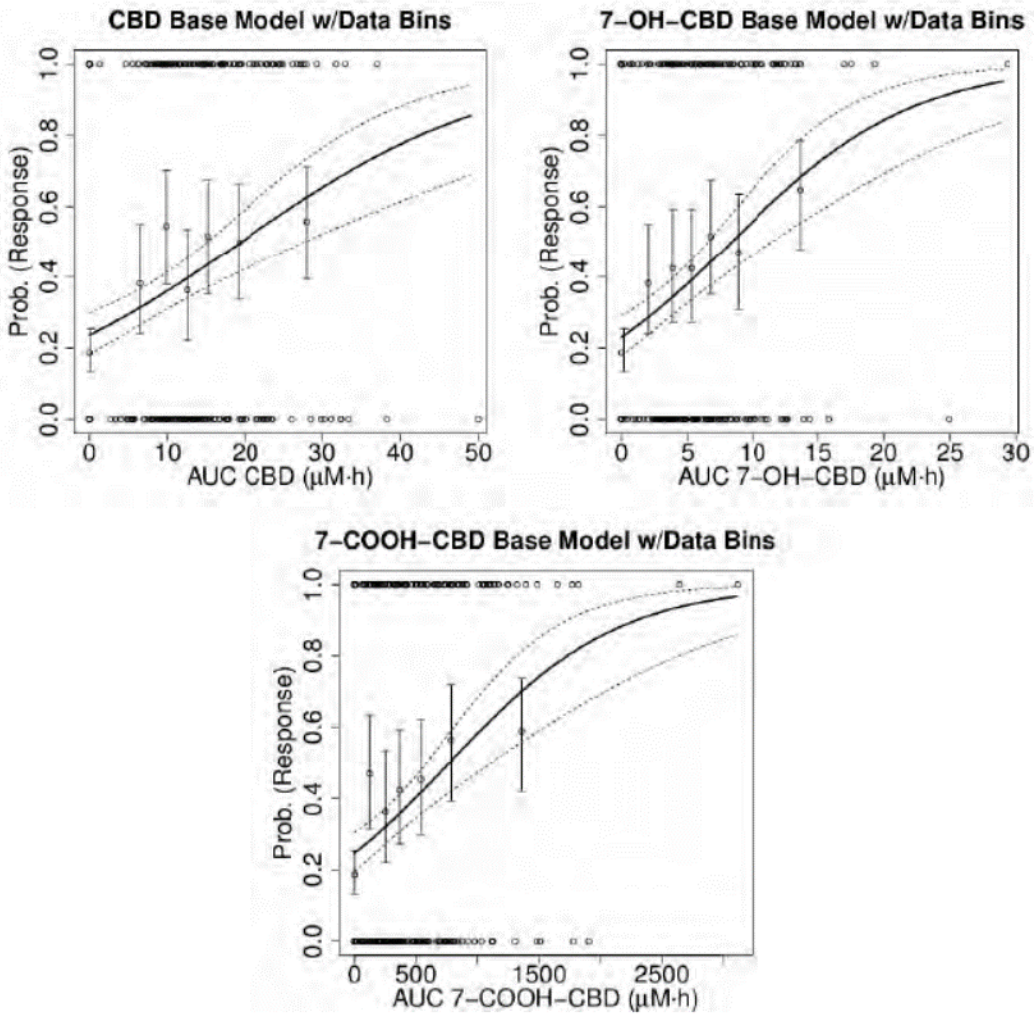
Pharmacodynamic interactions with other medicinal products or substances have not been presented by the applicant.

Relationship between plasma concentration and effect

The relationships between the exposures of CBD, 7-OH CBD and 7-COOH-CBD, and efficacy in terms of effect on the occurrence of seizures were investigated in LGS patients through exploratory logistic regression analyses. In these analyses, the concomitant use of CLB was also included as a potential covariate on the exposure response slope.

The main analysis from logistic regression are illustrated below.

Figure 14 Logistic Regression of the Probability of an LGS Patient being a Drop Seizure Responder vs. the AUC of the 3 Analytes with Binned Responder Rates Overlaid



[a] *Having a reduction in drop seizures ≥ 50%.*
Markers represent individual observed drop seizure response (0 = no response; 1 = response). Solid lines represent predicted probability from logistic regression model and dotted lines represent the 95% CI of the prediction. Vertical lines represent 95% CIs of observed responder rate (marker) by AUC bin.

Logistic regression analysis suggests a positive exposure-response relationship for the occurrence of drop seizure response across the dose range tested (placebo, 10 and 20 mg/kg/day). There was a significant positive correlation between the derived AUC of CBD at Visit 8 and the probability of a subject being a drop seizure responder. Similar correlations were observed for 7-OH-CBD and 7-

COOH-CBD. In DS patients no data is presented as this comprise much smaller patient numbers and patients who had infrequent seizures. No correlations were likely to materialize.

2.4.4. Discussion on clinical pharmacology

A national GLP inspection questioned the validity and reliability of the bioanalytical data in the preclinical studies. As similar analytical methods were used throughout the clinical pharmacology studies, serious concerns were raised about the validity of the results of the above-mentioned PK studies.

Consequently, for all studies comprising analyses of CBD, CLB, THC, STP, VPA, LEV, TPM (and its main metabolites), the applicant was requested to clarify the extent of Non-GLP/GCP compliance in details and discuss the impact of these findings on the reliability of the results.

Furthermore, an EMA GCP- inspection was triggered of a number of studies: GWEP1544, GWEP1428, GWEP1543, GWEP1332, GWEP1423, and GWEP1414 with special focus on the analytical quality and the nature of any GCP deviations.

Several concerns were raised during the EMA GCP-inspection. Despite the fact that the concerns and deficiencies were related to GCP compliance and integrity of the data, the inspector recommended the efficacy data for the assessment. The inspector´s conclusion was that the analysis of the samples and the PK calculations were conducted in overall compliance with national legislation and ICH-GCP. The bioanalytical results generated across the trials are comparable without suspicious deviations and are not significantly devalued by the exclusion of a small amount of metabolites data. Therefore, the CHMP considered that the overall PK/PD data included in the MA application was valid.

The pharmacokinetics of CBD and its main metabolites have been studied in healthy volunteers and in the target populations of DS and LGS patients. A substantial proportion of the patients studied is below the age of 18 years. Generally, the pharmacokinetics have been studied in accordance with the scientific requirements. Reported results appear consistent across studies.

Bioavailability of CBD was approximately 6.5 % following oral administration in fasting conditions. Cannabidiol appears rapidly in plasma with a time to maximum plasma concentration of 2.5–5 hours at steady state. However, distribution is expected to be similar to animal species.

The Applicant has presented data illustrating that concomitant intake of food greatly increases AUC and Cmax exposure to CBD-OS (about 4-fold) and major metabolites, including active metabolites, (about 2-fold) in healthy volunteers. It is unknown how this affects efficacy and safety as no restrictions related to concomitant food intake were included in the protocols of the phase 3 clinical studies. In addition, no data with regards to dosing in relations to meals were collected. The applicant proposes that CBD-OS should be administered with a meal. It is acknowledged that the proposed posology reads that dosage should be titrated taking into consideration response and tolerability, and furthermore that the CBD efficacy data presented is achieved on random fed status information. However, from the submitted data it is not possible to define the conditions under which CBD-OS should be administered. In order to alleviate this concern and provide meaningful instructions to the prescriber and patients, the applicant proposed that CBD-OS is administered consistently either with or without food intake. This proposal was found acceptable by the CHMP and reflected in SmPC section 4.2 and PL.

Approximately 16% of an oral dose of CBD is excreted in the urine after 72 hours suggesting renal excretion be a minor elimination pathway. However, a 72 hours urine collection period appears to be very a short period to obtain a reasonable estimate of the cumulative amount of drug excreted unchanged in the urine, as CBD-OS T1/2 has been estimated from 51-202 hours. A large proportion of CBD was excreted unchanged in faeces. In humans, hepatic clearance is a major route of CBD

metabolism. The mean CL/F of CBD in healthy subjects ranged between 375 and 1909 L/h (fasted after a single CBD-OS dose of between 200-6000 mg).

The metabolism of CBD has been appropriately studied in vitro. CBD undergoes extensive CYP-mediated metabolism to primary (active) and main (likely inactive) secondary metabolism. The main P450 enzymes are CYP2C19 which catalyses the formation of active metabolites 6-OH and, mainly, 7-OH-CBD. In turn CYP3A4 catalyses the inactivation of 7-OH-CBD to 7-COOH-CBD. This suggest that polymorphism in CYP2C19 maybe of clinical relevance to PK of CBD. When investigated, the number of different CYP2C19 phenotypes was too small, and no conclusion could be made. Study GWEP17075 investigated the relative contributions of CYP2C19 and CYP3A4 in the metabolism of CBD. It showed that itraconazole (potent CYP3A4 inhibitor) did not affect CBD exposure and caused only minor increases in 7-hydroxy-cannabidiol (7-OH-CBD) (17%) and 7-carboxy-cannabidiol (7-COOH-CBD) (12%) exposure (AUC_{0-t}). Fluconazole (a potent CYP2C19 inhibitor) had only a minor effect on CBD exposure (approximately 20% increase) and caused small decreases in 7-OH-CBD (29%) and 7-COOH-CBD (34%) exposure (AUC_{0-t}). These results suggest that CBD exposure would be unaffected in subjects/patients with genetic variants of these enzymes leading to decreased catalytic activity. In addition, that it is thought that the multiple metabolic enzymes involved in the metabolism of CBD are able to compensate should one pathway be inhibited or dysfunctional.

The Applicant has illustrated and presented data in healthy subjects in accordance with a substantial less than dose-proportional relation between dose and exposure of CBD and its primary metabolites in the dose-interval from 1500 mg to 6000 mg. The dose-ranging PK of CBD-OS was also studied in patients. In DS patients aged 4–10 years old (GWEP1332 Part A), exposure (AUC) to CBD and its metabolites increased in a dose-related manner after multiple doses of 5, 10, or 20 mg/kg/day CBD-OS (GWEP1332 CSR). A POPPK model in patients with LGS, which contained data from more patients over a wider age range, predicted that with a doubling in dose (from 10 to 20 mg/kg/day CBD-OS), there would be a near doubling in CBD plasma exposure (AUC) (GWPP17004). The suggested saturation observed for absorption at supra-therapeutic CBD doses is in accordance with the zero-order absorption kinetics reported, and therefore accepted.

Inter-individual variability (IIV) of clearance and apparent volume of distribution is substantial, with CV% estimates of about 30 to 90% (and higher in DS patients for clearance), for CBD and its main metabolites. The applicant was requested to analyse repeated dose data for intra-individual variability of the principal PK parameters. Subsequently, the applicant has presented a joint population PK model for CBD, 7-OH-CBD and 7-COOH-CBD, which was developed using data from 11 trials. All structural components (i.e., typical PK parameters) as well as variability (i.e., IIV and RUV) terms have been retested, which is endorsed. Inter-individual variability was significant for Q12 (drop of the objective function value > −3.84 i.e., p-value < 0.05) leading to a stable, converging model as well as a good precision on the IIV Q12 (RSE=14.6%). Noticeably the RSE of VP2 was also much improved (0.9%) (GWPP18097). The population model predictions corresponded well to the observed concentrations for CBD, 7-OH-CBD and 7-COOH-CBD in the pooled population.

The applicant has presented several PoP-PK models in healthy volunteers and in the target populations. The models are overall presented in accordance with the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007). CBD displayed linear two-compartmental PK while 1 compartment for each metabolite, and zero-order absorption. None of the included covariates were included in the final model. However, the Applicant should test additional weight covariates. Missing information regarding the impact of food on CBD PK in the paediatric population is considered problematic for the interpretation of the PK models developed in paediatric patients, and results of the simulated exposures in children. Furthermore, in accordance with RMP, missing data in children < 2 years is problematic due to relevance for Dravet patients. The applicant confirmed that the development of an updated PBPK model is ongoing. Information from the

latest population PK modelling will be incorporated (GWPP18097). However, in order to obtain the most refined and predictive model, the plan is to wait for data from multiple ongoing drug-drug interaction (DDI) trials which will provide crucial data to support the understanding of contributions from metabolic enzymes. These data including an updated PBPK model will be available in the first quarter of the calendar year 2020. The investigation into potential sampling techniques for very young patients has been initiated. When available, this will be applied to any trials involving patients under 2 years of age. At this point in time, no specific trials have been identified/scheduled so no specific timelines are available. This plan was found acceptable by the CHMP.

The PK of CBD and its metabolites have been studied in patients with varying degrees of renal impairment. The PK of CBD and its metabolites was not affected in patients, who had mild (CLCR 50-80 ml/min) to severe (CLCR <30 ml/min) renal impairment. Patients with end-stage renal disease (CLCR< 15 ml/min) were not studied and this information has been included in the SmPC.

The PK of CBD has been studied in subjects with impaired hepatic function. There was a substantial increase in AUC and Cmax exposure to CBD and its active metabolite (7-OH-CBD) in subjects with moderate and severe hepatic impairment versus subjects with normal hepatic function; AUC exposures increased about 2.5 and 5-fold, respectively, while Cmax exposure were about 2-3 fold for CBD. In subjects with mild hepatic impairment an increase in total Cmax and AUC about 1.5 was observed for CBD, and 1.3 for 7-OH-CBD. Unbound CBD was not affected. Therefore, the CHMP found acceptable the applicant's SmPC proposal to recommend a lower starting dose and target dose for patients with moderate or severe hepatic impairment. Simulated exposures achieved in patients with moderate hepatic impairment were similar to exposures in subjects with normal hepatic function when the dosing recommendations provided in the SmPC were applied. However, simulated exposures for subjects with severe hepatic impairment were approximately half those for subjects with normal hepatic function. This finding is adequately reflected in the SmPC by the wording included in section 4.2 which indicates that efficacy may be reduced in subjects with severe hepatic impairment.

Crude PK data from efficacy trials in children suggest a lower exposure to CBD and its primary metabolites in children below the age of 18 compared to adults. Exposure simulations from the PoP-PK model did not recover these findings in that age did not have a significant effect on the PK of CBD at the given weight-based posology. These findings are pertinent to the sought indication and primary patient population and must be further pursued. The applicant should present and comment on cross-trial actual data stratified by age groups according to EMA Guidelines. Furthermore, based on PoP-PK analysis (GWPP17004, based on data from GWEP1414 and GWEP1423), systemic exposure to CBD appears to be significantly reduced in subjects weighing less than 60 kg. This likely reflects allometric scaling effect suggesting no isolated effect from body weight. In order to address the concerns, the applicant conducted a pooled population pharmacokinetic analysis (POPPK) in subjects and patients participating in trials GWEP1544, GWEP1332A, GWEP1414, GWEP1423, GWEP1428, GWEP1539, GWEP1540, GWEP1541, GWEP1543, GWEP1446 and GWEP17028. The objective was to develop a joint population pharmacokinetic (PK) model for cannabidiol (CBD) and 2 major circulating metabolites 7-hydroxy cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOH-CBD), based on the data collected in healthy adult subjects, adult subjects with various degrees of renal and hepatic impairments, adult patients with epilepsy, patients with Dravet syndrome (DS) and patients with Lennox-Gastaut syndrome (LGS). The analysis focused on several potential covariates, such as baseline body weight, unit dose of GWP42003-P, prandial state, body mass index, age and concomitant medications. The results showed IIV was high in the pooled PK data for all PK parameters ranging from 47-113% probably due to unknown food status in most of the subjects. Nevertheless, the analysis did not identify significant impact of gender age, race on PK parameters of CBD. It can be therefore concluded that these variables have minor or no influence on CBD pharmacokinetics.

The in-silico analysis suggests a strong inhibitory effect on CYP3A4 substrates of CBD across all age groups. This further supports the conduct of an in vivo study to quantify this interaction. *A weak inhibition of CYP2C8 and UTG1A9, 2B7 is predicted, while the simulation model suggests other CYP mediated DDIs with CBD as perpetrator appears less likely. In vitro* conducted studies are sufficient for its purpose. These suggest that clinically relevant DDIs between CBD and other drugs may be relevant for quite a variety enzymes and transporters involved. Important signals are potent inhibition of CYP1A2, 2B6, 2C8, 2C19 and 3A4. CYP2C19 and CYP3A4 is discussed below in the in vivo section. In vitro data suggests potential for DDIS between the major metabolite 7-COOH-CBD and BRCP, OAT3 and OATP1B3. During the procedure, the Applicant indicated that a DDI study was planned to investigate the effects of CBD-OS on warfarin exposure, specifically examining the impact on exposure to S-warfarin and the CYP2C9 mediated metabolite S-7-hydroxywarfarin. While these data are awaited it would be appropriate to have a note of caution in the SmPC section 4.5 for prescribers whose patients are receiving warfarin treatment. This proposal was supported by the CHMP. With respect to the major metabolite 7-COOH-CBD and interaction with BRCP, OAT3, and OATP1B3, a warning against a potential interaction between the metabolite 7-COOH-CBD and several transporters is included in the SmPC until more data is generated with the updated PBPK model.

Studies conducted by the applicant do not suggest pharmacokinetic clinically important interactions between CBD and stiripentol or valproate. However, a bi-directional pharmacokinetic clinically important interaction with clobazam emerges, leading to an approximately 3 -fold increase in clobazam active metabolite N-CLB exposure and an increase in exposure of CBD active metabolite 7-OH-CBD. Both N-CLB and 7-OH-CBD have been demonstrated to have anticonvulsant properties in model systems. Concomitant use of Epidyolex and clobazam increases the incidence of somnolence and sedation. According to the applicant it is not possible to provide a rational clobazam dose reduction recommendation based upon population PK simulations since a PK model for CLB and N-CLB is not available. No increases were observed in CLB or N-CLB when CBD-OS was initiated in patients receiving concomitant treatment with stiripentol and clobazam. Furthermore, according to the Applicant the decision to reduce the CLB dose cannot be based solely on the known drug-to-drug interaction, which results in N-CLB exposure and an increase in 7-OH-CBD but with no meaningful increase to the parent compounds, CLB and CBD. As per the SmPC the management of DDIs between CBD and CLB should be left to the treating physician, who is experienced in the treatment of epilepsy. This point should be included in the SmPC. Furthermore, the DDI potential of CBD includes other AEDs. CBD is proposed as add on adjunctive use with any appropriate antiepileptic drug therapy, and the treating physician should therefore have a very thorough knowledge of the pharmacology of CBD and other AEDs to be able to manage all potential DDIs. Therefore, for other AEDs commonly concomitantly administered with CBD-OS, the SmPC includes specific guidance in terms of relevant precautions and/or monitoring.

A positive association between AUC exposure and elevated liver function test (> 2xULN), somnolence or loss of appetite was identified. The risk appears to increase disproportionally at levels about 50% higher than the median AUC values achieved at 20mg/kg/day.

Logistic regression analysis suggests a positive exposure-response relationship at steady state in LGS patients. This is relevant to the posology related to food intake and the actual procedure used in clinical trials as concomitant administration of food substantially increases exposure to CBD and its main active metabolites. It should be noted, that the extent of concomitant food intake was not known in the population of LGS patients the Exposure-Response Analysis was based on.

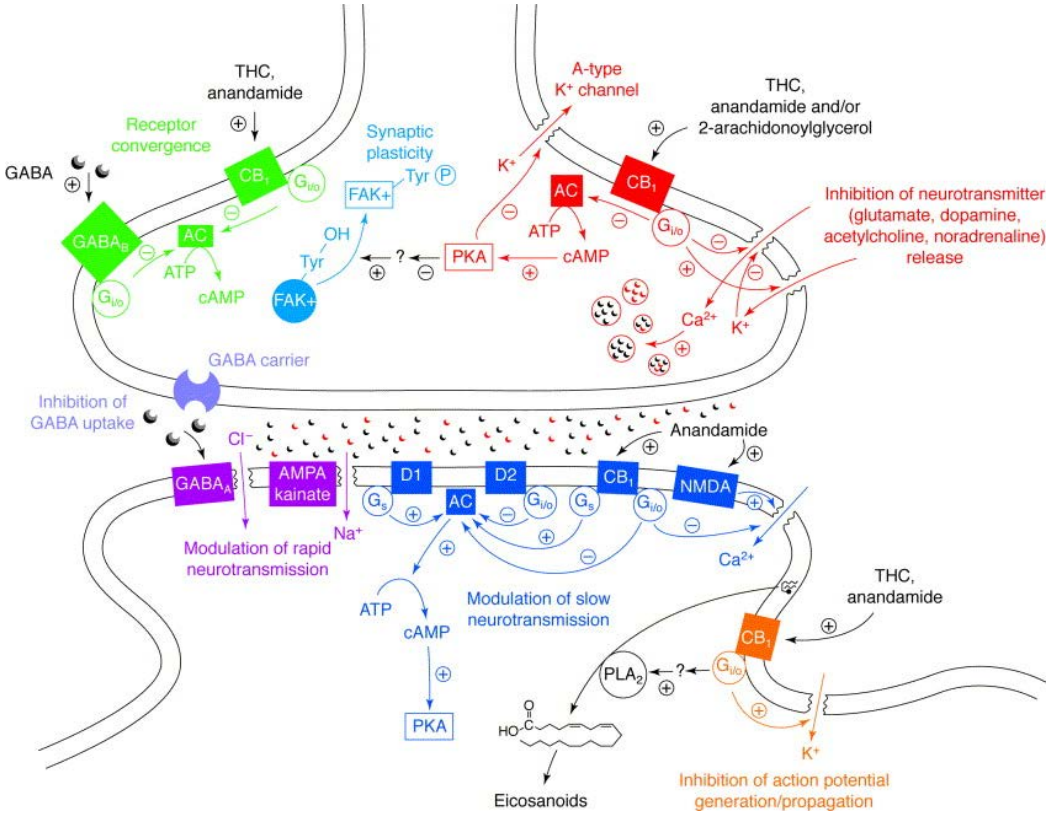
The applicant has conducted a lege artis QTc study. CBD at therapeutic and supratherapeutic doses does not influence QTcF interval.

The applicant presented the results of a PK and PD study of CBD conducted in recreational drug users in order to investigate on the abuse potential of CBD. THC plasma concentrations were low during treatment with CBD (substantially lower than during treatment with cannabidiol), consistent with levels of the impurity in the CBD product. Some subjective drug effects were reported at the highest doses as compared to placebo, but these effects were significantly lower than reported for dronabinol and alprazolam (as positive controls) and less likely to be of clinical relevance. No effects on other subjective or objective psychomotor tests were noted. However, extrapolations to real-life settings should be made very cautiously. Keeping in mind notably lower drug exposure and positive results in several endpoints, the abuse potential cannot be excluded on the basis of data submitted. Consequently, the low abuse potential is reflected in SmPC section 5.1.

CBD does not appear to affect sleeping quality in healthy adult volunteers.

The applicant has addressed current known PD interactions in a separate section the SmPC. Herein, the observed effects on CNS and liver, e.g. somnolence and appetite loss are frequent AEs to both CBD and medicinal products often used concomitantly in the target population (clobazam, stiripentol and valproate), as well as an increase in liver parameters is common for CBD and valproate. These findings are appropriately reflected in SmPC section 4.8 and adequate warnings on increase of the hepatic transaminases and occurrence of somnolence and sedation are included in SmPC section 4.4.

The mechanism of action for CBD is not fully elucidated. According to the presented data, CBD most likely modulates intracellular calcium, which in turn may confer reduced neuronal hyperexcitability. There are no studies on primary pharmacology in humans. In non-clinical data, different efficacy was observed in each type of convulsions. This phenomenon was also observed in clinical trials, where the effect of CBD differs in individual types of seizures (See the efficacy section of this report for further details). Specific warning on the potential for increased seizure frequency is included in SmPC section 4.4.



2.4.5. Conclusions on clinical pharmacology

The CHMP was of the view that the available information from scientific literature as well the PK data collected in the clinical trials were sufficient to support the application for Epidyolex for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients from 2 years of age and older from a clinical pharmacology perspective. In addition, the CHMP considered the following measures necessary to address the issues related to pharmacology:

In order to generate PK data in patients of < 2 years of age, the applicant should develop an updated PBPK model, and should also explore the development of a technique for direct sampling and analysis from patients in the below 2 years old age group, followed by implementation of sparse sampling approaches in appropriate clinical trials.

A clinical drug-drug interaction study is being designed and is planned to be completed during 2019. The results will be provided post-authorisation.

2.5. Clinical efficacy

2.5.1. Dose response study

Dose-ranging safety and PK study (GWEP1332A)

Dose selection for the 4 randomised controlled trials (RCTs) was based upon findings in a single randomized, placebo-controlled dose-ranging safety and pharmacokinetic (PK) trial of 5, 10, and 20 mg/kg/day CBD-OS in children with DS (GWEP1332 Part A). This was a 3-week treatment period, multi-site, randomised, double-blind trial of GWP42003-P vs. placebo. Following a 4-week baseline period, eligible patients were randomised to 1 of 3 doses of CBD-OS or placebo at a 4:1 ratio. Assessments of safety and tolerability took place at 1, 2, and 3 weeks as well as following taper of investigational medicinal product (IMP) and 4 weeks after final dose.

A total of 41 patients were screened, of which 34 patients were randomised into the trial: 27 to CBD-OS (10, 8, and 9 to the 5, 10, and 20 mg/kg/day groups, respectively) and 7 to placebo. Patients had a documented history of Dravet syndrome (DS) with seizures not completely controlled by their current AEDs, and were taking at least 1 AED. All medications or interventions for epilepsy were stable for 4 weeks prior to the trial and were to be maintained throughout the trial. Part A patients were aged 4–10 years old (inclusive) with fewer than 4 convulsive seizures (i.e., tonic–clonic, tonic, clonic, atonic seizures) during the 4-week baseline period.

Thirty-four patients were randomized to double-blind treatment. Thirty-two patients (94%) completed the treatment period of the trial; of these 29 (91%) completed the subsequent taper period.

Since efficacy was not evaluated, Study GWEP1332A did not provide dose-response information. Thus, the minimally effective dose has not been determined in Dravet Syndrome, and no dose-response information was available for any indication before entering phase 3.

2.5.2. Main studies

The clinical development program supporting the efficacy of CBD-OS comprises 2 randomised, placebo-controlled trials in LGS; 1 investigating 10 and 20 mg/kg/day CBD-OS (GWEP1414) and 1 investigating 20 mg/kg/day CBD-OS (GWEP1423), and 2 randomised, placebo-controlled trials in DS; 1 investigating 10 and 20 mg/kg/day CBD-OS (GWEP1424) and 1 investigating 20 mg/kg/day CBD-OS (GWEP1332

Part B). A total of 715 patients were randomised into the now completed pivotal trials, comprising 396 patients with LGS (GWEP1414 and GWEP1423) and 319 patients with DS (GWEP1332 Part B).

Dose selection for the randomised controlled trials (RCTs) was based upon findings in a single randomised, placebo-controlled dose-ranging safety and pharmacokinetic (PK) trial of 5, 10, and 20 mg/kg/day CBD-OS in children with DS (GWEP1332 Part A). Following assessment of the data from GWEP1332 Part A, an independent data safety monitoring committee (DSMC) approved 20 mg/kg/day as an appropriate dose of CBD-OS to use in all subsequent trials.

Table 20 Overview of Pivotal Phase 3 Efficacy Trials in Patients with LGS

	GWEP1414	GWEP1423
Description	Adjunct to existing AEDs in patients with LGS who had inadequately controlled drop seizures	
Patient Population	2–55 years with a clinical diagnosis of LGS, ≥ 2 drop seizures each week during the 28-day baseline period despite taking ≥ 1 AED at a stable dose for ≥ 4 weeks	
Regions	US, UK, France, Spain	US, The Netherlands, Poland
Patients Planned/Randomized[a]	150/225	100/171
Treatment Group: Number of Patients Treated	CBD-OS 10 mg/kg/day: 73 CBD-OS 20 mg/kg/day: 76 PBO: 76	CBD-OS 20 mg/kg/day: 86 PBO: 85
Treatment Plan	Baseline Period (Days −28 to −1)	Baseline Period (Days −28 to −1)
	Double-blind Treatment Period (Weeks 1–14): • Titration Period (Weeks 1–2): - CBD-OS 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 7 days to 10 mg/kg/day, or 11 days to 20 mg/kg/day - PBO volumes equivalent to 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 7 or 11 days	Double-blind Treatment Period (Weeks 1–14): • Titration Period (Weeks 1–2): - CBD-OS 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 11 days - PBO volumes equivalent to 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 11 days
	• Maintenance Period (Weeks 3–14): - CBD-OS 10 or 20 mg/kg/day[b] - PBO volumes equivalent to 10 or 20 mg/kg/day	• Maintenance Period (Weeks 3–14): - CBD-OS 20 mg/kg/day[b] - PBO volumes equivalent to 20 mg/kg/day
	Optional OLE trial or taper (10% per day) and follow-up	Optional OLE trial or taper (10% per day) and follow-up
Efficacy Endpoints	Primary: • Percentage change from baseline in drop seizure frequency during the treatment period	
	Key secondary (tested hierarchically): • Proportion of patients with a ≥ 50% reduction from baseline in drop seizure frequency during the treatment period	
	• Percentage change from baseline in total seizure frequency during the treatment period	
	• S/CGIC at last visit	

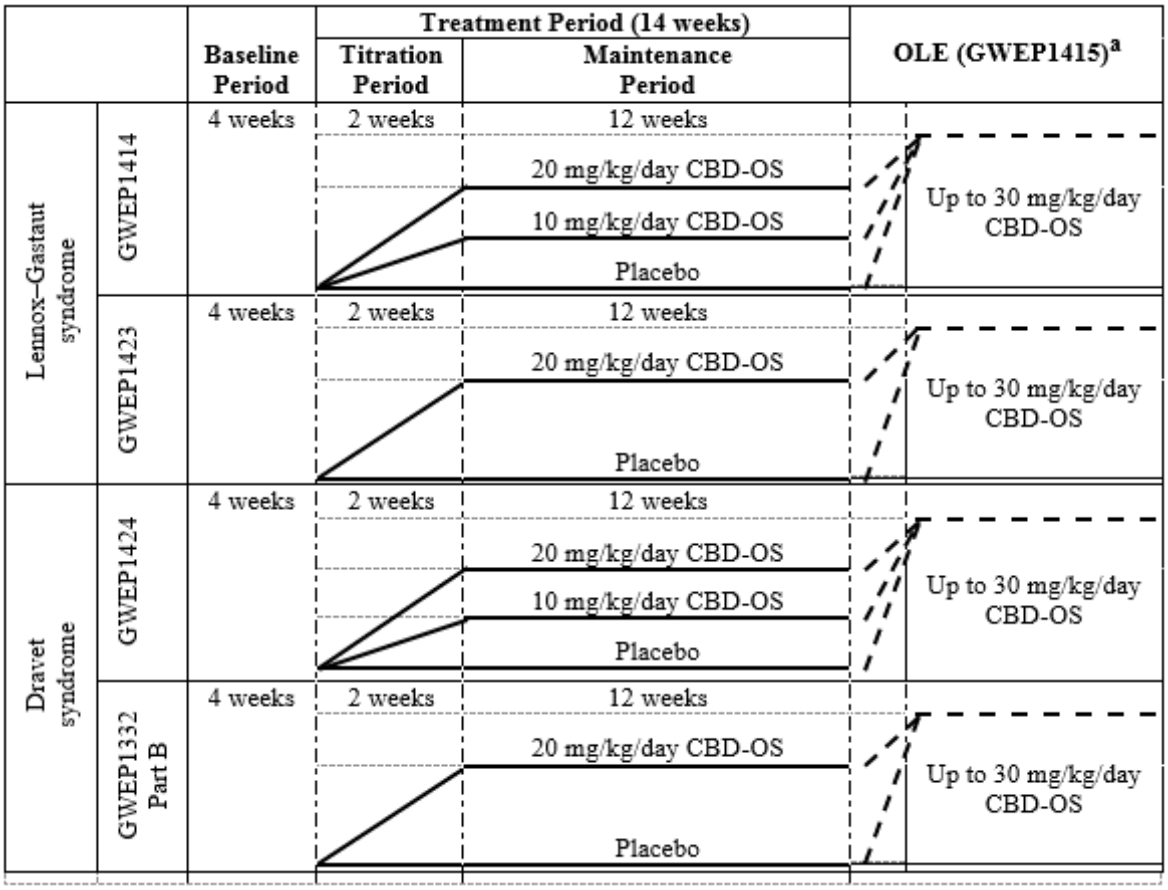
Abbreviations: AED, antiepileptic drug; CBD-OS, cannabidiol oral solution; LGS, Lennox–Gastaut syndrome; OLE, open-label extension; PBO, placebo; QOD, every other day; S/CGIC, Subject/Caregiver Global Impression of Change.

Table 21 Overview of Pivotal Phase 3 Efficacy Trials in Patients with DS

	GWEP1424	GWEP1332B
Description	Adjunct to existing AEDs in patients with DS who had inadequately controlled convulsive seizures	
Patient Population	2–18 years with a clinical diagnosis of DS, ≥ 4 convulsive seizures during the 28-day baseline period despite taking ≥ 1 AED at a stable dose for ≥ 4 weeks	
Regions	US, Spain, Poland, the Netherlands, Australia, Israel	US, UK, France, Poland
Patients Planned/Randomized[a]	186/199	100/120
Treatment Group: Number of Patients Treated	CBD-OS 10 mg/kg/day: 66[b] CBD-OS 20 mg/kg/day: 67 PBO: 65	CBD-OS 20 mg/kg/day: 61 PBO: 59
Treatment Plan	Baseline Period (Days −28 to −1)	Baseline Period (Days −28 to −1)
	Double-blind Treatment Period (Weeks 1–14): • Titration Period (Weeks 1–2): - CBD-OS 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 7 days to 10 mg/kg/day, or 11 days to 20 mg/kg/day - PBO volumes equivalent to 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 7 or 11 days	Double-blind Treatment Period (Weeks 1–14): • Titration Period (Weeks 1–2): - CBD-OS 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 11 days - PBO volumes equivalent to 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 11 days
	• Maintenance Period (Weeks 3–14): - CBD-OS 10 or 20 mg/kg/day[c] - PBO volumes equivalent to 10 or 20 mg/kg/day	• Maintenance Period (Weeks 3–14): - CBD-OS 20 mg/kg/day[c] - PBO volumes equivalent to 20 mg/kg/day
	Optional OLE trial or taper (10% per day) and follow-up	Optional OLE trial or taper (10% per day) and follow-up
Efficacy Endpoints	Primary: • Change in convulsive seizures during the treatment period compared to baseline	Primary: • Percentage change from baseline in convulsive seizure frequency during the treatment period
	Key secondary (tested hierarchically): • Change in total seizures during the treatment period compared to baseline	Key secondary: • Proportion of patients with a ≥ 50% reduction from baseline in convulsive seizure frequency during the treatment period
	• Proportion of patients with a ≥ 50% reduction from baseline in convulsive seizure frequency during the treatment period	
	• CGIC at last visit	

Abbreviations: AED, antiepileptic drug; CBD-OS, cannabidiol oral solution; DS, Dravet syndrome; OLE, open-label extension; PBO, placebo; QOD, every other day; CGIC, Caregiver Global Impression of Change.

Figure 15 Pivotal Trial Design Schematic



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

Subjects restarted titration from 2.5 mg/kg/d and titrated to target dose of 10-20 mg/kg/d over 2 weeks. Once in the maintenance phase, the PI could titrate up to a max of 30 mg/kg/d.

Patients who completed one of the controlled trials were eligible to enter an open-label extension (OLE) trial (GWEP1415), for which the primary objective was monitoring long-term safety. Long-term exposure was also assessed within an EAP for patients with DREs including those with DS or LGS who were not candidates for the controlled trials. The EAP comprised a number of physician-initiated investigational new drug (IND) applications (including emergency INDs, individual INDs, and intermediate INDs), State-initiated IND applications in the US, and a Compassionate Access Scheme (CAS) in New South Wales, Australia. As of the data cut-off date (08 December 2016) the EAP had enrolled 684 patients, including 64 with DS (9.4%) and 97 with LGS (14.2%).

Phase 1 and 2 clinical pharmacology trials were conducted in healthy subjects and specific populations to evaluate intrinsic and extrinsic factors which may affect the PK characteristics of CBD, as well as to evaluate drug-drug interactions (DDIs) with AEDs commonly used in LGS and DS.

Main studies, Lennox-Gastaut Syndrome (Studies GWEP1414 and GWEP1423)

Methods

Study Participants

In order to be eligible for the trials, patients had to be aged 2–55 years with a clinical diagnosis of LGS. Patients must have had at least 2 drop seizures each week during the first 28 days of the baseline period and have a history of slow (< 3.0 Hz) spike-and-wave pattern in an EEG prior to their enrolment into the baseline period. Patients must have been taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening and have documented failures on more than 1 AED. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for 4 weeks prior to screening and the patient was willing to maintain a stable regimen throughout the trial. Patients and/or parent(s)/legal representative were willing and able to give informed consent, were willing to meet all trial requirements and had satisfactorily completed the IVRS telephone diary on at least 25 days of the baseline period.

Patients were ineligible if they had used recreational or medicinal cannabis, or synthetic cannabinoid-based medications, within 3 months prior to screening and were to abstain from taking them during the trial. Patients were also ineligible if they had a history of alcohol or substance abuse, if they had known or suspected hypersensitivity to any ingredients of the investigational product, or if they did not meet laboratory and clinical health requirements at screening or baseline.

Regions and sites:

GWEP1414:

A total of 293 patients were screened, 68 (23.2%) of which were screen failures. A total of 225 patients were randomized to double-blind treatment. All randomized patients received at least 1 dose of double-blind IMP and thus were included in the safety analysis set. In total, 30 sites screened patients, of which 29 sites randomized patients into the trial (20 sites in the US, 5 in Spain, 1 in France and 3 in the UK). An additional 7 sites in the US were selected but did not screen patients. Of the 225 randomized patients, 181 were randomized from the US, 32 from Spain, 11 from the UK and 1 from France.

GWEP1423:

A total of 200 patients were screened, 29 (14.5%) of which were screen failures. A total of 171 patients were randomized to double-blind treatment. All randomized patients received at least 1 dose of double-blind IMP and thus were included in the safety analysis set. In total, 24 sites screened patients (17 in the US, 1 in the Netherlands and 6 in Poland), all of which randomized patients into the trial. An additional 11 sites were selected but did not screen patients (9 in the US and 2 in the Netherlands). Of the 171 randomized patients, 5 were randomized from the Netherlands, 38 from Poland, and 128 from the US.

Treatments

IMP was taken twice daily (morning and evening) without regard to meals, and could be taken with other concomitant medications.

CBD-OS was presented as an oral solution containing 100 mg/mL CBD in sesame oil with anhydrous ethanol (79 mg/ml), added sweetener (sucralose), and strawberry flavouring. Placebo was presented as an oral solution of sesame oil containing anhydrous ethanol, added sweetener (sucralose), and strawberry flavouring.

Patients titrated CBD-OS to 10 mg/kg/day over 7 days or 20 mg/kg/day over 11 days and remained at this dose level for the duration of the treatment period. Following the end of treatment (or early withdrawal), all patients who did not immediately enter the OLE were to taper GWP42003-P over 10 days (10% per day). However, the taper period could be interrupted if the patient wished to enter the OLE trial within a 7-day timeframe.

Objectives

The primary objective was to evaluate the efficacy of CBD-OS as adjunctive treatment in reducing the number of drop seizures (per 28 days) when compared with placebo in patients with Lennox-Gastaut syndrome (LGS). A drop seizure was defined as an attack or spell (atonic, tonic or tonic-clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.

The key efficacy secondary objectives were to assess the following in LGS patients taking CBD-OS as adjunctive treatment, when compared with placebo: 50% responder rate (in terms of ≥50% reduction in drop seizures); reduction in the number (per 28 days) of total seizures and changes from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score.

Other secondary objectives are listed below:

- To assess the following in LGS patients taking CBD-OS as adjunctive treatment, when compared with placebo: number of episodes of status epilepticus (SE); need for hospitalization due to epilepsy; change in duration of subtypes of seizures; sleep disruption and daytime sleepiness; quality of life; adaptive behaviour; cognitive function; growth and development.
- To determine the pharmacokinetics (PKs) of cannabidiol (CBD) and its major metabolites following single and multiple doses of CBD-OS.

To determine the effects of CBD-OS on plasma concentrations of concomitant antiepileptic drugs (AEDs), where available.

Safety and tolerability of CBD-OS was assessed through monitoring of the following: adverse events (AEs), serious adverse events (SAEs), deaths, injuries, suicidal ideation, abuse liability, cannabis withdrawal effects, clinical laboratory tests, vital signs, and menstruation cycles (in females).

Outcomes/endpoints

Reduction in drop seizure frequency was the primary endpoint. During the screening visit investigators recorded a detailed clinical description of their patient's current seizures using a Seizure Identification Form (SIF) and by completing a list of seizures experienced by the patient in lay terms on the epilepsy diary reference sheet. Both were submitted to a committee of independent experts within 24 hours of the visit. Following review by an independent expert member of a committee the seizure classifications provided by the investigator were either confirmed, or a request for further information was sent back to the investigator.

An IVRS was used throughout the baseline and treatment periods to record the number of each type of seizure experienced by the patient daily. Seizure data from withdrawn patients were included only up

until the time they discontinued the treatment period. For the majority of patients all assessments, including daily seizure recording, were completed on their behalf by caregivers. Seizures were recorded daily on a validated electronic patient reported outcomes (ePRO) using the IVRS. Sites had been trained on the use of this system, both by the vendor and by the sponsor, and conducted a diary demonstration with the caregiver during the first trial visit. At the screening visit, the training consisted in confirmation and discussion of the different known seizure presentations of each patient. The LGS ePRO consisted of a maximum of 14 questions; the first to ask if the patient had any seizures. If the answer was yes, questions were asked on how many seizures were observed for each of the following types: (1) atonic; (2) tonic; (3) tonic-clonic; (4) myoclonic; (5) clonic; (6) countable partial; (7) other partial; (8) absence; (9) convulsive seizures > 30 minutes; and (10) non-convulsive seizures > 30 minutes. Following the questions relating atonic, tonic and tonic-clonic seizures the LGS ePRO also asked: (1) how many tonic seizures were drop seizures; (2) how many atonic seizures were drop seizures; and (3) how many tonic–clonic seizures were drop seizures. Only yes/no answers and numerical answers, using the telephone keypad, were recorded. The average call duration was around 3.5 minutes.

The ePRO calls could be made in local language and had to be made daily between 6 PM and midnight local time; they were to be reflective of the number of seizures since the last call on the previous day or the last 24 hours if no call was made. If a call was missed, there was an opportunity to enter data for the previous day only.

The primary efficacy outcome variable was the percentage change from baseline in number of drop seizures (average per 28 days) during the treatment period of the study (Day 1 to the end of the evaluable period) in patients taking GWP42003-P compared with placebo.

Key secondary efficacy variables were as follows (testing order):

1. Number of patients considered treatment responders, defined as those with a ≥ 50% reduction in drop seizures from baseline.
2. Percentage change from baseline in number of total seizures (average per 28 days).
3. Changes from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score.

The other secondary efficacy variables were as follows:

- Percentage change from baseline in number of drop seizures (average per 28 days) during the Weeks 1–4, 5–8 and 9–12 of the maintenance period.
- Number of patients considered treatment responders, defined as those with a ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in drop seizures from baseline (overall and 4-weekly).
- Number of patients experiencing a >25% worsening, ≤−25 to ≥ 0% no change, >0% to <+25% no change, ≥25 to <50% improvement, ≥50 to <75% improvement or ≥75% improvement in drop seizures from baseline.
- Percentage change from baseline in frequencies (average per 28 days) of non-drop seizures, convulsive seizures, non-convulsive seizures and subtypes of seizures.
- Changes from baseline in duration of seizure subtypes (as assessed by the Subject/Caregiver
- Global Impression of Change in Seizure Duration [S/CGICSD]), number of episodes of SE, number of inpatient hospitalizations due to epilepsy, quality of life as assessed by the Quality of Life in Childhood Epilepsy (QOLCE; for patients aged 2–18 years) or Quality of Life in Epilepsy, version 2 (QOLIE-31-P; for patients aged 19 years and older) score, Vineland Adaptive Behaviour Scales Second Edition (Vineland-II) score, Cognitive Assessment Battery

score, Sleep Disruption 0–10 Numerical Rating Scale (0–10 NRS) score, and Epworth Sleepiness Scale (ESS) score.

The exploratory efficacy variables were time to baseline drop seizure frequency and number of drop seizure-free days.

Sample size

The planned number of randomized patients for trial GWEP1414 was 150 (50 per CBD-OS treatment group and 25 per placebo treatment group, which subsequently became 1 pooled placebo group). The planned number of randomized patients for trial GWEP1423 was 100 (50 per treatment group). It was assumed that patients in the placebo group would experience a mean reduction in drop seizure frequency of 18% (from baseline); the sample size of 50 patients per treatment group would then be sufficient to detect a difference of 32% between treatments (i.e., patients receiving CBD-OS would experience at least a 50% reduction in drop seizures). This was based on a standard deviation (SD) of 56%, using a 2-tailed 5% significance level and 80% power.

Randomisation

A unique patient number was assigned to each patient at Visit 1, using the IWRS. At Visit 2 the IWRS was used to randomly allocate patients who met all eligibility criteria following the baseline period to either CBD-OS or placebo; both were provided in identical 100 mL amber glass bottles with unique identification numbers.

In trial GWEP1423 patients were randomized to 1 of 2 treatment groups (CBD-OS 20 mg/kg/day or placebo) at a 1:1 ratio. In trial GWEP1414, patients were randomized to 1 of 4 treatment groups (CBD-OS 20 mg/kg/day, CBD-OS 10 mg/kg/day, placebo 20 mg/kg/day dose volume equivalent, or placebo 10 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio; patients in the placebo groups were pooled for the analyses of efficacy and safety.

The randomization scheme for each trial was generated by an independent statistician using random permuted blocks and was stratified by age group as follows: 2 to < 6, 6 to < 12, 12 to < 18, and 18 to < 56 years.

Blinding (masking)

All pivotal trials were double-blind. All IMP, i.e., CBD-OS or placebo, was provided in identical 100 ml amber glass bottles. IMP was presented as an oral solution containing 100 mg/ml CBD in the excipients sesame oil and anhydrous ethanol (79 mg/ml) with added sweetener (sucralose) and strawberry flavouring; the matched placebo comprised only the excipients.

Statistical methods

Primary efficacy outcome variable:

The primary efficacy outcome variable was the percentage change from baseline in drop seizure frequency (average per 28 days) during the treatment period, based on the ITT analysis set. The data were analysed using a Wilcoxon rank-sum test. An estimate of the median difference between CBD and placebo, together with approximate 95% CI, was calculated using the Hodges-Lehmann approach. Several sensitivity analyses were performed to assess the effect of the assumptions of the primary endpoint:

1. Wilcoxon rank-sum test on percentage change from baseline in drop seizure frequency during the maintenance period
2. Wilcoxon rank-sum test on percentage change from baseline in drop seizure frequency during the treatment period using the PP analysis set.
3. A rank analysis of covariance (ANCOVA) on percentage change from baseline in drop seizure frequency during the treatment period.
4. ANCOVA of log transformed drop seizure frequency during the treatment period.
5. ANCOVA on percentage change from baseline in drop seizure frequency during the treatment period including baseline and age group as covariates and treatment group as a fixed factor.
6. Wilcoxon rank-sum test on percentage change from baseline in drop seizure frequency 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).
7. Wilcoxon rank-sum test on percentage change from baseline in drop seizure frequency during the treatment period, 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 to impute missing data arising from unreported days in IVRS during the treatment period only (not the baseline period). Any intermittent missing data for the number of drop seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period based on using non-missing data.
8. Wilcoxon rank-sum test on percentage change from baseline in drop seizure frequency during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption
9. Only for Study GWEP1423: Wilcoxon rank-sum test on percentage change from baseline in drop seizure frequency during the treatment period using patients from ITT analysis set but analysed by actual treatment received rather than treatment randomized. This analysis was only to be performed if 2 patients were randomised to different treatment groups e.g. if a patient randomized to placebo received GWP42003-P and a patient randomised to GWP42003-P received placebo.

Key secondary efficacy outcome variable:

1. Drop Seizure Treatment Responders (≥ 50% Reduction in Drop Seizure Frequency):

The proportion of patients considered treatment responders, defined as those with a ≥50% reduction in drop seizure frequency from baseline, during the treatment period, was summarized by treatment group and analysed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group. The analysis was performed on the ITT analysis set and repeated on the PP analysis set. Sensitivity analyses were performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, 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). There was no imputation for missing IVRS days or withdrawals. In addition at the CHMP request, applicant provided additional sensitivity analyses considering (1) patients with unreported days in the IVRS and patients that withdraw from the study considered as non-responders and (2) patients with unreported days in the IVRS considered as non-responders if the average of their observed seizures was above 50 % and patients who withdraw from the study considered non-responders.

2. Total Seizures:

The analysis was performed on the ITT analysis set and repeated on the PP analysis set. Sensitivity analyses were performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance 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). There was no imputation for missing IVRS days or withdrawals In addition at the CHMP request, applicant provided additional sensitivity analyses to account for missing data by (1) presenting a 'worst case' sensitivity analysis (similar to sensitivity analysis 7 for the primary endpoint) and (2) investigating whether a negative binomial model incorporating the actual observational time could be applied considering different strategies to handle missing unreported days before the dropout date.

3, Change from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score:

It was anticipated that only a small percentage of patients would complete the subject version of the questionnaire. Hence, a combined score was used 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 scores at the end of treatment visit and last visit (if different from the end of treatment) were analysed using ordinal logistic regression. Proportional odds modelling was carried out by including treatment group as a factor. The estimated odds ratio (CBD-OS vs. placebo), 95% CI for the odds ratio, and the p-value testing the null hypothesis that the odds ratio is equal to 1, were presented. The analysis performed at the last visit was considered the main analysis with the analysis at the end of treatment being considered a sensitivity analysis. A sensitivity analysis was also performed using only the CGIC score.

The key secondary endpoints were tested hierarchically to control the type I error.

Other secondary endpoints:

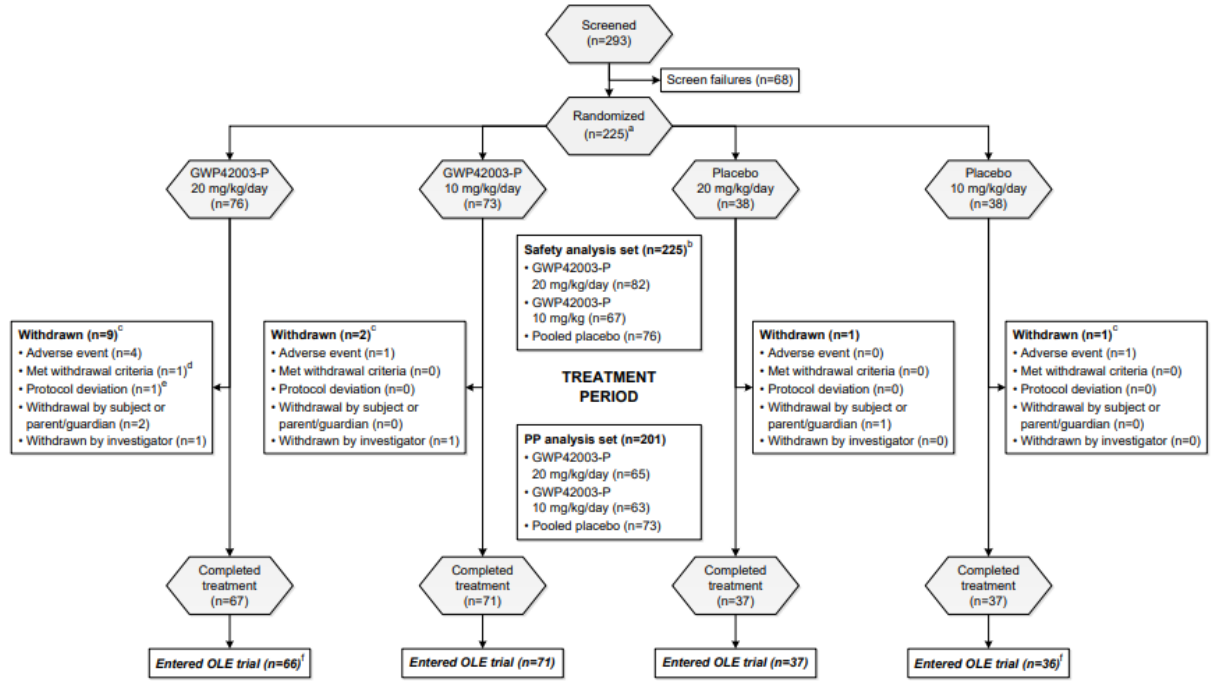
For some of the secondary endpoints e.g. the Epworth Daytime Sleepiness scale and the Quality of Life scales, if fewer than 50% of the items were missing, the missing items were imputed as the mean of the remaining non-missing scores. If more than 50% were missing, the total score would be missing. For the Quality of Life in Childhood Epilepsy, “not applicable” responses were treated as missing values. However, imputation of one item as a mean of other items may not be appropriate since items may measure different domains.

Results study GWEP1414

Participant flow

A total of 293 patients were screened, 68 (23.2%) of which were screen failures. A total of 225 patients were randomized to double-blind treatment. All randomized patients received at least 1 dose of double-blind IMP and thus were included in the safety analysis set. In total, 30 sites screened patients, of which 29 sites randomized patients into the trial (20 sites in the US, 5 in Spain, 1 in France and 3 in the UK). An additional 7 sites in the US were selected but did not screen patients. Of the 225 randomized patients, 181 were randomized from the US, 32 from Spain, 11 from the UK and 1 from France.

Figure 16 Disposition of Patients (ITT Analysis Set)



[a]*Six patients randomized to receive GWP42003-P 10 mg/kg/day and 3 patients randomized to receive placebo 10 mg/kg/day were given dosing schedules for 20 mg/kg/day patients and received > 10 mg/kg/day dosing volumes before the mistake was corrected. These patients are analyzed according to the treatment group to which they were randomized, unless otherwise stated.* [b]*Within the safety analysis set, the patients who mistakenly received > 10 mg/kg/day dosing volumes (see footnote "a") are analyzed within the 20 mg/kg/day dose groups.*
[c]*Five patients entered taper following withdrawal (2 in each GWP42003-P group and 1 in the 10 mg/kg/day placebo group); the remaining patients who withdrew did not taper.*
[d]*Patient met liver function withdrawal criteria and had TEAEs relating to liver transaminases that led to discontinuation*
[e]*Patient had a protocol deviation deemed to compromise the safety of the patient (would not attend the withdrawal visit) and had 4 serious TEAEs that led to discontinuation*
[f]*Includes 2 patients (1 in the 20 mg/kg/day GWP42003-P group and 1 in the 10 mg/kg/day placebo group) who were not captured as entering the OLE trial but did enter the OLE trial*

Recruitment

A total of 293 patients were screened, 68 (23.2%) of which were screen failures. A total of 225 patients were randomized to double-blind treatment (Figure 15). The number of recruited patients exceeded the planned number according to sample size estimations.

Conduct of the study

Protocol deviations:

During blinded review, a number of patients were deemed to have important protocol deviations with the potential to compromise the assessment of efficacy. In total, 24 patients were excluded from the PP analysis set; 10 patients (13.7%) randomized to 10 mg/kg/day CBD-OS, 11 patients (14.5%) randomized to 20 mg/kg/day CBD-OS, 3 patients (3.9%) randomized to placebo. Of the 24 patients excluded from the PP analysis set, 11 patients (8 randomized to 10 mg/kg/day CBD-OS, 2 randomized to 20 mg/kg/day CBD-OS, and 1 randomized to placebo) were excluded due to protocol deviations; the remaining 13 patients that were excluded from the PP analysis set were patients that withdrew during the treatment period and were not exclusions due to protocol deviations.

Among protocol deviations not leading to exclusion from the PP analysis set were e.g. one 10 mg/kg/day patient missing IMP doses for 10 days, and three 10 mg/kg/day patients receiving halved

doses for 43 days. These three patients were retained in the PP analysis since dosing with study drug was continued throughout the trial.

Protocol amendments:

There were 7 protocol amendments of which 5 were before the date of first informed consent (8 June 2015), and the remaining 2 a few days after (11 June and 15 June, respectively). Thus, it is considered likely that all amendments came into effect before patients were included in the study.

Baseline data

Baseline characteristics were generally similar across the treatment groups with only minor imbalances e.g. regarding the frequency of certain seizure types (atonic and myoclonic seizures). There were more patients with autism spectrum disorders in the 20 mg/kg/day arm than in the two other treatment arms. All patients had failed 2 or more AEDs prior to starting the trial. Only 4 patients were reported to have previously used cannabis.

Table 22 Demographics and Baseline Characteristics (Safety Analysis Set)

Demographic Characteristic	GWP42003-P (n=149)		Pooled Placebo (n=76)	Total (n=225)
	20 mg.kg/day (n=82)	10 mg/kg/day (n=67)		
Age (years)				
n	82	67	76	225
Mean (SD)	16.5 (11.1)	14.7 (8.8)	15.3 (9.3)	15.6 (9.8)
Median	13.8	12.4	12.7	12.9
Min, Max	2.6, 48.0	2.6, 38.2	2.6, 43.4	2.6, 48.0
Age Group [n (%)]				
2–5 years	9 (11.0)	8 (11.9)	9 (11.8)	26 (11.6)
6–11 years	27 (32.9)	22 (32.8)	24 (31.6)	73 (32.4)
12–17 years	21 (25.6)	18 (26.9)	20 (26.3)	59 (26.2)
18–55 years	25 (30.5)	19 (28.4)	23 (30.3)	67 (29.8)
Sex [n (%)]				
Female	33 (40.2)	31 (46.3)	32 (42.1)	96 (42.7)
Male	49 (59.8)	36 (53.7)	44 (57.9)	129 (57.3)
Race [n (%)]				
White/ Caucasian	73 (89.0)	56 (83.6)	69 (90.8)	198 (88.0)
Black/African American	4 (4.9)	4 (6.0)	3 (3.9)	11 (4.9)
Asian	1 (1.2)	1 (1.5)	2 (2.6)	4 (1.8)
Not Applicable[a]	0	1 (1.5)	0	1 (0.4)
Other	4 (4.9)	5 (7.5)	2 (2.6)	11 (4.9)
Country [n (%)]				
France	0	1 (1.5)	0	1 (0.4)
Spain	11 (13.4)	9 (13.4)	12 (15.8)	32 (14.2)
US	65 (79.3)	54 (80.6)	62 (81.6)	181 (80.4)
UK	6 (7.3)	3 (4.5)	2 (2.6)	11 (4.9)
Region [n (%)]				
Rest of the World	17 (20.7)	13 (19.4)	14 (18.4)	44 (19.6)
US	65 (79.3)	54 (80.6)	62 (81.6)	181 (80.4)
Weight at Baseline (kg)				
n	82	67	76	225
Mean (SD)	41.78 (20.712)	43.53 (26.629)	45.65 (23.170)	43.61 (23.376)

Median	39.00	35.80	40.90	38.70
Min, Max	10.8, 104.3	12.8, 140.2	11.9, 112.6	10.8, 140.2
Height at Baseline (cm)				
n	82	67	76	225
Mean (SD)	142.93 (23.230)	139.42 (23.166)	142.20 (24.165)	141.64 (23.473)
Median	148.30	140.80	146.25	145.50
Min, Max	92.0, 185.0	93.0, 182.9	63.0, 187.6	63.0, 187.6
Body Mass Index at Baseline (kg/m^2)				
n	82	67	76	225
Mean (SD)	19.26 (5.710)	20.75 (7.834)	21.37 (6.915)	20.41 (6.835)
Median	17.68	18.45	20.25	18.78
Min, Max	10.4, 44.2	11.2, 50.0	12.4, 51.1	10.4, 51.1

[a]*Not applicable as per country specific data protection law.*

Numbers analysed

All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group

The primary efficacy analyses were conducted using the ITT analysis set, which comprised a total of 225 patients: 73 patients in the 10 mg/kg/day GWP42003-P group, 76 patients in the 20 mg/kg/day GWP42003-P group and 76 patients in the placebo group.

Additional analyses were conducted using the PP analysis set, which excluded 24 patients (10 patients in the 10 mg/kg/day GWP42003-P group, 11 patients in the 20 mg/kg/day GWP42003-P group, and 3 patients in the placebo group), comprising 13 patients who withdrew from the trial early and a further 11 patients with major protocol deviations. Accordingly, the PP analysis set comprised a total of 201 patients: 63 patients in the 10 mg/kg/day GWP42003-P group, 65 patients in the 20 mg/kg/day GWP42003-P group, and 73 patients in the placebo group.

The safety analysis set comprised all randomized patients who received at least 1 dose of IMP; no patients were excluded from the safety analysis set.

Outcomes and estimation

Primary efficacy variable:

During the baseline period, the median drop seizure frequency (28-day average) was slightly lower in the placebo group than in the active treatment groups. A greater median reduction in drop seizure frequency during the treatment period was seen in both CBD-OS groups (20 mg/kg/day and 10 mg/kg/day), compared with the placebo group; the difference between each CBD-OS group and placebo was statistically significant (p=0.0047 and p=0.0016, respectively).

Table 23 Primary Endpoint: Percentage Change from Baseline in Drop Seizure Frequency During the Treatment Period (ITT Analysis Set)

Variable	20 mg/kg/day GWP42003-P (N=76)	10 mg/kg/day GWP42003-P (N=73)	Placebo (N=76)
Drop Seizure Frequency (per 28 Days)	n=76	n=73	n=76
Baseline Period Median (Q1, Q3)	85.53 (38.3, 161.5)	86.90 (40.6, 190.0)	80.25 (47.8, 148.0)

Treatment Period Median (Q1, Q3)	44.86 (14.4, 117.4)	50.00 (20.5, 113.2)	72.66 (35.3, 125.0)
Median Percentage Change During Treatment (Q1, Q3)	−41.86 (−72.4, −1.3)	−37.16 (−63.8, −5.6)	−17.17 (−37.1, 0.9)
20 mg/kg/day GWP42003-P vs. placebo			
Estimated Median Difference (CI) [a]	−21.57 (−34.79, −6.67)		
P-value [a]	0.0047		
10 mg/kg/day GWP42003-P vs. placebo			
Estimated Median Difference (CI) [a]	−19.19 (−31.24, −7.69)		
P-value [a]	0.0016		

[a]*The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test are presented*

Sensitivity analyses for the primary efficacy variable using the PP analysis set and during the maintenance period (and during each 4 weeks thereof) using the ITT analysis set were consistent with the result obtained for the primary analysis:

In the PP analysis set, the median percentage change from baseline in drop seizure frequency during the treatment period was −45.79 in the 20 mg/kg/day CBD-OS group, and −36.44 in the 10 mg/kg/day CBD-OS group, compared with −17.25 in the placebo group (estimated median difference 20 mg/kg/day: −26.28; 95% CI: −40.08, −10.70; estimated median difference 10 mg/kg/day: −17.88; 95% CI: −30.35, −5.66); the difference in favour of both 20 mg/kg/day and 10 mg/kg/day CBD-OS over placebo was statistically significant (p=0.0009 and p=0.0054, respectively).

In the ITT analysis set, the median percentage change from baseline in drop seizure frequency during the whole maintenance period was −47.15 in the 20 mg/kg/day CBD-OS group, and −39.99 in the 10 mg/kg/day GWP42003-P group, compared with −18.73 in the placebo group; the difference in favour of both 20 mg/kg/day CBD-OS and 10 mg/kg/day CBD-OS over placebo was statistically significant (p=0.0067 and p=0.0033, respectively). The median percentage reduction from baseline in drop seizure frequency was also greater in both CBD-OS treatment groups compared with placebo for each of the consecutive 4-week periods of the maintenance period; in all cases the treatment difference in favour of CBD-OS was statistically significant with the exception of 20 mg/kg/day during the last 4-week period of the maintenance period (Week 9–12).

Sensitivity analyses of imputing missing data from unreported days in the IVRS (using the worst case of LOCF, NOCB, or the mean daily number of seizures during the treatment period, based on non-missing data) and of MNAR using a model with MI determined that the primary analysis is robust against missing data, and that the assumption of data missing not at random does not alter the result of the primary analysis.

Patients with a ≥ 50% reduction in Drop Seizure Frequency from Baseline:

The proportion of patients with a ≥ 50% reduction in drop seizure frequency from baseline was calculated for the 20 mg/kg/day CBD-OS and placebo groups during the entire treatment period and during the maintenance period. Results are presented as OR (20 mg/kg/day CBD-OS:Placebo) along with 95% CI, where values >1 are in favour of CBD-OS. Statistical significance was determined using a CMH test stratified by age group. During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline drop seizure frequency (28-day average) was greater in the 20 mg/kg/day and 10 mg/kg/day CBD-OS groups, compared with the placebo group. The difference in favour of CBD-OS was statistically significant for both the 20 mg/kg/day group (p=0.0006) and the 10

mg/kg/day group (p=0.0030). Results of sensitivity analyses were concordant with those of the primary analysis.

Table 24 Patients with a ≥ 50% Reduction in Drop Seizure Frequency from Baseline During the Treatment Period (ITT Analysis Set)

Variable	20 mg/kg/day GWP42003-P (N=76)	10 mg/kg/day GWP42003-P (N=73)	Placebo (N=76)
≥ 50% Reduction in Drop Seizure Frequency from Baseline	n=76	n=73	n=76
Yes (%)	30 (39.5)	26 (35.6)	11 (14.5)
No (%)	46 (60.5)	47 (64.4)	65 (85.5)
20 mg/kg/day GWP42003-P vs. placebo			
Odds Ratio (CI) [a]	3.85 (1.75, 8.47)		
P-value [a]	0.0006		
10 mg/kg/day GWP42003-P vs. placebo			
Odds Ratio (CI) [a]	3.27 (1.47, 7.26)		
P-value [a]	0.0030		

[a] *p-value calculated from a CMH test stratified by age group (2-5, 6-11, 12-17 and 18-55 years)*

Change from Baseline in Total Seizure Frequency:

A greater median reduction in total seizure frequency (28-day average) during the treatment period was seen in both the 20 mg/kg/day and 10 mg/kg/day CBD-OS groups, compared with the placebo group. The difference between each CBD-OS group and placebo was statistically significant (p=0.0091 and p=0.0015, respectively). Analysis of the median percentage change in total seizure frequency during the treatment period, for the PP analysis set, also showed a statistically significant difference in favour of each of the CBD-OS groups. Results of sensitivity analyses were concordant with those of the primary analysis.

Table 25 Percentage Change from Baseline in Total Seizure Frequency During the Treatment Period (ITT Analysis Set)

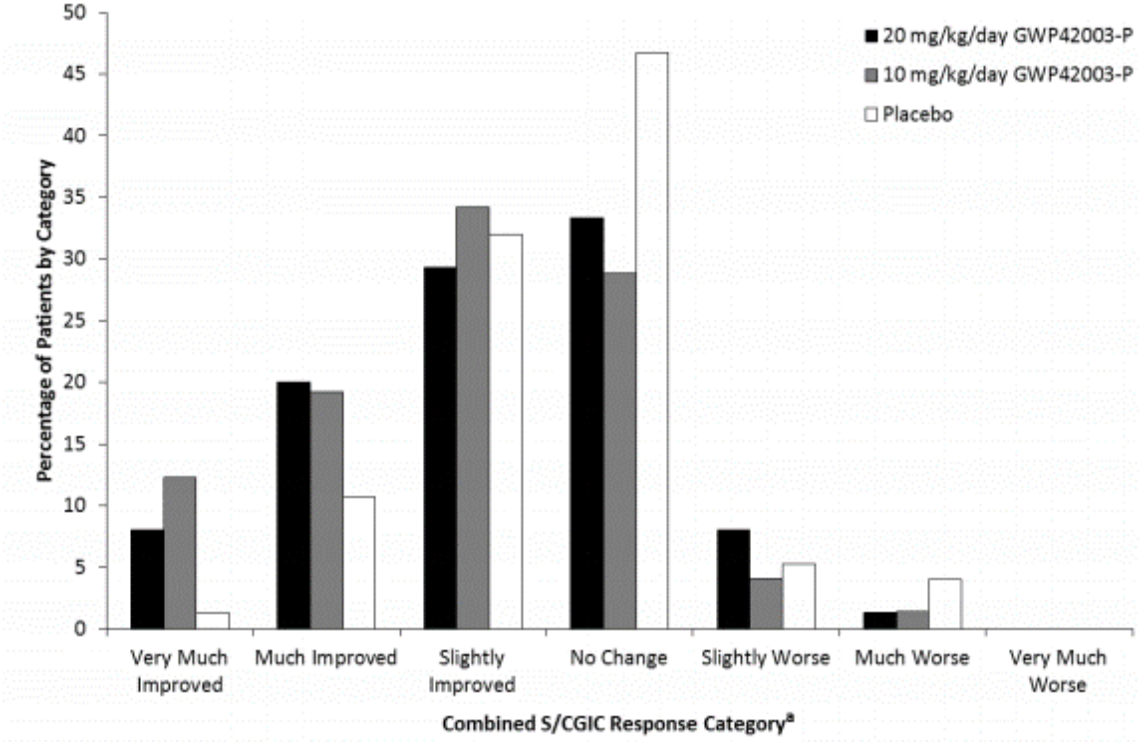
Variable	20 mg/kg/day GWP42003-P (N=76)	10 mg/kg/day GWP42003-P (N=73)	Placebo (N=76)
Total Seizure Frequency (per 28 Days)	n=76	n=73	n=76
Baseline Period Median (Q1, Q3)	174.29 (82.7, 392.4)	165.00 (81.3, 359.0)	180.63 (90.4, 431.3)
Treatment Period Median (Q1, Q3)	90.33 (28.7, 234.0)	76.08 (38.5, 188.4)	138.91 (65.2, 403.4)
Median Percentage Change During Treatment (Q1, Q3)	−38.40 (−64.6, −0.7)	−36.44 (−64.5, −10.8)	−18.47 (−39.0, 0.5)
20 mg/kg/day GWP42003-P vs. placebo			
Estimated Median Difference (CI)[a]	−18.76 (−31.80, −4.43)		
P-value[a]	0.0091		
10 mg/kg/day GWP42003-P vs. placebo			
Estimated Median Difference (CI)[a]	−19.47 (−30.37, −7.47)		
P-value[a]	0.0015		

[a] *The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test are presented*

Change from Baseline in the Subject/Caregiver Global Impression of Change Score:

The change from baseline in overall condition, assessed using the S/CGIC, was reported for each treatment group during the treatment period and was the final key secondary endpoint tested using the ITT analysis set. When measured on a numerical scale, a lower score represents an improvement in condition. At their last visit (i.e., incorporating LOCF, the last visit at which the S/CGIC assessment was conducted for an individual patient) higher proportions of 20 mg/kg/day CBD-OS patients, and 10 mg/kg/day patients, than placebo patients were reported as having an improvement in overall condition (slightly improved, much improved, or very much improved) compared to their status before the trial; 57.3% (43/75) and 65.8% (48/73) vs. 44.0% (33/75), respectively. Only 1 placebo patient (1.3%) was reported as 'very much improved' compared with 6 patients (8.0%) in the 20 mg/kg/day CBD-OS group and 9 patients (12.3%) in the 10 mg/kg/day group. The treatment differences in favour of 20 mg/kg/day and 10 mg/kg/day CBD-OS were both statistically significant (p=0.0439 and p=0.0020, respectively). Sensitivity analyses using just the caregiver scores, and/or the PP analysis set also showed statistically significant improvements in favour of both doses of CBD-OS.

Figure 17 Subject/Caregiver Global Impression of Change at Last Visit (ITT Analysis Set)



[a] *If both CGIC and SGIC were completed the CGIC score was used, if only the CGIC was completed the CGIC was used, and if only the SGIC was completed the SGIC was used*

Other secondary efficacy variables:

For all seizure types, findings were in line with the primary analysis: Greater median reductions from baseline were seen in the 20 mg/kg/day and 10 mg/kg/day CBD-OS groups than in the placebo groups.

Table 26 Percentage Change from Baseline in Seizure Frequency (Average per 28 Days) during the Treatment Period by Seizure Type in LGS Trials GWEP1414 and GWEP1423 (ITT Analysis Set)

Seizure Type	GWEP1414					GWEP1423		
	CBD-OS 10 mg/kg N	CBD-OS 20 mg/kg N	Placebo N	CBD-OS 10 mg/kg vs. Placebo Estimated Median Difference (95% CI)	CBD-OS 20 mg/kg vs. Placebo Estimated Median Difference (95% CI)	CBD-OS 20 mg/kg N	Placebo N	CBD-OS 20 mg/kg vs. Placebo Estimated Median Difference (95% CI)
Non-drop	55	64	70	−28.31	−22.36	77	79	−26.06
				(−43.75, −10.54)	(−40.10, −2.22)			(−46.09, −8.34)
Convulsive	73	76	76	−22.08	−18.58	86	85	−21.28
				(−33.48, −10.42)	(−31.11, −5.45)			(−33.42, −8.73)
Non-	45	59	60	−16.62	−18.87	67	67	−27.44
convulsive				(−37.77, 3.39)	(−40.22, 0.00)			(−45.74, −9.43)
Tonic	56	59	57	−21.78	−18.67	71	65	−25.76
				(−35.90, −7.36)	(−35.02, −1.62)			(−40.84, −9.84)
Atonic	40	50	41	−28.77	−16.98	47	59	−12.16
				(−45.55, −7.08)	(−37.79, 8.52)			(−31.27, 6.22)
Tonic–	37	41	34	−39.92	−27.95	49	53	−22.77
clonic				(−64.55, −19.66)	(−51.99, −2.86)			(−44.94, 0.37)

Note: The Hodges–Lehmann estimated median difference and 95% CI are presented.
Note: Negative values are in favor of CBD-OS.

However, 3 patients with seizures of a new type recurring more than twice were in the active (10 mg/kg/day and 20 mg/kg/day) groups. Also, non-convulsive SE was seen in 4 patients that did not report non-convulsive SE during the baseline period.

Quality of Life in Childhood Epilepsy (2–18 Years) scores should be interpreted with caution due to the very low number of patients included in these analyses. The scores improved more in the placebo group than in the 20 mg/kg/day CBD-OS group, and the difference was statistically significant for the attention/concentration subscale. Other areas where placebo appeared numerically superior were anxiety, behavioural difficulties, memory, and other cognitive skills. Executive functioning improved in the placebo group, worsened in the 20 mg/kg/day CBD-OS group and was unchanged in the 10 mg/kg/day CBD-OS group. The index of 'internalizing behaviours showed worsening in 20 mg/kg/day CBD-OS patients, but an improvement in 10 mg/kg/day GWP42003-P and placebo patients. The index of 'behavioural symptoms' showed an improvement in the 10 mg/kg/day CBD-OS group, a slight worsening in the 20 mg/kg/day CBD-OS group and no change in the placebo group. The index of adaptive skills showed worsening in both CBD-OS groups and improved in the placebo group. Thus, negative effects of CBD-OS, in particular the 20 mg/kg/day dose, on cognition and behaviour cannot be excluded.

Drop Seizure Free Days:

The mean number of drop seizure free days (28-day average) was similar between the 3 treatment groups during the baseline period (range 4.57–5.29). It increased in all treatment groups during the treatment period and the maintenance period, although greater increases were seen in the 20 mg/kg/day and 10 mg/kg/day CBD-OS groups compared with placebo. Analysis showed that the treatment difference in favour of 20 mg/kg/day CBD-OS was statistically significant for both the treatment period ($p<0.0001$; treatment difference: 4.64; 95% CI: 2.46, 6.81) and the maintenance period ($p<0.0001$; treatment difference: 4.84; 95% CI: 2.54, 7.13); equivalent to approximately 5 extra drop seizure free days (per 28 days). Similarly, analysis showed that the treatment difference in favour of 10 mg/kg/day CBD-OS was statistically significant for both the treatment period ($p=0.0030$; treatment difference: 3.34; 95% CI: 1.15, 5.53) and the maintenance period ($p=0.0024$; treatment

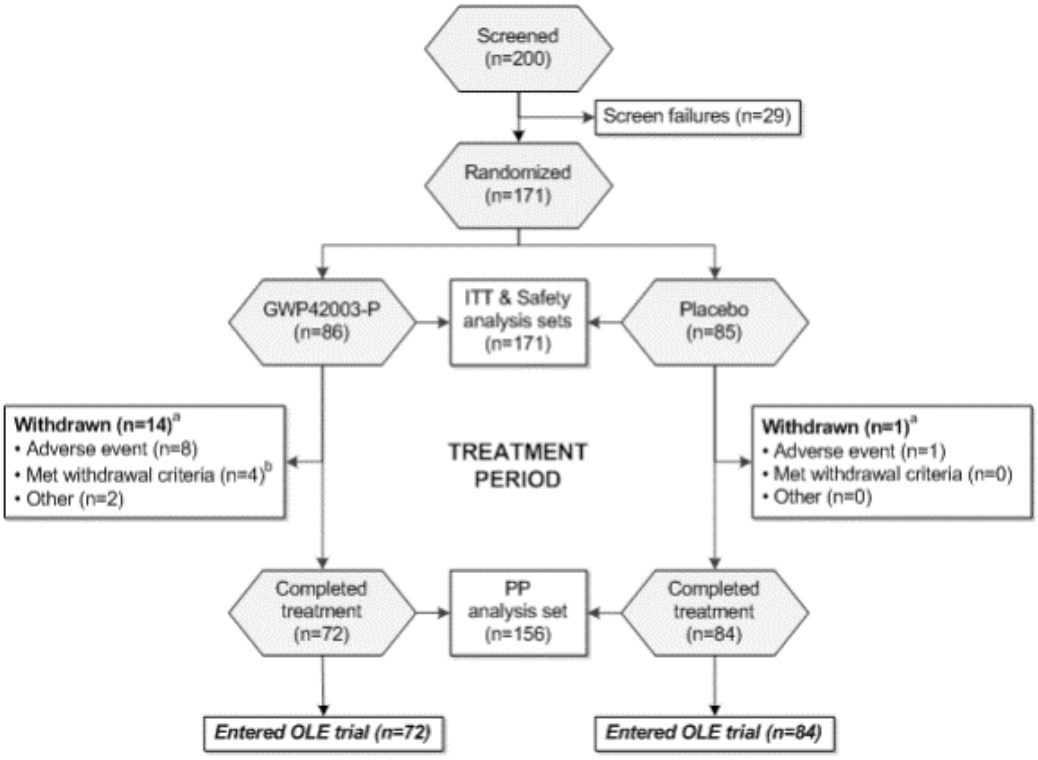
difference: 3.61; 95% CI: 1.29, 5.93); equivalent to approximately 3–4 days extra drop seizure free days (per 28 days).

Results GWEP1423

Participant flow

A total of 200 patients were screened, 29 (14.5%) of which were screen failures. A total of 171 patients were randomized to double-blind treatment. All randomized patients received at least 1 dose of double-blind IMP and thus were included in the safety analysis set. In total, 24 sites screened patients (17 in the US, 1 in the Netherlands and 6 in Poland), all of which randomized patients into the trial. An additional 11 sites were selected but did not screen patients (9 in the US and 2 in the Netherlands). Of the 171 randomized patients, 5 were randomized from the Netherlands, 38 from Poland, and 128 from the US.

Figure 1. Disposition of Patients



a5 GWP42003-P entered taper following withdrawal; the remaining patients who withdrew did not.
b3 patients met liver function withdrawal criteria and in all cases had TEAEs relating to liver transaminase elevations that were reported to have led to withdrawal (see Section 9.3.1.3).

Of the 171 patients that were randomized in the trial (86 CBD-OS patients and 85 placebo patients), 156 patients (91.2%) completed the treatment period (72 CBD-OS patients [83.7%] and 84 placebo patients [98.8%]). Fifteen patients (8.8%) were withdrawn during the treatment period (14 CBD-OS patients [16.3%] and 1 placebo patient [1.2%]).

Recruitment

A total of 200 patients were screened, 29 (14.5%) of which were screen failures. A total of 171 patients were randomized to double-blind treatment. The number of recruited patients exceeded the planned number according to sample size estimations. Additionally, many patients were recruited after protocol amendment 4 which included an increased number of participants based on a revised estimate of the placebo response (from 10% to 18%).

Conduct of the study

Protocol deviations:

During blinded review, it was determined that only the 15 patients who withdrew during the treatment period (14 GWP42003-P patients and 1 placebo patient) were to be excluded from the PP analysis set. All protocol deviations reported in the patients who completed the trial were regarded as either important or minor, but would not compromise the assessment of efficacy and therefore would not warrant removal from the PP analysis set.

Protocol amendments:

Amendments 3 and 4 were performed while recruitment was ongoing. The changes included an increase in patient numbers and changes in eligibility criteria in particular regarding IVRS compliance.

Baseline data

Baseline characteristics were generally similar across treatment groups with only minor imbalances.

Table 27 Demographic Characteristics (Safety Analysis Set)

Demographic Characteristic	GWP42003-P (N=86)	Placebo (N=85)	Total (N=171)
Age (years)			
n	86	85	171
Mean (SD)	15.478 (8.6850)	15.284 (9.7945)	15.381 (9.2264)
Median	14.196	13.284	13.873
Min, Max	2.72, 38.96	2.81, 45.09	2.72, 45.09
Age Group [n (%)]			
2–5 years	11 (12.8)	12 (14.1)	23 (13.5)
6–11 years	26 (30.2)	27 (31.8)	53 (31.0)
12–17 years	19 (22.1)	18 (21.2)	37 (21.6)
18–55 years	30 (34.9)	28 (32.9)	58 (33.9)
Sex [n (%)]			
Female	41 (47.7)	42 (49.4)	83 (48.5)
Male	45 (52.3)	43 (50.6)	88 (51.5)
Race [n (%)]			
White/Caucasian	75 (87.2)	79 (92.9)	154 (90.1)
Black/African American	2 (2.3)	3 (3.5)	5 (2.9)
Asian	3 (3.5)	3 (3.5)	6 (3.5)
Other[a]	6 (7.0)	0	6 (3.5)
Country [n (%)]			
Netherlands	3 (3.5)	2 (2.4)	5 (2.9)
Poland	21 (24.4)	17 (20.0)	38 (22.2)
US	62 (72.1)	66 (77.6)	128 (74.9)

Region [n (%)]			
Rest of World	24 (27.9)	19 (22.4)	43 (25.1)
US	62 (72.1)	66 (77.6)	128 (74.9)
Weight at Baseline (kg)			
n	86	85	171
Mean (SD)	42.81 (22.515)	42.89 (23.005)	42.85 (22.693)
Median	36.90	36.30	36.80
Min, Max	13.6, 98.7	13.4, 106.0	13.4, 106.0
Height at Baseline (cm)			
n	86	85	171
Mean (SD)	140.03 (25.057)	141.59 (24.548)	140.81 (24.745)
Median	145.00	147.30	145.00
Min, Max	52.5, 190.0	96.5, 190.5	52.5, 190.5
Body Mass Index at Baseline (kg/m^2)			
n	86	85	171
Mean (SD)	21.02 (9.942)	19.70 (5.666)	20.37 (8.107)
Median	18.67	18.41	18.48
Min, Max	10.3, 94.3	10.0, 39.4	10.0, 94.3

[a]5 patients were recorded as being Hispanic and 1 patient was recorded as being Arabian

Numbers analysed

All patients who were randomized, received at least 1 dose of IMP, and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group.

The primary efficacy analyses were conducted using the ITT analysis set, which comprised a total of 171 patients: 86 patients in the GWP42003-P group and 85 patients in the placebo group

Additional analyses were conducted using the PP analysis set, which excluded 15 patients (14 GWP42003-P patients and 1 placebo patient) who withdrew during the treatment period. The PP analysis set comprised a total of 156 patients: 72 patients in the GWP42003-P group and 84 patients in the placebo group. No other major deviations were identified (see Section 7.2).

The safety analysis set comprised all patients who received at least 1 dose of IMP; no patients were excluded from the safety analysis set.

Outcomes and estimation

Primary efficacy variable:

During the baseline period, the median drop seizure frequency (28-day average) was similar for both treatment groups. A greater median reduction was seen in the CBD-OS group, and the difference between treatment groups was statistically significant (p=0.0135).

Table 28 Primary Endpoint: Percentage Change from Baseline in Drop Seizure Frequency During the Treatment Period (ITT Analysis Set)

Variable	GWP42003-P (N=86)	Placebo (N=85)
Drop Seizure Frequency (per 28 Days)	n=86	n=85
Baseline Period Median (Q1, Q3)	71.43 (27.0, 156.0)	74.67 (47.3, 144.0)

Treatment Period Median (Q1, Q3)	31.38 (14.4, 92.0)	56.29 (29.7, 129.3)
Median Percentage Change During Treatment (Q1, Q3)	−43.90 (−69.6, −1.9)	−21.80 (−45.7, 1.7)
Estimated Median Difference (CI)[a]	−17.21 (−30.32, −4.09)	
P-value[a]	0.0135	

[a]*The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test are presented.*

Sensitivity analyses for the primary efficacy variable using the PP analysis set and during the maintenance period (and during each 4 weeks thereof) using the ITT analysis set were consistent with the result obtained for the primary analysis. In the PP population, the median percentage change from baseline in drop seizure frequency during the treatment period was −46.12 in the CBD-OS group compared with −21.73 in the placebo group (estimated median difference: −19.43; 95% CI: −32.79, −5.76); the difference in favour of CBD-OS was statistically significant (p=0.0062). In the ITT analysis set, the median percentage change from baseline in drop seizure frequency during the whole maintenance period was −48.77 in the CBD-OS group compared with −20.45 in the placebo group; the difference between treatment groups was statistically significant in favour of CBD-OS over placebo (p=0.0096). The median percentage reduction from baseline in drop seizure frequency was also greater in the CBD-OS group compared with placebo for each of the consecutive 4-week periods of the maintenance period; in all cases the treatment difference in favour of CBD-OS was statistically significant.

Sensitivity analyses of imputing missing data from unreported days in the IVRS (using the worst case of LOCF, NOCB, or the mean daily number of seizures during the treatment period, based on non-missing data) and of MNAR using a model with MI determined that the primary analysis is robust against missing data, and that the assumption of data MNAR does not alter the result of the primary analysis.

Patients with a ≥ 50% reduction in Drop Seizure Frequency from Baseline:

Results are presented as OR (CBD-OS:Placebo) along with 95% CI for the OR, where values > 1 are in favour of CBD-OS. Statistical significance was determined using a CMH test stratified by age group. During the treatment period, the proportion of patients with a reduction of half or more in their baseline drop seizure frequency (28-day average) was greater in the CBD-OS group than in the placebo group. There were approximately 2.6-times the odds of achieving a ≥ 50% reduction in drop seizure frequency in the CBD-OS group compared with the placebo group; the difference was statistically significant (p=0.0043).

Table 29 Patients with a ≥ 50% Reduction in Drop Seizure Frequency from Baseline During the Treatment Period (ITT Analysis Set)

Variable	GWP42003-P (N=86)	Placebo (N=85)
≥ 50% Reduction in Drop Seizure Frequency from Baseline	n=86	n=85
Yes (%)	38 (44.2)	20 (23.5)
No (%)	48 (55.8)	65 (76.5)
Odds Ratio (CI)[a]	2.57 (1.33, 4.97)	
P-value[a]	0.0043	

[a] *p-value calculated from a CMH test stratified by age group (2-5, 6-11, 12-17 and 18-55 years)*

Analyses for the treatment period using the PP analysis set, and for the maintenance period (and during each 4 weeks thereof) using the ITT analysis set, were consistent with the result obtained for the primary analysis.

Change from Baseline in Total Seizure Frequency:

A greater median reduction in total seizure frequency (28-day average) during the treatment period was seen in the CBD-OS group compared with the placebo group; the difference between treatment groups was statistically significant (p=0.0005). Analysis of the median percentage change in total seizure frequency during the treatment period, for the PP analysis set, also showed a statistically significant difference in favour of CBD-OS.

Table 30 Percentage change from baseline in total seizure frequency during the treatment period (ITT Analysis Set)

Variable	GWP42003-P (N=86)	Placebo (N=85)
Total Seizure Frequency (per 28 Days)	n=86	n=85
Baseline Period Median (Q1, Q3)	144.56 (72.0, 385.7)	176.69 (68.6, 359.5)
Treatment Period Median (Q1, Q3)	83.75 (27.4, 255.4)	128.68 (59.3, 337.4)
Median Percentage Change During Treatment (Q1, Q3)	−41.24 (−62.8, −13.0)	−13.70 (−45.0, 7.3)
Estimated Median Difference (CI)[a]	−21.13 (−33.26, −9.37)	
P-value[a]	0.0005	

[a] *The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test are presented*

Change from Baseline in the Subject/Caregiver Global Impression of Change Score:

At their last visit (i.e., incorporating LOCF, the last visit at which the S/CGIC assessment was conducted for an individual patient) a higher proportion of CBD-OS patients than placebo patients were reported as having an improvement in overall condition (slightly improved, much improved, or very much improved) compared to their status before the trial; 58.3% (49/84 patients) vs. 34.1% (29/85 patients), respectively. Thrice as many CBD-OS patients than placebo patients were reported as 'very much improved' (15 patients [17.9%] vs. 5 patients [5.9%], respectively). There were approximately 2.5-times the odds of patients recording a lower score (improvement) in overall condition in the CBD-OS group compared with the placebo group at last visit (OR: 2.54; 95% CI: 1.45, 4.47) and the difference was statistically significant (p=0.0012); a statistically significant improvement in favour of CBD-OS was also observed at the end of treatment (p=0.0021; OR: 2.45; 95% CI: 1.38, 4.33).

Main studies, Dravet Syndrome (Studies GWEP1332B and GWEP1424)

Methods

Study Participants

Study participants:

GWEP1332B

Patients had to be aged 2-18 years (inclusive) with a clinical diagnosis of DS and current seizure types confirmed by a committee of independent experts and to have experienced 4 or more convulsive seizures during the 4-week baseline period. A convulsive seizure was defined as a tonic, clonic, tonic-clonic, or atonic seizure. Patients were taking 1 or more AEDs at a dose which had been stable for at

least 4 weeks. All medications or interventions for epilepsy (including ketogenic diet and VNS) were stable for 4 weeks prior to screening and patient and caregiver were willing to maintain a stable regimen throughout the trial. The ketogenic diet and VNS treatments were not counted as an AED.

Patients were ineligible if they had used recreational or medicinal cannabis, or synthetic cannabinoid-based medications, within 3 months prior to screening and were to abstain from taking them during the trial. Patients were also ineligible if they had a history of alcohol or substance abuse, if they had known or suspected hypersensitivity to any ingredients of the investigational product, or if they did not meet laboratory and clinical health requirements at screening or baseline.

GWEP1424

Eligibility criteria were comparable to those of study 1332B with only minor differences e.g. marginally stricter criteria for liver enzyme abnormalities at study entry.

Regions and sites:

GWEP1332B

A total of 177 patients were screened for Part B of this trial, 57 of which were screen failures. The main reasons for screen failure were that inclusion criteria were not met (46%) and 'other reasons' (42%). A total of 120 patients were randomized to double-blind treatment. All randomized patients received at least 1 dose of double-blind IMP and thus were included in the safety analysis set. Part B of this trial was conducted at 23 trial sites; 2 in Poland, 4 in France, 3 in the UK and 14 in the US. All sites screened patients and 22 sites (2 in Poland, 4 in France, 3 in the UK and 13 in the US) randomized patients into the trial. Of the 120 randomized patients, 14 were randomized from Poland, 18 from France, 16 from the UK and 72 from the US.

GWEP1424

In total, 43 sites screened patients (26 in the US, 7 in Spain, 5 in Poland, 2 in the Netherlands, 2 in Australia, and 1 in Israel) of which 38 sites randomised patients into the trial. Of the 199 randomised patients, 94 were randomised in the US, 39 in Spain, 25 in Poland, 25 in the Netherlands, 13 in Australia, and 3 in Israel.

Treatments

IMP was taken twice daily (morning and evening) without regard to meals, and could be taken with other concomitant medications.

CBD-OS was presented as an oral solution containing 100 mg/mL CBD in sesame oil with anhydrous ethanol (79 mg/ml), added sweetener (sucralose), and strawberry flavouring. Placebo was presented as an oral solution of sesame oil containing anhydrous ethanol (79 mg/ml), added sweetener (sucralose), and strawberry flavouring.

Patients titrated CBD-OS to 10 mg/kg/day over 7 days or 20 mg/kg/day over 11 days and remained at this dose level for the duration of the treatment period. Following the end of treatment (or early withdrawal), all patients who did not immediately enter the OLE were to taper CBD-OS over 10 days (10% per day). However, the taper period could be interrupted if the patient wished to enter the OLE trial within a 7-day timeframe.

Objectives

The primary objective was to assess the efficacy of CBD-OS as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the treatment period of the study in convulsive seizure frequency.

Secondary objectives:

- To assess changes from baseline in convulsive, total, and non-convulsive seizure frequency, duration of seizures, usage of rescue medication, number of inpatient hospitalisations due to epilepsy, sleep disruption, daytime sleepiness, quality of life, menstruation cycles (in females), growth and development, and conduct behavioural assessments in patient taking CBD-OS as an adjunctive treatment, when compared with placebo.
- To determine effects of CBD-OS on plasma concentrations of concomitant AEDs, where available.
- To assess the safety of CBD-OS when compared with placebo.

Outcomes/endpoints

The primary endpoint was the percentage change from baseline in total convulsive seizure frequency during the treatment period of the study in patients taking CBD-OS compared with placebo.

GWEP1332B

The key secondary endpoint was the number of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline. The key secondary endpoint was tested hierarchically to control the type I error.

GWEP1424

The key secondary endpoints were

1) Change in total seizure frequency

2) Number of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline

3) CGIC score

The key secondary endpoints were tested hierarchically to control the type I error.

Sample size

Study GWEP1424

The planned number of randomized patients for trial GWEP1424 was 186 (62 per CBD-OS treatment group and 31 per placebo treatment group, which subsequently became 1 pooled placebo group). For a Wilcoxon–Mann–Whitney test comparing 2 distributions with a 2-sided significance level of 0.05, a sample size of 62 per group (after pooling the placebo groups) was required to obtain a power of at least 80%. This was based on a gamma distribution for the GWP42003-P groups with scale parameter of 65.614 and shape parameter of 1.0886, and a gamma distribution for the placebo group with scale parameter of 40.887 and shape parameter of 2.3059.

Study GWEP1332B

The planned number of randomized patients for trial GWEP1332B was 100 (50 per treatment group). It was assumed that patients in the placebo group would experience a mean reduction in convulsive seizure frequency of 18% (from baseline), meaning the sample size of 50 patients per group would be sufficient to detect a difference of 32% between treatments (i.e., patients receiving GWP42003-P would experience at least a 50% reduction in convulsive seizures). This was based on a standard deviation of 56%, using a 2-sided 5% significance level and 80% power.

Randomisation

A unique patient number was assigned to each patient at Visit 1, using the IWRS. At Visit 2 the IWRS was used to randomly allocate patients who met all eligibility criteria following the baseline period to either CBD-OS or placebo; both were provided in identical 100 mL amber glass bottles with unique identification numbers.

In trial GWEP1332B, patients were randomized to 1 of 2 treatment groups (CBD-OS 20 mg/kg/day or placebo) at a 1:1 ratio. In trial GWEP1424, patients were randomized to 1 of 4 treatment groups (CBD-OS 20 mg/kg/day, CBD-OS 10 mg/kg/day, placebo 20 mg/kg/day dose volume equivalent, or placebo 10 mg/kg/day dose volume equivalent) at a 2:2:1:1 ratio; patients in the placebo groups were pooled for the analyses of efficacy and safety.

The randomization scheme for each trial was generated by an independent statistician using random permuted blocks and was stratified by age group as follows: 2 to < 6, 6 to < 13, and 13 to < 19 years.

Blinding (masking)

All pivotal trials were double-blind. All IMP, i.e., CBD-OS or placebo, was provided in identical 100 ml amber glass bottles. IMP was presented as an oral solution containing 100 mg/ml CBD in the excipients sesame oil and anhydrous ethanol (79 mg/ml) with added sweetener (sucralose) and strawberry flavouring; the matched placebo comprised only the excipients.

Statistical methods

GWEP1332B

Primary efficacy outcome variable:

Primary null hypothesis: Following 14 weeks of treatment there is no difference in effect between the CBD-OS treatment group and the placebo treatment group in terms of the percentage change from baseline in convulsive seizure frequency during the treatment period.

The null hypothesis is rejected if there is statistical evidence of a difference between the treatment groups at the α-level of 0.05 for the primary endpoint.

Percentage change from baseline is calculated as:

((Frequency during the treatment period – Frequency during baseline) ÷ Frequency during baseline) × 100

The frequency during each period will be based on 28-day averages and calculated as:

(Number of seizures in the period ÷ Number of reported days in IVRS in the period) × 28

The data is analysed using a Wilcoxon rank-sum test. An estimate of the median difference between CBD-OS and placebo, together with approximate 95% confidence interval (CI), are calculated using the Hodges-Lehmann approach.

The following sensitivity analyses were planned for the primary endpoint:

1. Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period using the PP analysis set.
2. A rank analysis of covariance (ANCOVA) on percentage change from baseline in convulsive seizure frequency during the treatment period.
3. ANCOVA of log transformed convulsive seizure frequency during the treatment period.
4. ANCOVA on percentage change from baseline in convulsive seizure frequency during the treatment period including baseline and age group as covariates and treatment group as a fixed factor. The estimated least squares means, treatment difference, together with the 95% CIs and p-value will be presented.
5. Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the maintenance period.
6. Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency 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).
7. Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period, 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 to impute missing data arising from unreported days in IVRS during the treatment period only (not the baseline period). Any intermittent missing data for the number of convulsive seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period based using non-missing data: Number of seizures ÷ Number of reported days in IVRS. Upon CHMP request, an additional sensitivity analysis calculating the number of seizure free days with and without the following missing values strategy: Unreported days are considered days with the highest reported number of seizures and for patients that withdraw days without observations are considered days with the highest reported number of seizures.
8. Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption.

Key secondary efficacy outcome variable:

The proportion of patients with a ≥ 50% reduction in convulsive seizure frequency from baseline for each treatment group during the entire treatment period was considered a key secondary endpoint for the EU submission. The proportion was summarised by treatment group and analysed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group. The analysis was performed on the ITT analysis set and repeated on the PP analysis set. There was no imputation for missing IVRS days or withdrawals. Sensitivity analyses were performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, 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). Upon CHMP request, the Applicant performed additional sensitivity analyses for handling this missing data using

following approach: (1) patients with unreported days in the IVRS and patients that withdraw from the study are considered non-responders; (2) patients with unreported days in the IVRS are considered non-responders if the average of their observed seizures is above 50 % and patients that withdraw from the study are considered non-responder.

Other secondary endpoints:

For some of the secondary endpoints e.g. the Epworth Daytime Sleepiness scale and the Quality of Life scales, if fewer than 50% of the items were missing, the missing items were imputed as the mean of the remaining non-missing scores. If more than 50% were missing, the total score would be missing. For the Quality of Life in Childhood Epilepsy, "not applicable" responses were treated as missing values. However, imputation of one item as a mean of other items may not be appropriate since items may measure different domains.

GWEP1424

Calculation of the primary endpoint

The primary null hypothesis is:

• Following 14 weeks of treatment there is no difference in effect between the 20 mg/kg/day (or 10 mg/kg/day if 20 mg/kg/day is statistically significant) GWP42003-P treatment group and the placebo treatment group in terms of the change in convulsive seizure frequency during the treatment period compared to baseline.

The null hypothesis will be rejected if there is statistical evidence of a difference between the treatment groups at the α-level of 0.05 for the primary endpoint.

The primary endpoint is the change in convulsive seizure frequency during the treatment period of the study compared to baseline in patients taking GWP42003-P compared with placebo.

The primary endpoint will be analyzed using negative binomial regression on the sum of the convulsive seizure counts during the treatment period. However, convulsive seizure frequency (28-day average) and percentage change in seizure frequency will be presented using summary statistics. Percentage change from baseline in convulsive seizure frequency will be calculated as:

((Frequency during the treatment period – Frequency during baseline) ÷

Frequency during baseline) × 100

The frequency during each period will be based on 28-day averages and calculated as:

(Number of seizures in the period ÷ Number of reported days in IVRS in the period) × 28

A mixed effect model with repeated measures will be performed modelling the observed number of convulsive 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 (2–5 years, 6–12 years and 13–18 years), time, treatment arm and treatment arm by time interaction as fixed effects and patient as a random effect.

The applicant performed the following sensitivity analyses to account for missing data arising from unreported days in the IVRS, and missing data arising from patients withdrawing during the treatment period:

1. Primary endpoint analysis repeated using the PP analysis set.

2. Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period. An estimate of the median differences between each GWP42003-P group and placebo, together with approximate 95% CIs, will be calculated using the Hodges–Lehmann approach.

3. A rank analysis of covariance (ANCOVA) on percentage change from baseline in convulsive seizure frequency during the treatment period. The ranks of the percentage change from baseline and the baseline convulsive seizure frequency will be calculated. The rank of the percentage change from baseline will then be analyzed using an ANCOVA model with the rank of the baseline convulsive seizure frequency and age group (2–5 years, 6–12 years and 13–18 years) as covariates and treatment group as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.

4. ANCOVA of log transformed convulsive seizure frequency during the treatment period. The convulsive seizure frequency during the treatment period and the baseline convulsive seizure frequency will be log transformed prior to analysis. The log transformed convulsive seizure frequency during the treatment period will then be analyzed using an ANCOVA model with the log transformed baseline convulsive seizure frequency and age group as covariates and treatment group as a fixed factor. The back transformed estimated treatment ratios, together with the 95% CIs and p-values will be presented. If there are any patients with no seizures during the baseline or treatment periods, then 1 will be added to the convulsive seizure frequency for all patients prior to log transformation.

5. ANCOVA on percentage change from baseline in convulsive seizure frequency during the treatment period including baseline and age group as covariates and treatment group as a fixed factor. The estimated least squares means, treatment differences, together with the 95% CIs and p-values will be presented.

6. Primary endpoint analysis repeated using the maintenance period rather than the treatment period. This analysis will include only patients who have at least 7 days of seizure data within the maintenance period.

7. Primary endpoint analysis repeated using each 4 weeks of the maintenance period (Week 1–4, Week 5–8 and Week 9–12 of the 12-week maintenance period). This analysis will include only patients who have at least 7 days of seizure data within each corresponding 4-week period rather than the treatment period.

8. Primary endpoint analysis repeated using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB) and the daily 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). Any intermittent missing data for the number of convulsive seizures arising from unreported days in IVRS will be imputed using the worst (highest number of seizures) of the following for each patient: LOCF, NOCB and the mean daily number of seizures during the treatment period (rounded up to the nearest integer) based on using non-missing data: Number of seizures ÷ Number of reported days in IVRS

9. Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period, using multiple imputation (MI) to impute data under the Missing Not at Random (MNAR) assumption.

10. Primary endpoint analysis repeated using the safety analysis set.

Calculations of the key secondary endpoints

Total Seizures

The analysis is performed in the same manner as the analyses of frequencies for convulsive seizures (primary endpoint). The analysis was performed on the ITT analysis set and repeated on the PP analysis set. Sensitivity analyses are performed on the ITT analysis set, repeating the above analysis, using data for only the maintenance 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).

Treatment Responders (≥50% Reduction in Convulsive Seizure Frequency)

The proportion of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizure frequency from baseline, during the treatment period, are summarized by treatment group and analyzed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group. The analysis is performed on the ITT analysis set and repeated on the PP analysis set.

Sensitivity analyses will be performed on the ITT analysis set, repeating the above analysis, using data for the maintenance period only, 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).

Changes from baseline in the Caregiver Global Impression of Change (CGIC) score

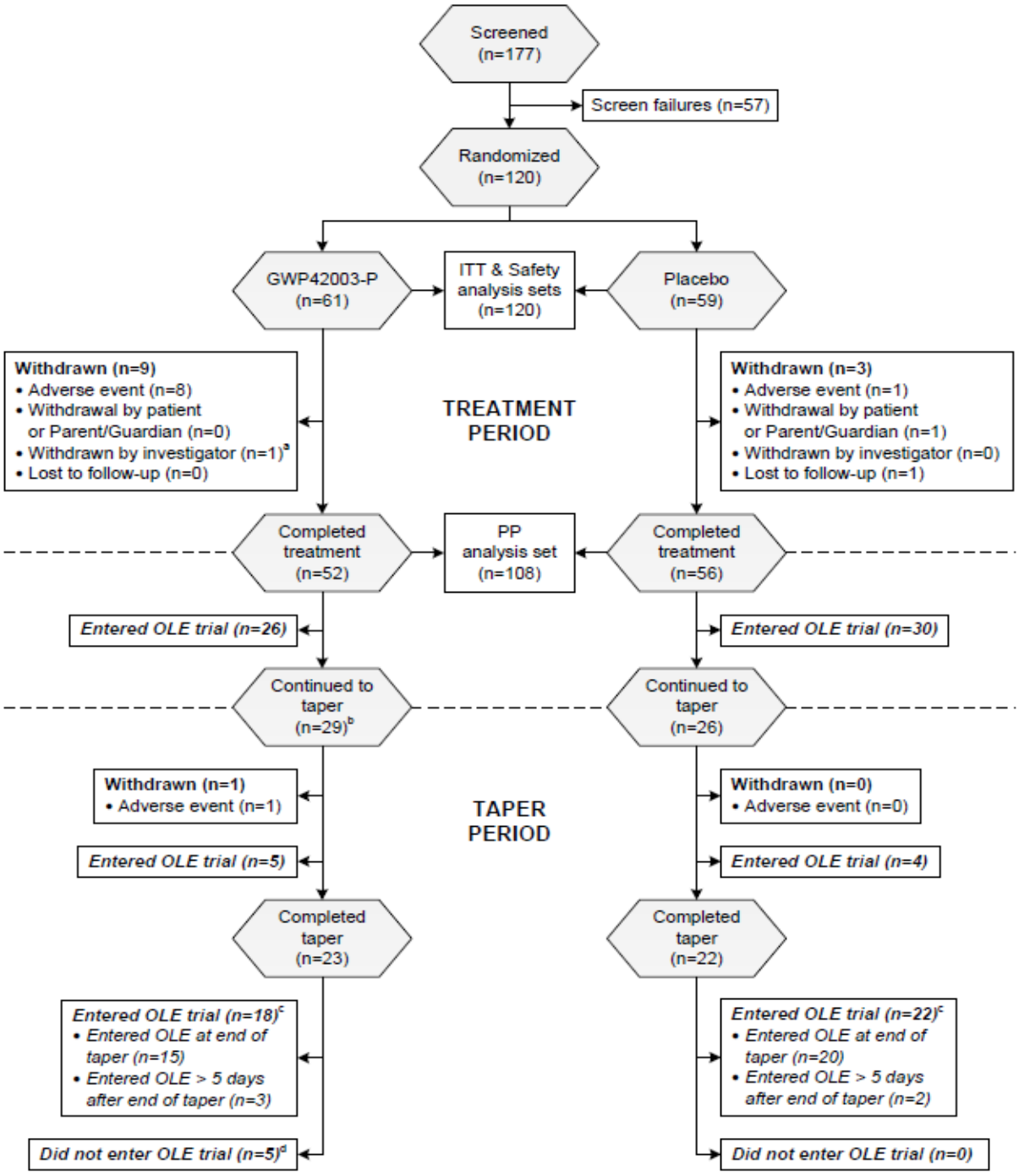
The CGIC will be assessed at Visits 3, 4, 6 and 8 (end of treatment).
The score at the end of treatment visit and last visit (if different to the end of treatment) will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment group as a factor. The estimated odds ratios (GWP42003-P arms vs. placebo), 95% CI for the odds ratios, 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 main analysis for this endpoint, with the analysis at the end of treatment visit considered a sensitivity analysis.

Results GWEP1332B

Participant flow

A total of 177 patients were screened for Part B of this trial, 57 of which were screen failures. A total of 120 patients were randomized to double-blind treatment. All randomized patients received at least 1 dose of double-blind IMP and thus were included in the safety analysis set. Part B of this trial was conducted at 23 trial sites; 2 in Poland, 4 in France, 3 in the UK and 14 in the US. All sites screened patients and 22 sites (2 in Poland, 4 in France, 3 in the UK and 13 in the US) randomized patients into the trial. Of the 120 randomized patients, 14 were randomized from Poland, 18 from France, 16 from the UK and 72 from the US.
Of the 120 patients that were randomized in Part B of the trial, 108 patients (90.0%) completed the treatment period (52 CBD-OS patients [85.2%] and 56 placebo patients [94.9%]). Twelve patients (10.0%) were withdrawn during the treatment period of Part B (9 GWP42003-P patients [14.8%] and 3 placebo patients [5.1%]); of these, 9 patients (7.5%) withdrew due to an AE (8 GWP42003-P patients [13.1%] and 1 placebo patient [1.7%]), 1 placebo patient (1.7%) was lost to follow-up, 1 placebo patient (1.7%) was withdrawn from the trial by their parents, and 1 CBD-OS patient (1.6%) was withdrawn from the trial by the investigator for non-compliance with IMP dosing.

Figure 18 Disposition of Patients: Part B



[a]*The patient was withdrawn by the investigator on Day 43. The primary reason for withdrawal was non-compliance with IMP dosing; however, the patient also had 7 serious TEAEs on Day 32 resulting in discontinuation of IMP. For this reason the patient is summarized as experiencing TEAEs leading to discontinuation of IMP*

[b]*Includes 3 patients who were withdrawn during the treatment period and tapered IMP.*
[c]*Includes patients who entered the OLE trial > 5 days after the end of taper visit*
[d]*Includes 2 patients that were not eligible to enter the OLE trial as they were withdrawn during the treatment period*

Recruitment

Conduct of the study

Protocol deviations:

During a blinded data review meeting, prior to unblinding of the Part B database, it was confirmed that only the 12 patients (10%) who withdrew early were to be excluded from the PP analysis set. Protocol deviations reported in the patients who completed the trial were all regarded as minor (i.e., not compromising the assessment of efficacy, and therefore not warranting exclusion from the PP analysis set). A total of 94 patients (78%) had at least 1 protocol deviation during the trial, with similar numbers of patients across the treatment groups (50 CBD-OS patients [82.0%] and 48 placebo patients [81.4%]). The most common minor protocol deviation (i.e., not deemed to compromise efficacy) was visit dates being outside the time windows specified in the protocol (28 CBD-OS patients [45.9%] and 21 placebo patients [35.6%]). The second most common minor protocol deviation was the omission of urine collection at 1 or more visits (14 CBD-OS patients [23.0%] and 13 placebo patients [22.0%]).

There were 4 instances of patients meeting withdrawal criteria during Part B of the trial, but not being withdrawn. In 3 cases the patients had raised levels of ALT or AST to levels > 3 × ULN, with a concurrent TEAE of fatigue (2 patients, 1 of whom also had concurrent INR > 1.5) or concurrent eosinophilia (1 patient). In the remaining case, the patient had levels of ALT or AST > 8 ×ULN at end of treatment. These were all regarded as important deviations since they related to patient safety; however, they were also regarded as minor since all 3 patients completed the trial, and the deviations were not expected to impact any assessments of efficacy.

Protocol amendments:

Amendment 7 (implementing also changes from Amendment 5) and Amendment 8 were performed several months after study start. The changes included an increase in patient numbers and changes in eligibility criteria in particular regarding IVRS compliance.

Baseline data

Baseline characteristics were generally similar across the treatment groups. However, as described below, there was an imbalance regarding total seizure frequency at baseline (median 24.00 in the CBD-OS group vs. 41.48 in the placebo group). There were also minor imbalances regarding the frequency of certain seizure types (atonic and myoclonic seizures). Of the total number of recruited subjects, 111 (93%) had a *SCN1A* mutation either a truncating variant (n=61) or missense variant (n=50).

Table 31 Demographic Characteristics: Part B (Safety Analysis Set)

Demographic Characteristic	GWP42003-P (N=61)	Placebo (N=59)	Total (N=120)
Age (years)			
n	61	59	120
Mean (SD)	9.736 (4.7309)	9.779 (4.8505)	9.757 (4.7699)
Median	9.084	9.232	9.164
Min, Max	2.51, 18.02	2.26, 18.40	2.26, 18.40
Age group [n (%)]			

2–5 years	18 (29.5)	17 (28.8)	35 (29.2)
6–12 years	23 (37.7)	24 (40.7)	47 (39.2)
13–18 years	20 (32.8)	18 (30.5)	38 (31.7)
Sex [n (%)]			
Female	26 (42.6)	32 (54.2)	58 (48.3)
Male	35 (57.4)	27 (45.8)	62 (51.7)
Race [n (%)]			
White/Caucasian	44 (72.1)	50 (84.7)	94 (78.3)
Black/African American	2 (3.3)	2 (3.4)	4 (3.3)
Asian	1 (1.6)	0	1 (0.8)
Not Applicable[a]	11 (18.0)	6 (10.2)	17 (14.2)
Other	3 (4.9)	1 (1.7)	4 (3.3)
Country [n (%)]			
France	12 (19.7)	6 (10.2)	18 (15.0)
Poland	6 (9.8)	8 (13.6)	14 (11.7)
US	35 (57.4)	37 (62.7)	72 (60.0)
UK	8 (13.1)	8 (13.6)	16 (13.3)
Height (cm)			
n	60	59	119
Mean (SD)	132.18 (26.314)	131.08 (24.404)	131.63 (25.284)
Median	127.50	127.00	127.00
Min, Max	89.3, 188.0	87.6, 189.0	87.6, 189.0
Weight (kg)			
n	61	59	120
Mean (SD)	33.82 (16.631)	35.11 (18.328)	34.45 (17.424)
Median	28.40	29.40	29.00
Min, Max	10.8, 88.6	12.0, 88.4	10.8, 88.6
Body Mass Index (kg/m^2)			
n	60	59	119
Mean (SD)	18.33 (4.464)	19.08 (4.692)	18.71 (4.574)
Median	17.35	18.08	17.43
Min, Max	13.0, 38.7	13.5, 35.6	13.0, 38.7

[a]*Not applicable as per country-specific data protection law*

Numbers analysed

All patients who were randomized, received at least 1 dose of IMP, and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. The primary efficacy analyses were conducted using the ITT analysis set, which comprised a total of 120 patients: 61 patients in the GWP42003-P group and 59 patients in the placebo group. Additional analyses were conducted using the PP analysis set, which excluded 12 patients who withdrew during the treatment period. The PP analysis set comprised a total of 108 patients: 52 patients in the GWP42003-P group and 56 patients in the placebo group. No other major deviations were identified.

The safety analysis set comprised all patients who received at least 1 dose of IMP; no patients were excluded from the safety analysis set.

Outcomes and estimation

Primary efficacy variable:

In the CBD-OS group, the median convulsive seizure frequency decreased (improved) from 12.44 during the baseline period to 5.92 during the treatment period. In the placebo group, the median convulsive seizure frequency decreased (improved) from 14.88 during the baseline period to 14.14 during the treatment period. The median percentage change from baseline in total convulsive seizure frequency during the treatment period was −38.94 in the CBD-OS group compared with −13.29 in the placebo group. The estimated median difference was in favour of CBD-OS treatment over placebo (−22.79; 95% CI: −41.06, −5.43) and the difference between treatments was statistically significant (p=0.0123).

Table 32 Primary Endpoint (Part B): Percentage Change from Baseline in Convulsive Seizure Frequency During the Treatment Period (ITT Analysis Set)

Variable	GWP42003-P (N=61)	Placebo (N=59)
Total Convulsive Seizure Frequency (per 28 Days)	n=61	n=59
Baseline Period Median (Q1, Q3)	12.44 (6.2, 28.0)	14.88 (7.0, 36.0)
Treatment Period Median (Q1, Q3)	5.92 (3.2, 17.3)	14.14 (4.2, 31.1)
Median Percentage Change During Treatment (Q1, Q3)	−38.94 (−69.5, −4.8)	−13.29 (−52.5, 20.2)
Estimated Median Difference (CI)[a]	−22.79 (−41.06, −5.43)	
P-value[a]	0.0123	

[a]*The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test are presented.*

Sensitivity analyses for the primary efficacy variable using the PP analysis set and during the maintenance period (and during each 4 weeks thereof) using the ITT analysis set were consistent with the result obtained for the primary analysis. In the PP population, the median percentage change from baseline in total convulsive seizure frequency during the treatment period was −39.60 in the CBD-OS group compared with −13.30 in the placebo group (estimated median difference: −25.99; 95% CI: −44.79, −8.94). In the ITT population, the median percentage change from baseline in total convulsive seizure frequency during the maintenance period was −40.67 in the CBD-OS group compared with −15.95 in the placebo group (estimated median difference: −26.06; 95% CI: −45.07, −8.24). In both cases, the difference between treatments was statistically significant in favour of CBD-OS treatment over placebo (p=0.0037 and p=0.0052, respectively).

Sensitivity analyses of imputing missing data from unreported days in the IVRS (using the worst case of LOCF, NOCB, or the mean daily number of seizures during the treatment period, based on non-missing data) and of MNAR using a model with MI determined that the primary analysis is robust against missing data and that the assumption of data missing not at random does not alter the result of the primary analysis.

Key secondary efficacy variable:

The proportion of patients with a ≥ 50% reduction in convulsive seizure frequency from baseline was calculated for each treatment group during the entire treatment period (including the dose titration phase [ITT and PP analysis sets]). For the purpose of the EU submission this was the key secondary endpoint. For the EU submission only, the secondary endpoints were tested hierarchically, starting with the key secondary endpoint followed by all other secondary endpoints. For submissions outside the EU, there was no hierarchical testing of secondary endpoints. During the treatment period, the proportion of patients with a reduction of half or more in their baseline convulsive seizure frequency was greater in the CBD-OS group (42.6%) than in the placebo group (27.1%). There were twice the odds of achieving a ≥ 50% reduction in convulsive seizure frequency in the CBD-OS group compared with the

placebo group (OR: 2.00; 95% CI: 0.93, 4.30); however, the difference between treatments was not statistically significant (p=0.0784).

Table 33 Patients with a ≥ 50% Reduction in Convulsive Seizure Frequency from Baseline during the Treatment Period: Part B (ITT Analysis Set)

Variable	GWP42003-P (N=61)	Placebo (N=59)
≥ 50% Reduction in Convulsive Seizure Frequency from Baseline	n=61	n=59
Yes (%)	26 (42.6)	16 (27.1)
No (%)	35 (57.4)	43 (72.9)
Odds Ratio (CI)[a]	2.00 (0.93, 4.30)	
P-value[a]	0.0784	

Note: For the purpose of the EU submission this was the key secondary endpoint.

[a]The 95% CI and the p-value from the CMH test (stratified by age group) are presented

Other secondary efficacy variables:

Three patients in the CBD-OS group had emergent status epilepticus during the treatment period (one convulsive, two non-convulsive). This should be interpreted with caution due to the low number of events. Furthermore, in the CBD-OS group five patients (8.2%) experienced inpatient hospitalisations due to epilepsy during the treatment period vs. one patient (1.7%) in the placebo group. For the energy/fatigue, depression, anxiety, and self-esteem subscores of the Quality of Life in Childhood Epilepsy score the treatment difference was in favour of placebo over GWP42003-P.

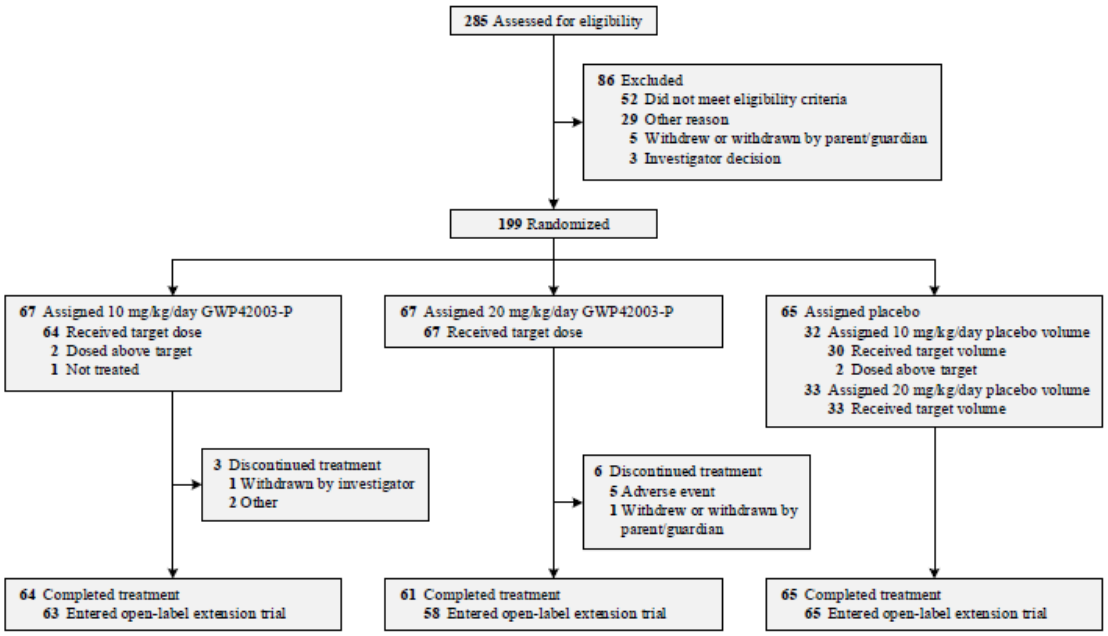
For the communication and motor skills scores in the Vineland Adaptive Behaviour Scales, the adjusted mean difference was in favour of placebo treatment over GWP42003-P and the difference between treatments was statistically significant. Only one-third of caregivers completed the Vineland-II for the subdomains of communication and motor skills, and the mean changes from baseline were small for both treatment groups.

As requested, applicant presented analysis of change from baseline in convulsive seizure free days, per 28 days, using the same definition of the treatment period as used in the primary endpoint. The observed treatment difference (95% CI) of 1.44 (0.07, 2.81) seizure free days per 28 days favoured CBD-OS (p=0.0396). However, analysis of the number of total seizure free days did not reach statistical significance (p=0.1684).

Results GWEP1424

Participant flow

Figure 19 Patient Disposition (All Randomized Patients)



Note: Among the 29 patients who had some "other reason" for exclusion, 22 were not approved, 1 withdrew consent but was also captured under 'withdrew or withdrawn by parent/guardian', 1 was noncooperative but was also captured under 'investigator decision', 1 was unknown but was also captured under 'investigator decision', 1 had no caregiver present at randomization, 1 was due to a family bereavement, 1 was due to a parent's decision, and 1 was due to the Sponsor's decision. One patient assigned 10 mg/kg/day GWP42003-P was randomized but not treated and was therefore excluded from both the efficacy and safety analyses. A further 2 patients assigned 10 mg/kg/day GWP42003-P temporarily received a dose that was above the target and were therefore included in the 20 mg/kg/day GWP42003-P group for the safety analysis. Among the 2 patients assigned 10 mg/kg/day GWP42003-P who had some "other reason" for withdrawal, 1 was due to lack of effect and 1 was on the advice of the GW medical monitor as the patient started a new AED treatment. Withdrawals are shown according to the primary reason reported for each patient.

A total of 285 patients were screened; 86 (30.2%) of whom were screen failures. A total of 199 patients were randomised to double-blind treatment. All but 1 randomised patient received at least 1 dose of double-blind IMP and thus 198 patients were included in the safety analysis set.
In total, 43 sites screened patients (26 in the US, 7 in Spain, 5 in Poland, 2 in the Netherlands, 2 in Australia and 1 in Israel), of which 38 sites randomised patients into the trial. An additional 2 sites were selected but did not screen patients (1 in the US and 1 in Israel). Of the 199 randomised patients, 94 were randomised in the US, 39 in Spain, 25 in Poland, 25 in the Netherlands, 13 in Australia and 3 in Israel. The date of the first informed consent/assent form signed by a patient or their parent(s)/legal representative was 13 April 2015 and the date of the last trial observation was 09 April 2018.
Of the 199 patients that were randomised into the trial (67 in the 10 mg/kg/day GWP42003-P group, 67 in the 20 mg/kg/day GWP42003-P group, and 65 in the pooled placebo group), 190 (95.5%) completed the treatment period (64 in the 10 mg/kg/day GWP42003-P group [95.5%], 61 in the 20 mg/kg/day group [91.0%], and 65 in the pooled placebo group [100%]).
Nine patients (4.5% of total) were withdrawn during the treatment period (3 in the 10 mg/kg/day group [4.5%], and 6 in the 20 mg/kg/day group [9.0%]).

Recruitment

Conduct of the study

Protocol deviations:

During blinded review, a number of patients were deemed to have important protocol deviations with the potential to compromise the assessment of efficacy. In total, 17 patients were excluded from the PP analysis set; 6 patients (9.0%) randomised to 10 mg/kg/day GWP42003-P, 8 patients (11.9%) randomised to 20 mg/kg/day GWP42003-P, 3 patients (4.6%) randomised to placebo. Of the 17 patients excluded from the PP analysis set, 3 patients (2 randomized to 10 mg/kg/day GWP42003-P, and 1 randomized to placebo) were excluded due to protocol deviations; the remaining 14 patients that were excluded from the PP analysis set either withdrew during the treatment period (8 patients), initiated a new AED during the trial (2 patients; 1 of whom was also captured as having withdrawn early), had fewer than 4 convulsive seizures during the first 28 days of the baseline period as captured by IVRS (4 patients), or did not receive any IMP (1 patient), and were not excluded due to protocol deviations.

Protocol amendments:

Changes in the statistical analyses were performed several times - until about two months before unblinding. The 3 key secondary endpoints and the hierarchical testing procedure were not defined in the protocol but were included in the SAP prior to unblinding. Changes made by protocol amendment 6 were based upon the results of completed GW Phase 3 trial in DS showed seizure data were not normally distributed and required non-parametric analysis. The statistical analysis has therefore been changed from a parametric based analysis (analysis of covariance [ANCOVA]) to a non-parametric based analysis (Wilcoxon rank-sum test). By means of protocol amendment 7, the primary analysis method was updated from the Wilcoxon rank-sum test to a negative binomial regression analysis and primary endpoint was amended from “percentage change in total convulsive seizure frequency…” to ”change in total convulsive seizure frequency…”, since percentage change does not apply to negative binomial regression. ‘

Baseline data

The demographic characteristics were similar across the treatment groups. Overall, there was a similar proportion of male (47.5%) and female (52.5%) patients. The distribution of current seizure types reported at screening was similar across the treatment groups, with generalized tonic-clonic being most common, followed by myoclonic, absence and complex partial.

Table 34 Demographics and Baseline Characteristics (Safety Analysis Set)

Demographic Characteristic Statistics	10 mg/kg/day GWP42003-P (N=64)	20 mg/kg/day GWP42003-P (N=69)	Placebo (N=65)	Total (N=198)
Age (years)				
n	64	69	65	198
Mean (SD)	9.2 (4.2)	9.2 (4.4)	9.6 (4.6)	9.3 (4.4)
Median	8.2	10.0	9.1	9.0
Min, Max	2.3, 17.7	2.2, 18.9	2.2, 18.1	2.2, 18.9
Age Group [n (%)]				
2–5 years	18 (28.1)	21 (30.4)	18 (27.7)	57 (28.8)
6–12 years	31 (48.4)	31 (44.9)	28 (43.1)	90 (45.5)
13–18 years	15 (23.4)	17 (24.6)	19 (29.2)	51 (25.8)
Sex [n (%)]				
Female	38 (59.4)	32 (46.4)	34 (52.3)	104 (52.5)
Male	26 (40.6)	37 (53.6)	31 (47.7)	94 (47.5)
Race [n (%)]				
White/Caucasian	55 (85.9)	66 (95.7)	55 (84.6)	176 (88.9)
Black/African American	1 (1.6)	0	4 (6.2)	5 (2.5)

American Indian/Alaska Native	0	0	1 (1.5)	1 (0.5)
Asian	0	1 (1.4)	4 (6.2)	5 (2.5)
Other	8 (12.5)	2 (2.9)	1 (1.5)	11 (5.6)
Country [n (%)]				
Australia	6 (9.4)	4 (5.8)	3 (4.6)	13 (6.6)
Israel	0	1 (1.4)	2 (3.1)	3 (1.5)
Netherlands	9 (14.1)	7 (10.1)	9 (13.8)	12 (12.6)
Poland	8 (12.5)	11 (15.9)	6 (9.2)	25 (12.6)
Spain	12 (18.8)	14 (20.3)	13 (20.0)	39 (19.7)
US	29 (45.3)	32 (46.4)	32 (49.2)	93 (47.0)
Region [n (%)]				
Rest of the World	35 (54.7)	37 (53.6)	33 (50.8)	105 (53.0)
US	29 (45.3)	32 (46.4)	32 (49.2)	93 (47.0)
Weight at Baseline (kg)				
n	64	69	65	198
Mean (SD)	32.83 (16.413)	34.18 (19.268)	34.03 (14.870)	33.69 (16.926)
Median	26.75	31.50	28.60	29.25
Min, Max	14.0, 88.9	11.8, 133.8	14.0, 70.0	11.8, 133.8
Height at Baseline (cm)				
n	64	69	65	198
Mean (SD)	129.24 (21.366)	129.95 (23.475)	131.49 (22.307)	130.23 (22.332)
Median	125.30	131.00	131.00	130.00
Min, Max	90.0, 171.0	90.0, 174.5	90.0, 173.5	90.0, 174.5
Body Mass Index at Baseline (kg/m^2)				
n	64	69	65	198
Mean (SD)	18.52 (4.554)	18.78 (4.585)	18.80 (3.896)	18.70 (4.340)
Median	16.70	17.69	17.89	17.69
Min, Max	13.3, 32.7	13.9, 43.9	13.0, 31.2	13.0, 43.9

Numbers analysed

All randomized 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 randomized. The ITT analysis set therefore excluded 1 patient in the 10 mg/kg/day GWP42003-P group who was randomized in error and did not receive IMP, and thus comprised a total of 198 patients: 66 patients in the 10 mg/kg/day GWP42003-P group, 67 patients in the 20 mg/kg/day GWP42003-P group, and 65 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 treatment group to which they were randomized. In addition to the 1 patient in the 10 mg/kg/day GWP42003-P group who was randomized but not treated, the PP analysis set excluded a further 16 patients (5 patients in the 10 mg/kg/day GWP42003-P group, 8 patients in the 20 mg/kg/day GWP42003-P group, and 3 patients in the placebo group) comprising 8 patients who withdrew from the trial early, 3 patients with major protocol deviations (1 patient satisfied both of these criteria) (see Section 7.1), 2 patients who had new AEDs initiated during the trial, and 4 patients who, during the baseline period, mistakenly entered seizure types into the IVRS that did not meet the description approved by the committee of external experts. Accordingly, the PP analysis set comprised a total of 182 patients: 61 patients in the 10 mg/kg/day GWP42003-P group, 59 patients in the 20 mg/kg/day GWP42003-P group, and 62 patients in the placebo group.

All randomized patients who received at least 1 dose of IMP were included in the safety analysis set according to the treatment they received. The safety analysis set therefore excluded 1 patient in the

10 mg/kg/day GWP42003-P group who was randomized in error and did not receive IMP. Furthermore, upon blinded review of the data, it was identified that 4 patients randomized to receive 10 mg/kg/day dosing volumes (comprising 2 patients assigned GWP42003-P and 2 patients assigned placebo) were given dosing schedules for 20 mg/kg/day volumes and thus titrated above the 10 mg/kg/day target dose; therefore, these patients were assigned to the 20 mg/kg/day treatment groups (GWP42003-P or placebo) in the safety analysis set. Accordingly, the safety analysis set comprised a total of 198 patients: 64 patients in the 10 mg/kg/day GWP42003-P group, 69 patients in the 20 mg/kg/day GWP42003-P group, and 65 patients in the placebo group.

Outcomes and estimation

Primary efficacy variable:

The primary endpoint was the change in total convulsive seizures during the treatment period (including the initial dose titration period) compared to baseline. The primary endpoint was analysed using negative binomial regression; therefore, results are 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 GWP42003-P group to placebo was 1.

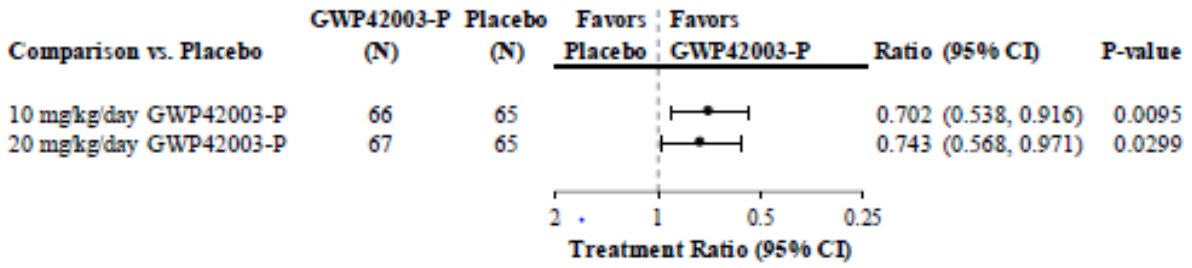
During the baseline period, the median convulsive seizure frequency (28-day average) was highest in the placebo group and lowest in the 20 mg/kg/day GWP42003-P group. The placebo effect was considerable.

Table 35 Primary Endpoint: Change in Convulsive Seizures during the Treatment Period Compared to Baseline (ITT Analysis Set)

Variable Statistics	10 mg/kg/day GWP42003-P (N=66)	20 mg/kg/day GWP42003-P (N=67)	Placebo (N=65)
Convulsive Seizure Frequency (Average per 28 Days) During the Baseline Period			
Median	13.53	9.03	16.63
Q1, Q3	6.0, 31.2	6.3, 21.2	7.0, 51.1
Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods			
Percentage Reduction	48.7	45.7	26.9
95% CI	37.9, 57.6	34.2, 55.2	11.9, 39.4

Note: Convulsive seizures include tonic, clonic, tonic–clonic, and atonic seizures.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.
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.

Figure 20 Primary Endpoint: Negative Binomial Regression Analysis of Convulsive Seizure Count during Baseline and Treatment Periods (ITT Analysis Set)



Note: Convulsive seizures include tonic, clonic, tonic–clonic, and atonic seizures.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.

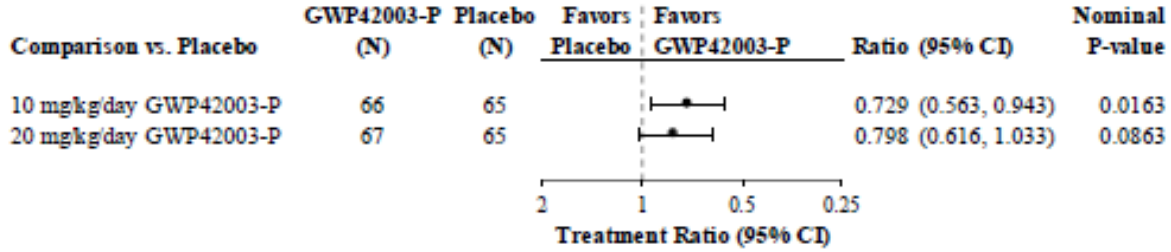
Note: Model includes total number of seizures as a response variable, age group, time (baseline and treatment period), treatment, and treatment by time interaction as fixed effects, and subject as a random effect. Log-transformed number of days in which seizures were reported by period is included as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

Sensitivity analyses:

Results were consistent with the primary analysis when repeated using the PP analysis set. The Hodges–Lehmann estimated median difference between treatments was in favor of GWP42003-P over placebo for both GWP42003-P groups (20 mg/kg/day and 10 mg/kg/day). Using Wilcoxon rank–sum tests, rank ANCOVA approach and an ANCOVA approach were in favour of GWP42003-P over placebo for both GWP42003-P groups (20 mg/kg/day and 10 mg/kg/day) but results were statistically significant only for 20 mg/kg/day vs placebo.

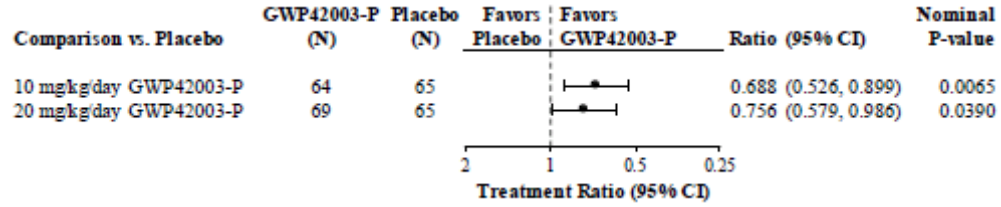
Results of the primary analysis after imputing unreported days in the IVRS are presented in Figure 21. For this analysis, missing data from the treatment period arising from unreported days in the IVRS were imputed using the worst (highest number of seizures) of the following for each GWP42003-P patient 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 favour of GWP42003-P over placebo for both GWP42003-P groups (20 mg/kg/day and 10 mg/kg/day). The difference between treatments was statistically significant for 10 mg/kg/day vs. placebo (P=0.0163) but was not statistically significant for 20 mg/kg/day vs. placebo (P=0.0563).

Figure 21 Sensitivity Analyses of the Primary Endpoint: Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods After Imputing Unreported Days in IVRS (ITT Analysis Set)



Note: Convulsive seizures include tonic, clonic, tonic–clonic, and atonic seizures.
Note: Baseline period included all data prior to Day 1. Maintenance period was defined as Day 15 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.
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.

Figure 22 Sensitivity Analyses of the Primary Endpoint: Negative Binomial Regression Analysis of Convulsive Seizure Count During Baseline and Treatment Periods (Safety Analysis Set)



Note: Convulsive seizures include tonic, clonic, tonic–clonic, and atonic seizures.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.
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.

Using multiple imputation, the difference between treatments was statistically significant for 20 mg/kg/day vs. placebo but was not statistically significant for 10 mg/kg/day vs. placebo.

Key secondary efficacy variables:

Change in Total Seizures during the Treatment Period Compared to Baseline

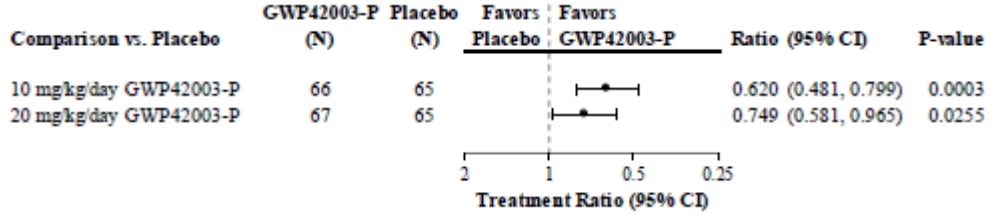
The percentage reduction in total seizures was greater in both GWP42003-P groups (20 mg/kg/day and 10 mg/kg/day) compared with the placebo group (Table 27). The differences between each GWP42003-P group and placebo were statistically significant (Figure 20).

Table 36 Key Secondary Endpoint #1: Change in Total Seizures during the Treatment Period Compared to Baseline (ITT Analysis Set)

Variable Statistics	10 mg/kg/day GWP42003-P (N=66)	20 mg/kg/day GWP42003-P (N=67)	Placebo (N=65)
Total Seizure Frequency (Average per 28 Days) During the Baseline Period			
Median	34.50	26.00	46.34
Q1, Q3	10.4, 104.5	10.0, 194.1	16.0, 217.0
Negative Binomial Regression Analysis of Total Seizure Count During Baseline and Treatment Periods			
Percentage Reduction	56.4	47.3	29.7
95% CI	47.8, 63.6	36.9, 56.0	16.0, 41.1

Note: Total seizures include all seizure types combined.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.
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.

Figure 23 Key Secondary Endpoint #1: Negative Binomial Regression Analysis of Total Seizure Count during Baseline and Treatment Periods (ITT Analysis Set)



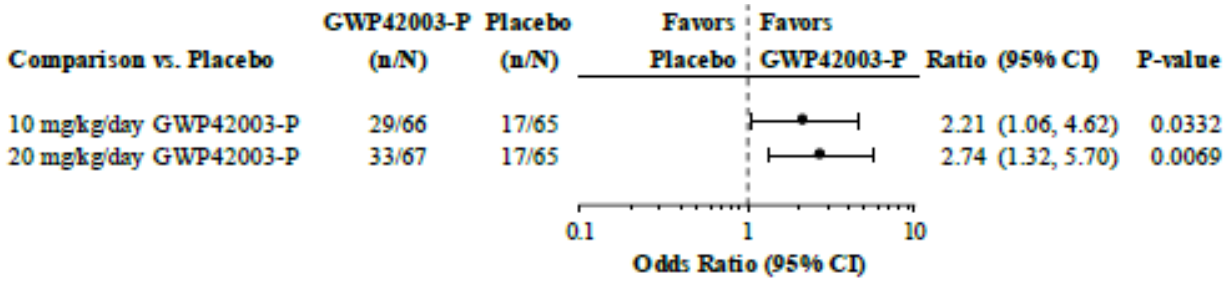
Note: Total seizures include all seizure types combined.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.
Note: Model includes total number of seizures as a response 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.

Patients with a ≥ 50% Reduction from Baseline in Convulsive Seizure Frequency

The proportion of patients with a ≥ 50% reduction from baseline in convulsive seizure frequency during the treatment period was higher in the in the 20 mg/kg/day GWP42003-P group (49.3%) and 10 mg/kg/day GWP42003-P group (43.9%) compared with the placebo group (26.2%). The OR for achieving a ≥ 50% reduction in convulsive seizure frequency was in favour of GWP42003-P over

placebo for both GWP42003-P groups (20 mg/kg/day and 10 mg/kg/day) and the differences in proportions were statistically significant when analysed using a Cochran–Mantel–Haenszel (CMH) test stratified by age group (Figure 21).

Figure 24 Key Secondary Endpoint #2: Convulsive Seizure Responders (≥ 50% Reduction from Baseline) During the Treatment Period (ITT Analysis Set)



Note: Convulsive seizures include tonic, clonic, tonic–clonic, and atonic seizures.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.
Note: P-value calculated from a CMH test stratified by age group (2–5, 6–12, and 13–18 years).

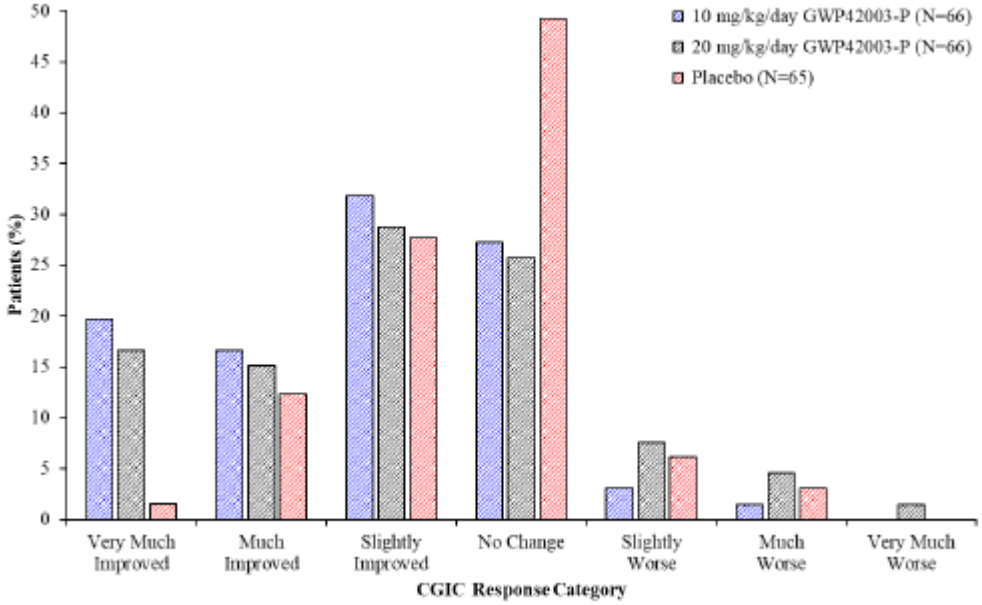
Note: Convulsive seizures include tonic, clonic, tonic–clonic, and atonic seizures.

Sensitivity analyses using the PP analysis set and for the maintenance period (and during each 4 weeks thereof) using the ITT analysis set were consistent with the results obtained for the primary analyses.

Caregiver Global Impression of Change Score

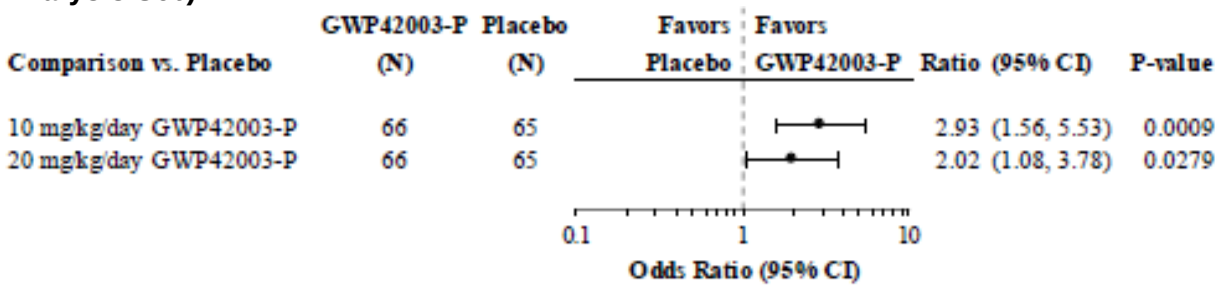
The proportion of patients with any improvement in overall condition (slightly improved, much improved, or very much improved) at their last visit (i.e., incorporating LOCF, the last visit at which the CGIC assessment was conducted for an individual patient) was higher in the 20 mg/kg/day GWP42003-P group (60.6%) and 10 mg/kg/day GWP42003-P group (68.2%) compared with the placebo group (41.5%). Only 1 placebo patient (1.5%) was reported as 'very much improved' compared with 11 patients (16.7%) in the 20 mg/kg/day GWP42003-P group and 13 patients (19.7%) in the 10 mg/kg/day GWP42003-P group. Approximately half (49.2%) of the patients in the placebo group who completed the assessment were reported as having no change. The proportion of patients reported as having a worsening in overall condition (slightly worse, much worse or very much worse) at last visit was numerically greater in the 20 mg/kg/day GWP42003-P group (13.6%) compared with the 10 mg/kg/day GWP42003-P group (4.5%) and the placebo group (9.2%) (Figure 23); similar trends were observed using the PP analysis set.

Figure 25 Key Secondary Endpoint #3: Caregiver Global Impression of Change in Overall Condition at Last Visit by Category (ITT Analysis Set)



When measured on a continuous scale (1 = very much improved; 7 = very much worse), the mean CGIC scores at last visit were 3.1 in the 20 mg/kg/day GWP42003-P group and 2.8 in the 10 mg/kg/day GWP42003-P group, each corresponding to "slightly improved". In the placebo group the mean CGIC score at last visit was 3.6 (most closely associated with "no change"). The OR for achieving a lower score (improvement) was in favor of GWP42003-P over placebo for both GWP42003-P groups (20 mg/kg/day and 10 mg/kg/day) and the differences were statistically significant when analyzed using ordinal logistic regression (Figure 26). Sensitivity analyses using end of treatment CGIC scores and the PP analysis set showed similar results.

Figure 26 Key Secondary Endpoint #3: Ordinal Logistic Regression Analysis of Caregiver Global Impression of Change in Overall Condition at Last Visit (ITT Analysis Set)



Note: The CGIC is analyzed using an ordinal logistic regression model with treatment group as a fixed factor

Summary of main studies

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 A1. Summary of efficacy for trial GWEP1414 (Lennox-Gastaut syndrome)			
A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD-OS) as adjunctive treatment for seizures associated with Lennox–Gastaut syndrome in children and adults.			
Trial Identifier	Protocol No: GWEP1414 EudraCT No: 2014-002940-42 ClinicalTrials.gov Identifier: NCT02224560		
Design	Trial GWEP1414 was a 14-week treatment period, multisite, randomized, double-blind trial of 2 dose levels of cannabidiol oral-solution (CBD-OS; 10 mg/kg/day and 20 mg/kg/day) vs. placebo. Information on seizures was recorded daily using an interactive voice response system. Information on investigational medicinal product (IMP) usage, concomitant medications, and adverse events was recorded daily in a paper diary. Following a 4-week baseline period, eligible patients were randomized to 10 mg/kg/day CBD-OS, 20 mg/kg/day CBD-OS or placebo at a 1:1:1 ratio. Following completion of the trial, patients were invited to receive CBD-OS in an open-label extension (OLE) trial under a separate protocol (GWEP1415).		
	Duration of Main Phase: Duration of Run-in Phase: Duration of Extension Phase:	14-week treatment period (12-week maintenance phase). 2-week titration period prior to maintenance phase. 1–3 years open-label treatment (patients who completed the trial were invited to receive CBD-OS in an OLE trial under a separate protocol [GWEP1415]).	
Hypothesis	Superiority: The hypothesis underlying this trial was that CBD-OS has a positive risk/benefit outcome in the adjunctive treatment of Lennox-Gastaut syndrome, compared with placebo.		
Treatment Groups	CBD-OS 20 mg/kg/day	Treatment: 20 mg/kg/day CBD-OS Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 76	
	CBD-OS 10 mg/kg/day	Treatment: 10 mg/kg/day CBD-OS Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 73	
	Placebo	Treatment: Placebo Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 76	
Endpoints and Definitions	Primary Endpoint	Primary Analysis: Percentage change in drop seizure frequency	The pre-defined primary efficacy outcome variable was the percentage change from baseline in drop seizure frequency (average per 28 days) during the 14-week treatment period, based on the intent to treat (ITT) analysis set, comparing CBD-OS with placebo as add-on treatment. The data were analyzed using a Wilcoxon rank-sum test (due to the nature of seizure data, normal distribution cannot be assumed). An estimate of the median difference between 20 mg/kg/day CBD-OS and placebo, and 10 mg/kg/day CBD-OS and placebo, together with approximate 95% confidence interval (CI), was calculated using the Hodges-Lehmann approach. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.

	Key Secondary Endpoint #1	Key Secondary Analysis: Patients with ≥ 50% reduction in drop seizure frequency	The first pre-specified key secondary endpoint was the number of patients considered treatment responders, defined as those with a ≥ 50% reduction in drop seizure frequency from baseline during the treatment period, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The proportion of patients who were considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratio (OR) (20 mg/kg/day CBD-OS vs. placebo and 10 mg/kg/day CBD-OS vs. placebo), 95% CI for the OR, and the p-value from the Cochran–Mantel–Haenszel (CMH) test were presented. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint #2	Key Secondary Analysis: Percentage change in total seizure frequency	The second pre-specified key secondary endpoint was the percentage change from baseline in total seizure frequency (average per 28 days) during the 14-week treatment period, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The data were analyzed using a Wilcoxon rank-sum test (due to the nature of seizure data, normal distribution cannot be assumed). An estimate of the median difference between 20 mg/kg/day CBD-OS and placebo, and 10 mg/kg/day CBD-OS and placebo, together with approximate 95% CI, was calculated using the Hodges-Lehmann approach. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint #3	Key Secondary Analysis: Change from baseline in S/CGIC score	The third pre-specified key secondary endpoint was change from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score at the last visit, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The scores at the last visit were analyzed using ordinal logistic regression. Proportional odds modelling was carried out by including treatment group as a factor. The estimated OR (20 mg/kg/day CBD-OS vs. placebo and 10 mg/kg/day CBD-OS vs. placebo), 95% CI for the OR, and the p-value testing the null hypothesis that the OR is equal to 1, were presented. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
Database Lock	Date: 24 Sep 2016		

Results and Analysis

Analysis Description	**Primary Analysis:** Percentage change in drop seizure frequency			
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	76	73	76
	Drop seizure frequency (number per 28 days)			
	Baseline Period Median (Q1, Q3)	85.53 (38.3, 161.5)	86.90 (40.6, 190.0)	80.25 (47.8, 148.0)
	Treatment Period Median (Q1, Q3)	44.86 (14.4, 117.4)	50.00 (20.5, 113.2)	72.66 (35.3, 125.0)
	Median Percentage Change During Treatment (Q1, Q3)	−41.86 (−72.4, −1.3)	−37.16 (−63.8, −5.6)	−17.17 (−37.1, 0.9)

Effect Estimate Per Comparison	Primary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo	
		Estimated Median Difference	−21.57	
		95% CI[a]	−34.79, −6.67	
		P-value[a]	0.0047	
	Co-Primary Endpoint	Comparison Groups	10 mg/kg/day CBD-OS vs. placebo	
		Estimated Median Difference	−19.19	
		95% CI[a]	−31.24, −7.69	
		P-value[a]	0.0016	
Notes	[a] The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test. Type 1 Error Control The primary endpoint, and key secondary endpoints, had 2 comparisons against placebo (20 mg/kg/day CBD-OS vs. placebo and 10 mg/kg/day CBD-OS vs. placebo). These endpoints were tested with their Type 1 error controlled by use of a pre-specified hierarchical gate-keeping procedure, in the following sequence (all vs. placebo): primary endpoint 20 mg/kg/day CBD-OS, primary endpoint 10 mg/kg/day CBD-OS, 1st key secondary endpoint 20 mg/kg/day CBD-OS, 2nd key secondary endpoint 20 mg/kg/day CBD-OS, 3rd key secondary endpoint 20 mg/kg/day CBD-OS, 1st key secondary endpoint 10 mg/kg/day CBD-OS, 2nd key secondary endpoint 10 mg/kg/day CBD-OS, 3rd key secondary endpoint 10 mg/kg/day CBD-OS. 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 testing would stop and all subsequent analyses would be declared not statistically significant. Patient Withdrawals A total of 13 patients withdrew from the trial (9 from the 20 mg/kg/day CBD-OS group, 2 from the 10 mg/kg/day CBD-OS group and 2 from the placebo group). The most common primary reason for withdrawal was adverse events (4 patients from the 20 mg/kg/day CBD-OS group, 1 patient from the 10 mg/kg/day CBD-OS group and 1 patient from the placebo group). Withdrawn patients were included in the ITT analysis set.			
Analysis Description	**Key Secondary Analysis #1:** Patients with ≥ 50% reduction in drop seizure frequency			
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	76	73	76
	Patients with ≥ 50% reduction in drop seizure frequency			
	Yes (%)	30 (39.5)	26 (35.6)	11 (14.5)
	No (%)	46 (60.5)	47 (64.4)	65 (85.5)
Effect Estimate Per Comparison	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo	
		OR	3.85	
		95% CI[a]	1.75, 8.47	
		P-value[a]	0.0006	
	Key Secondary Endpoint	Comparison Groups	10 mg/kg/day CBD-OS vs. placebo	
		OR	3.27	
		95% CI[a]	1.47, 7.26	

		P-value[a]		0.0030
Notes	[a] P-value calculated from a CMH test stratified by age group (2–5, 6–11, 12–17 and 18–55 years). A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis 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 #2:** Percentage change in total seizure frequency			
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	76	73	76
	Total seizure frequency (number per 28 days)			
	Baseline Period Median (Q1, Q3)	174.29 (82.7, 392.4)	165.00 (81.3, 359.0)	180.63 (90.4, 431.3)
	Treatment Period Median (Q1, Q3)	90.33 (28.7, 234.0)	76.08 (38.5, 188.4)	138.91 (65.2, 403.4)
	Median Percentage Change During Treatment (Q1, Q3)	−38.40 (−64.6, −0.7)	−36.44 (−64.5, −10.8)	−18.47 (−39.0, 0.5)
Effect Estimate Per Comparison	Key Secondary Endpoint	Comparison Groups		20 mg/kg/day CBD-OS vs. placebo
		Estimated Median Difference		−18.76
		95% CI[a]		−31.80, −4.43
		P-value[a]		0.0091
	Key Secondary Endpoint	Comparison Groups		10 mg/kg/day CBD-OS vs. placebo
		Estimated Median Difference		−19.47
		95% CI[a]		−30.37, −7.47
		P-value[a]		0.0015
Notes	[a] The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test. A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis 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 from baseline in S/CGIC score			
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: Patient's last visit.			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	76	73	76
	Combined S/CGIC score at last visit by category [n (%)][a]			
	Very Much Improved	6 (8.0)	9 (12.3)	1 (1.3)
	Much Improved	15 (20.0)	14 (19.2)	8 (10.7)
	Slightly Improved	22 (29.3)	25 (34.2)	24 (32.0)

	No Change	25 (33.3)	21 (28.8)	35 (46.7)
	Slightly Worse	6 (8.0)	3 (4.1)	4 (5.3)
	Much Worse	1 (1.3)	1 (1.4)	3 (4.0)
	Very Much Worse	0	0	0
Effect Estimate Per Comparison[b]	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo	
		OR	1.83	
		95% CI	1.02, 3.30	
		P-value	0.0439	
	Key Secondary Endpoint	Comparison Groups	10 mg/kg/day CBD-OS vs. placebo	
		OR	2.57	
		95% CI	1.41, 4.66	
		P-value	0.0020	
Notes	[a] A combined score was used as the primary analysis for this endpoint. The combined score was defined as follows: if both a CGIC and SGIC were completed then the CGIC was used, if only a CGIC was completed then the CGIC was used, and if only a SGIC was completed then the SGIC was used. [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). A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis section in this table. For information on patient withdrawals please see 'Notes' in the primary analysis section in this table.			

Table A2. Summary of efficacy for trial GWEP1423 (Lennox-Gastaut syndrome)		
A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD-OS) as adjunctive treatment for seizures associated with Lennox–Gastaut syndrome in children and adults.		
Trial Identifier	Protocol No: GWEP1423 EudraCT No: NCT02224690 ClinicalTrials.gov Identifier: 2014-002941-23	
Design	Trial GWEP1423 was a 14-week treatment period, multisite, randomized, double-blind trial of 20 mg/kg/day cannabidiol oral-solution (CBD-OS) vs. placebo. Information on seizures was recorded daily using an interactive voice response system. Information on investigational medicinal product (IMP) usage, concomitant medications, and adverse events was recorded daily in a paper diary. Following a 4-week baseline period, eligible patients were randomized to 20 mg/kg/day CBD-OS or placebo at a 1:1 ratio. Following completion of the trial, patients were invited to receive CBD-OS in an open-label extension (OLE) trial under a separate protocol (GWEP1415).	
	Duration of Main Phase: Duration of Run-in Phase: Duration of Extension Phase:	14-week treatment period (12-week maintenance phase). 2-week titration period prior to maintenance phase. 1–3 years open-label treatment (patients who completed the trial were invited to receive CBD-OS in an OLE trial under a separate protocol [GWEP1415]).
Hypothesis	Superiority: The hypothesis underlying this trial was that CBD-OS has a positive risk/benefit outcome in the adjunctive treatment of Lennox-	

	Gastaut syndrome, compared with placebo.		
Treatment Groups	CBD-OS 20 mg/kg/day	Treatment: 20 mg/kg/day CBD-OS Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 86	
	Placebo	Treatment: Placebo Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 85	
Endpoints and Definitions	Primary Endpoint	Primary Analysis: Percentage change in drop seizure frequency	The pre-defined primary efficacy outcome variable was the percentage change from baseline in drop seizure frequency (average per 28 days) during the 14-week treatment period, based on the intent to treat (ITT) analysis set, comparing CBD-OS with placebo as add-on treatment. The data were analyzed using a Wilcoxon rank-sum test (due to the nature of seizure data, normal distribution cannot be assumed). An estimate of the median difference between 20 mg/kg/day CBD-OS and placebo, together with approximate 95% confidence interval (CI), was calculated using the Hodges-Lehmann approach. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint #1	Key Secondary Analysis: Patients with ≥ 50% reduction in drop seizure frequency	The first pre-specified key secondary endpoint was the number of patients considered treatment responders, defined as those with a ≥ 50% reduction in drop seizure frequency from baseline during the treatment period, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The proportion of patients who were considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratio (OR) (20 mg/kg/day CBD-OS vs. placebo), 95% CI for the OR, and the p-value from the Cochran–Mantel–Haenszel (CMH) test were presented. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint #2	Key Secondary Analysis: Percentage change in total seizure frequency	The second pre-specified key secondary endpoint was the percentage change from baseline in total seizure frequency (average per 28 days) during the 14-week treatment period, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The data were analyzed using a Wilcoxon rank-sum test (due to the nature of seizure data, normal distribution cannot be assumed). An estimate of the median difference between 20 mg/kg/day CBD-OS and placebo, together with approximate 95% CI, was calculated using the Hodges-Lehmann approach. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint #3	Key Secondary Analysis: Change from baseline in S/CGIC score	The third pre-specified key secondary endpoint was change from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score at the last visit, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. Proportional odds modelling was carried out by including treatment group as a factor. The estimated OR (20 mg/kg/day CBD-OS vs. placebo), 95% CI for the OR, and the p-value testing the null hypothesis that the OR is equal to 1, were presented. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.

Database Lock	Date: 24 Jun 2016		
Results and Analysis			
Analysis Description	**Primary Analysis:** Percentage Change in drop seizure frequency		
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).		
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	Placebo
	Number of Subjects	86	85
	Drop seizure frequency (number per 28 days)		
	Baseline Period Median (Q1, Q3)	71.43 (27.0, 156.0)	74.67 (47.3, 144.0)
	Treatment Period Median (Q1, Q3)	31.38 (14.4, 92.0)	56.29 (29.7, 129.3)
	Median Percentage Change During Treatment (Q1, Q3)	−43.90 (−69.6, −1.9)	−21.80 (−45.7, 1.7)
Effect Estimate Per Comparison	Primary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo
		Estimated Median Difference	−17.21
		95% CI[a]	−30.32, −4.09
		P-value[a]	0.0135
Notes	[a] The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test. <u>Type 1 Error Control</u> The key secondary endpoints were tested with their Type 1 error controlled by use of a pre-specified hierarchical gate-keeping procedure, in the following sequence (all 20 mg/kg/day CBD-OS vs. placebo): primary endpoint, 1st key secondary endpoint, 2nd key secondary endpoint, 3rd key secondary endpoint. 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 testing would stop and all subsequent analyses would be declared not statistically significant. <u>Patient Withdrawals</u> A total of 15 patients withdrew from the trial (14 from the 20 mg/kg/day CBD-OS group and 1 from the placebo group). The most common primary reason for withdrawal was adverse events (8 patients from the 20 mg/kg/day CBD-OS group and 1 patient from the placebo group). Withdrawn patients were included in the ITT analysis set.		
Analysis Description	**Key Secondary Analysis #1:** Patients with ≥ 50% reduction in drop seizure frequency		
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).		
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	Placebo
	Number of Subjects	86	85
	Patients with ≥ 50% reduction in drop seizure frequency		
	Yes (%)	38 (44.2)	20 (23.5)
	No (%)	48 (55.8)	65 (76.5)

Effect Estimate Per Comparison	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo
		OR	2.57
		95% CI[a]	1.33, 4.97
		P-value[a]	0.0043
Notes	[a] P-value calculated from a CMH test stratified by age group (2–5, 6–11, 12–17 and 18–55 years). A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis 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 #2:** Percentage change in total seizure frequency		
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).		
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	Placebo
	Number of Subjects	86	85
	Total seizure frequency (number per 28 days)		
	Baseline Period Median (Q1, Q3)	144.56 (72.0, 385.7)	176.69 (68.6, 359.5)
	Treatment Period Median (Q1, Q3)	83.75 (27.4, 255.4)	128.68 (59.3, 337.4)
	Median Percentage Change During Treatment (Q1, Q3)	−41.24 (−62.8, −13.0)	−13.70 (−45.0, 7.3)
Effect Estimate Per Comparison	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo
		Estimated Median Difference	−21.13
		95% CI[a]	−33.26, −9.37
		P-value[a]	0.0005
Notes	[a] The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test. A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis 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 from baseline in S/CGIC score		
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: Patient's last visit.		
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	Placebo
	Number of Subjects	86	85
	Combined S/CGIC score at last visit by category [n (%)][a]		
	Very Much Improved	15 (17.9)	5 (5.9)
	Much Improved	14 (16.7)	9 (10.6)
	Slightly Improved	20 (23.8)	15 (17.6)
	No Change	27 (32.1)	43 (50.6)

	Slightly Worse	7 (8.3)	9 (10.6)
	Much Worse	1 (1.2)	2 (2.4)
	Very Much Worse	0	2 (2.4)
Effect Estimate Per Comparison[b]	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo
		OR	2.54
		95% CI	1.45, 4.47
		P-value	0.0012
Notes	[a] A combined score was used as the primary analysis for this endpoint. The combined score was defined as follows: if both a CGIC and SGIC were completed then the CGIC was used, if only a CGIC was completed then the CGIC was used, and if only a SGIC was completed then the SGIC was used. [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). A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis section in this table. For information on patient withdrawals please see 'Notes' in the primary analysis section in this table.		

Table A3. Summary of efficacy for trial GWEP1332 Part B (Dravet syndrome)

A double-blind, placebo-controlled, two-part study to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of cannabidiol (GWP42003-P; CBD-OS) in children and young adults with Dravet syndrome.		
Trial Identifier	Protocol No: GWEP1332 EudraCT No: 2014-000995-24 ClinicalTrials.gov Identifier: NCT02091375	
Design	Part B of trial GWEP1332 was a 14-week treatment period, multisite, randomized, double-blind trial of 20 mg/kg/day cannabidiol oral-solution (CBD-OS) vs. placebo. Information on seizures was recorded daily using an interactive voice response system. Information on investigational medicinal product (IMP) usage, concomitant medications, and adverse events was recorded daily in a paper diary. Following a 4-week baseline period, eligible patients were randomized to 20 mg/kg/day CBD-OS or placebo at a 1:1 ratio. Following completion of the trial, patients were invited to receive CBD-OS in an open-label extension (OLE) trial under a separate protocol (GWEP1415). Note: Part A of trial GWEP1332 was a 3-week dose-ranging, safety and pharmacokinetic trial; no efficacy data was collected.	
	Duration of Main Phase: Duration of Run-in Phase: Duration of Extension Phase:	14-week treatment period (12-week maintenance phase). 2-week titration period prior to maintenance phase. 1–3 years open-label treatment (patients who completed the trial were invited to receive CBD-OS in an OLE trial under a separate protocol [GWEP1415]).
Hypothesis	Superiority: The hypothesis underlying this trial was that CBD-OS has a positive risk/benefit outcome in the adjunctive treatment of Dravet syndrome, compared with placebo.	
Treatment Groups	CBD-OS 20 mg/kg/day	Treatment: 20 mg/kg/day CBD-OS Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 61
	Placebo	Treatment: Placebo Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase

		Number randomized: 59	
Endpoints and Definitions	Primary Endpoint	Primary Analysis: Percentage change in convulsive seizure frequency	The pre-defined primary efficacy outcome variable was the percentage change from baseline in total convulsive seizure frequency (average per 28 days) during the 14-week treatment period, based on the intent to treat (ITT) analysis set, comparing CBD-OS with placebo as add-on treatment. The data were analyzed using a Wilcoxon rank-sum test (due to the nature of seizure data, normal distribution cannot be assumed). An estimate of the median difference between 20 mg/kg/day CBD-OS and placebo, together with approximate 95% confidence interval (CI), was calculated using the Hodges-Lehmann approach. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint	Key Secondary Analysis: Patients with ≥ 50% reduction in convulsive seizure frequency	The first pre-specified key secondary endpoint was the number of patients considered treatment responders, defined as those with a ≥ 50% reduction in convulsive seizure frequency from baseline during the treatment period, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The proportion of patients who were considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratio (OR) (20 mg/kg/day CBD-OS vs. placebo), 95% CI for the OR, and the p-value from the Cochran-Mantel-Haenszel (CMH) test were presented. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
Database Lock	Date: 10 Mar 2016		

Results and Analysis

Analysis description	**Primary Analysis:** Percentage change in convulsive seizure frequency		
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).		
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	Placebo
	Number of Subjects	61	59
	Convulsive seizure frequency (number per 28 days)		
	Baseline Period Median (Q1, Q3)	12.44 (6.2, 28.0)	14.88 (7.0, 36.0)
	Treatment Period Median (Q1, Q3)	5.92 (3.2, 17.3)	14.14 (4.2, 31.1)
	Median Percentage Change During Treatment (Q1, Q3)	−38.94 (−69.5, −4.8)	−13.29 (−52.5, 20.2)
Effect Estimate Per Comparison	Primary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo
		Estimated Median Difference	−22.79
		95% CI[a]	−41.06, −5.43
		P-value[a]	0.0123
Notes	[a] The Hodges–Lehmann median difference and 95% CI, and the p-value from the Wilcoxon rank-sum test.		

	Type 1 Error Control The key secondary endpoint was tested with its Type 1 error controlled by use of a pre-specified hierarchical gate-keeping procedure, in the following sequence (both 20 mg/kg/day CBD-OS vs. placebo): primary endpoint followed by the key secondary endpoint. The null hypothesis of the primary endpoint had to be rejected at the level of 0.05 (2-sided) to test the hypothesis of the key secondary endpoint at the level of 0.05 (2-sided). If the null hypothesis for the primary endpoint was not rejected then testing would stop and the key secondary endpoint would be declared not statistically significant. Patient Withdrawals A total of 12 patients withdrew from the trial (9 from the 20 mg/kg/day CBD-OS group and 3 from the placebo group). The most common primary reason for withdrawal was an adverse event (8 patients from the 20 mg/kg/day CBD-OS group and 1 patient from the placebo group). Withdrawn patients were included in the ITT analysis set.		
Analysis Description	**Key Secondary Analysis:** Patients with ≥ 50% reduction in convulsive seizure frequency		
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: Entire 14-week treatment period (including 2-week titration period and 12-week maintenance period).		
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	Placebo
	Number of Subjects	61	59
	Patients with ≥ 50% reduction in convulsive seizure frequency		
	Yes (%)	26 (42.6)	16 (27.1)
	No (%)	35 (57.4)	43 (72.9)
Effect Estimate Per Comparison	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo
		OR	2.00
		95% CI[a]	0.93, 4.30
		P-value[a]	0.0784
Notes	[a] P-value calculated from a CMH test stratified by age group (2–5, 6–12, 13–18 years). A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis section in this table. For information on patient withdrawals please see 'Notes' in the primary analysis section in this table.		

Table A4. Summary of efficacy for trial GWEP1424 (Dravet syndrome)	
A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome	
Trial Identifier	Protocol No: GWEP1424 EudraCT No: 2014-002939-34 ClinicalTrials.gov Identifier: NCT02224703
Design	Trial GWEP1424 was a 14-week treatment period, multisite, randomized, double-blind trial of 2 dose levels of cannabidiol oral-solution (CBD-OS; 10 mg/kg/day and 20 mg/kg/day) vs. placebo. Information on seizures was recorded daily using an interactive voice response system. Information on investigational medicinal product (IMP) usage, concomitant medications, and adverse events was recorded daily in a paper diary. Following a 4-

	week baseline period, eligible patients were randomized to 10 mg/kg/day CBD-OS, 20 mg/kg/day CBD-OS or placebo at a 1:1:1 ratio. Following completion of the trial, patients were invited to receive CBD-OS in an open-label extension (OLE) trial under a separate protocol (GWEP1415).		
	Duration of Main Phase: Duration of Run-in Phase: Duration of Extension Phase:	14-week treatment period (12-week maintenance phase). 2-week titration period prior to maintenance phase. Up to 4 years' open-label treatment (patients who completed the trial were invited to receive CBD-OS in an OLE trial under a separate protocol [GWEP1415]).	
Hypothesis	Superiority: The hypothesis underlying this trial was that CBD-OS has a positive risk/benefit outcome in the adjunctive treatment of Dravet syndrome, compared with placebo.		
Treatment Groups	CBD-OS 20 mg/kg/day	Treatment: 20 mg/kg/day CBD-OS Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 67	
	CBD-OS 10 mg/kg/day	Treatment: 10 mg/kg/day CBD-OS Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 67 (Note: 1 patient randomized in error)	
	Placebo	Treatment: Placebo Treatment duration: 14 weeks including a 2-week titration period and a 12-week maintenance dose phase Number randomized: 65	
Endpoints and Definitions	Primary Endpoint	Primary Analysis: Change in convulsive seizures	The pre-defined primary efficacy outcome variable was the change in convulsive seizures during the treatment period compared to baseline. The data were analyzed using negative binomial regression to calculate the estimated ratio and 95% CIs of the ratio of least squares means (treatment vs. baseline) for each CBD-OS group to placebo, along with the p-value testing the null hypothesis that this ratio was 1. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary	Key Secondary	The first pre-specified key secondary endpoint was the change in total seizures during the

	Endpoint #1	Analysis: Change in total seizures	treatment period compared to baseline. The data were analyzed using negative binomial regression to calculate the estimated ratio and 95% CIs of the ratio of least squares means (treatment vs. baseline) for each CBD-OS group to placebo, along with the p-value testing the null hypothesis that this ratio was 1. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint #2	Key Secondary Analysis: Patients with ≥ 50% reduction in convulsive seizure frequency	The second pre-specified key secondary endpoint was the number of patients considered treatment responders, defined as those with a ≥ 50% reduction in convulsive seizure frequency from baseline during the treatment period, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The proportion of patients who were considered treatment responders, the difference in proportions along with the 95% CI for the difference, the estimated odds ratio (OR) (20 mg/kg/day CBD OS vs. placebo and 10 mg/kg/day CBD-OS vs. placebo), 95% CI for the OR, and the p-value from the Cochran-Mantel-Haenszel (CMH) test were presented. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
	Key Secondary Endpoint #3	Key Secondary Analysis: CGIC score	The third pre-specified key secondary endpoint was the Caregiver Global Impression of Change (CGIC) score at the last visit, based on the ITT analysis set, comparing CBD-OS with placebo as add-on treatment. The scores at the last visit were analyzed using ordinal logistic regression. Proportional odds modelling was carried out by including treatment group as a factor. The estimated OR (20 mg/kg/day CBD-OS vs. placebo and 10 mg/kg/day CBD-OS vs. placebo), 95% CI for the OR, and the p-value testing the null hypothesis that the OR is equal to 1, were presented. A step-down procedure was used to control the type 1 error; for further details see 'Notes' in the primary analysis section in this table.
Database Lock	Date: 17 Nov 2018		
Results and Analysis			
Analysis Description	**Primary Analysis:** Change in convulsive seizures during the treatment period compared to baseline		
Analysis Population and	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT		

Time Point Description	analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	67	66	65
	Convulsive seizure frequency (number per 28 days)			
	Baseline Period Median (Q1, Q3)	9.03 (6.3, 21.2)	13.53 (6.0, 31.2)	16.63 (7.0, 51.1)
	Negative binomial regression analysis of convulsive seizure count during baseline and treatment periods			
	Percent Reduction (95% CI)	45.7 (34.2, 55.2)	48.7 (37.9, 57.6)	26.9 (11.9, 39.4)
Effect Estimate Per Comparison	Primary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo	
		Treatment Ratio	0.743	
		95% CI	0.568, 0.971	
		P-value	0.0299	
	Co-Primary Endpoint	Comparison Groups	10 mg/kg/day CBD-OS vs. placebo	
		Treatment Ratio	0.702	
		95% CI	0.538, 0.916	
		P-value	0.0095	
Notes	Type 1 Error Control The primary endpoint, and key secondary endpoints, had 2 comparisons against placebo (20 mg/kg/day CBD-OS vs. placebo and 10 mg/kg/day CBD-OS vs. placebo). These endpoints were tested with their Type 1 error controlled by use of a pre-specified hierarchical gate-keeping procedure, in the following sequence (all vs. placebo): primary endpoint 20 mg/kg/day CBD-OS, primary endpoint 10 mg/kg/day CBD-OS, 1st key secondary endpoint 20 mg/kg/day CBD-OS, 1st key secondary endpoint 10 mg/kg/day CBD-OS, 2nd key secondary endpoint 20 mg/kg/day CBD-OS, 2nd key secondary endpoint 10 mg/kg/day CBD-OS, 3rd key secondary endpoint 20 mg/kg/day CBD-OS, 3rd key secondary endpoint 10 mg/kg/day CBD-OS. 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 testing would stop and all subsequent analyses			

	would be declared not statistically significant. Patient Withdrawals A total of 9 patients withdrew from the trial (6 from the 20 mg/kg/day CBD-OS group and 3 from the 10 mg/kg/day CBD-OS group; all patients in the placebo group completed the trial). The most common primary reason for withdrawal was adverse events (5 patients from the 20 mg/kg/day CBD-OS group). Withdrawn patients were included in the ITT analysis set.			
Analysis Description	**Key Secondary Analysis #1:** Change in total seizures during the treatment period compared to baseline			
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	67	66	65
	Total seizure frequency (number per 28 days)			
	Baseline Period Median (Q1, Q3)	26.00 (10.0, 194.1)	34.50 (10.4, 104.5)	46.34 (16.0, 217.0)
	Negative binomial regression analysis of total seizure count during baseline and treatment periods			
	Percent Reduction (95% CI)	47.3 (36.9, 56.0)	56.4 (47.8, 63.6)	29.7 (16.0, 41.1)
Effect Estimate Per Comparison	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo	
		Treatment Ratio	0.749	
		95% CI	0.581, 0.965	
		P-value	0.0255	
	Key Secondary Endpoint	Comparison Groups	10 mg/kg/day CBD-OS vs. placebo	
		Treatment Ratio	0.620	
		95% CI	0.481, 0.799	
		P-value	0.0003	

Notes	A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis 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 #2:** Patients with ≥ 50% reduction in convulsive seizure frequency			
Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: 14-week treatment period (including 2-week titration period and 12-week maintenance period).			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	67	66	65
	Patients with ≥ 50% reduction in convulsive seizure frequency			
	Yes (%)	33 (49.3)	29 (43.9)	17 (26.2)
	No (%)	34 (50.7)	37 (56.1)	48 (73.8)
Effect Estimate Per Comparison	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo	
		OR	2.74	
		95% CI[a]	1.32, 5.70	
		P-value[a]	0.0069	
	Key Secondary Endpoint	Comparison Groups	10 mg/kg/day CBD-OS vs. placebo	
		OR	2.21	
		95% CI[a]	1.06, 4.62	
		P-value[a]	0.0332	
Notes	[a] P-value calculated from a CMH test stratified by age group (2–5, 6–12 and 13–18 years). A step-down procedure was used to control the type 1 error; for further details see the 'Notes' in the primary analysis 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:** CGIC score			

Analysis Population and Time Point Description	ITT: All randomized patients who received at least 1 dose of IMP and had at least 1 post-baseline efficacy endpoint were included in the ITT analysis set according to their randomized treatment group. Time Point: Patient's last visit.			
Descriptive Statistics and Estimate Variability	Treatment Group	20 mg/kg/day CBD-OS	10 mg/kg/day CBD-OS	Placebo
	Number of Subjects	66	66	65
	CGIC score at last visit by category [n (%)]			
	Very Much Improved	11 (16.7)	13 (19.7)	1 (1.5)
	Much Improved	10 (15.2)	11 (16.7)	8 (12.3)
	Slightly Improved	19 (28.8)	21 (31.8)	18 (27.7)
	No Change	17 (25.8)	18 (27.3)	32 (49.2)
	Slightly Worse	5 (7.6)	2 (3.0)	4 (6.2)
	Much Worse	3 (4.5)	1 (1.5)	2 (3.1)
	Very Much Worse	1 (1.5)	0	0
Effect Estimate Per Comparison[a]	Key Secondary Endpoint	Comparison Groups	20 mg/kg/day CBD-OS vs. placebo	
		OR	2.02	
		95% CI	1.08, 3.78	
		P-value	0.0279	
	Key Secondary Endpoint	Comparison Groups	10 mg/kg/day CBD-OS vs. placebo	
		OR	2.93	
		95% CI	1.56, 5.53	
		P-value	0.0009	
Notes	[a] 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).			

	A step-down procedure was used to control the type 1 error; for further details see the ‘Notes’ in the primary analysis section in this table. For information on patient withdrawals please see ‘Notes’ in the primary analysis section in this table.

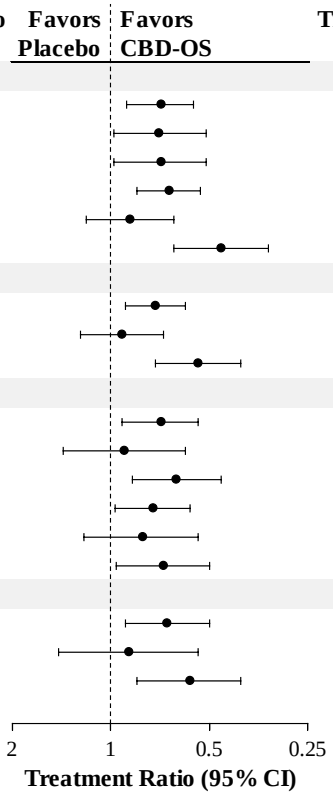
Analysis performed across trials (pooled analyses and meta-analysis)

Side-by-side presentation of the individual trial results was used to highlight consistencies and variations in the efficacy data across the indications and doses.

Of particular interest is a side-by-side presentation of subgroup analyses for the primary endpoint performed in all four pivotal studies. A trend towards larger treatment differences in patients taking clobazam as compared to patients not on clobazam was observed, and the treatment difference for patients not on clobazam was smaller (<15% change from placebo) in 4 out of 6 off-CLB groups .

Figure 27 Negative binomial regression (NBR) Effect Modifier for primary seizure count change from baseline

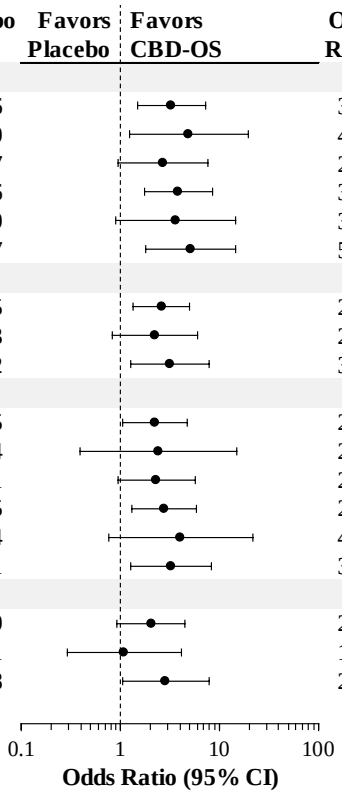
Trial Comparison vs. Placebo	CLB Use	CBD-OS (N)	Placebo (N)	Treatment Ratio (95% CI)	Interaction P-value
GWEP1414 (LGS)					
10 mg/kg/day CBD-OS	All Data	73	76	0.70 (0.56, 0.89)	
	Off CLB	36	39	0.71 (0.51, 0.98)	0.9727
	On CLB	37	37	0.70 (0.51, 0.98)	
20 mg/kg/day CBD-OS	All Data	76	76	0.66 (0.53, 0.83)	
	Off CLB	40	39	0.87 (0.64, 1.19)	0.0067
	On CLB	36	37	0.46 (0.33, 0.64)	
GWEP1423 (LGS)					
20 mg/kg/day CBD-OS	All Data	86	85	0.73 (0.59, 0.90)	
	Off CLB	44	43	0.92 (0.69, 1.24)	0.0123
	On CLB	42	42	0.54 (0.40, 0.73)	
GWEP1424 (DS)					
10 mg/kg/day CBD-OS	All Data	66	65	0.70 (0.54, 0.92)	
	Off CLB	21	24	0.91 (0.59, 1.39)	0.1691
	On CLB	45	41	0.63 (0.46, 0.86)	
20 mg/kg/day CBD-OS	All Data	67	65	0.74 (0.57, 0.97)	
	Off CLB	27	24	0.80 (0.54, 1.21)	0.5702
	On CLB	40	41	0.69 (0.50, 0.96)	
GWEP1332B (DS)					
20 mg/kg/day CBD-OS	All Data	61	59	0.67 (0.50, 0.90)	
	Off CLB	21	21	0.88 (0.54, 1.44)	0.1620
	On CLB	40	38	0.57 (0.40, 0.83)	



In support of the efficacy of CBD-OS, across the pivotal trials the applicant submitted the results of the key secondary (≥ 50% responder analysis) which shows a consistent pattern of greater efficacy compared to placebo for both on- and off-CLB subgroups.

Figure 28 Logistic regression effect modifier for primary seizure ≥ 50% responders by CLB use

Trial Comparison vs. Placebo	CLB Use	CBD-OS (n/N)	Placebo (n/N)	Odds Ratio (95% CI)	Interaction P-value
GWEP1414 (LGS)					
10 mg/kg/day CBD-OS	All Data	26/73	11/76	3.30 (1.48, 7.35)	
	Off CLB	11/36	3/39	4.92 (1.24, 19.61)	0.5021
	On CLB	15/37	8/37	2.72 (0.96, 7.67)	
20 mg/kg/day CBD-OS	All Data	30/76	11/76	3.87 (1.76, 8.53)	
	Off CLB	10/40	3/39	3.64 (0.91, 14.57)	0.7015
	On CLB	20/36	8/37	5.12 (1.81, 14.54)	
GWEP1423 (LGS)					
20 mg/kg/day CBD-OS	All Data	38/86	20/85	2.61 (1.35, 5.06)	
	Off CLB	15/44	8/43	2.23 (0.83, 6.01)	0.6190
	On CLB	23/42	12/42	3.14 (1.26, 7.81)	
GWEP1424 (DS)					
10 mg/kg/day CBD-OS	All Data	29/66	17/65	2.24 (1.06, 4.73)	
	Off CLB	4/21	2/24	2.42 (0.39, 15.07)	0.9722
	On CLB	25/45	15/41	2.33 (0.96, 5.68)	
20 mg/kg/day CBD-OS	All Data	33/67	17/65	2.77 (1.32, 5.82)	
	Off CLB	8/27	2/24	4.08 (0.76, 22.01)	0.8188
	On CLB	25/40	15/41	3.26 (1.28, 8.26)	
GWEP1332B (DS)					
20 mg/kg/day CBD-OS	All Data	26/61	16/59	2.04 (0.93, 4.51)	
	Off CLB	7/21	7/21	1.09 (0.29, 4.11)	0.2517
	On CLB	19/40	9/38	2.88 (1.06, 7.84)	

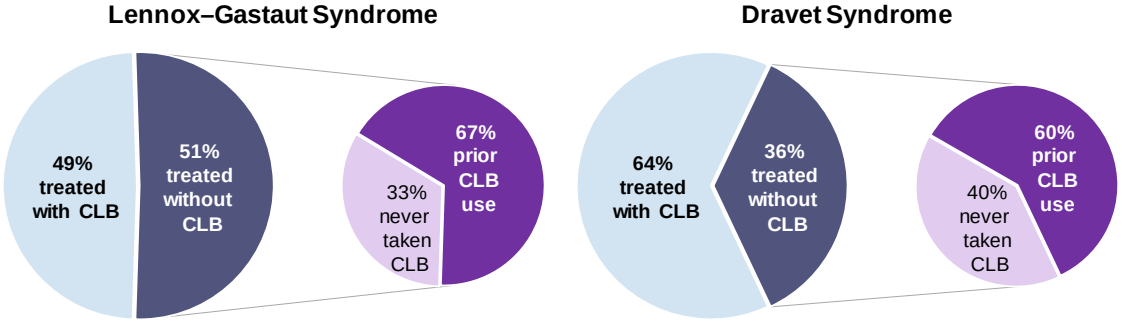


In order to address the CHMP concerns related to the observed trend towards larger treatment differences in patients taking clobazam as compared to patients not on clobazam when analysing change from baseline, and the fact that the treatment difference for patients not on clobazam was smaller in most treatment arms, the Applicant performed various analyses intended to demonstrate efficacy of CBD-OS independent from the co-administration of clobazam and that the treatment effect is clinically meaningful. The most relevant are reflected below:

- *Heterogeneous population of patients not taking clobazam*

Clobazam (CLB) is commonly used as part of multi-drug therapy in patients with LGS and DS. In the CBD-OS pivotal program, approximately half of patients with LGS and one-third of patients with DS were not taking CLB. Most of these patients had previously failed CLB therapy (Figure 26).

Figure 29 Prior Clobazam Use in LGS and DS Trials (ITT Analysis Set)



The subgroup of patients not taking concomitant CLB is more heterogenous and contains different patient populations that are not represented in the subgroup taking CLB, including a majority of patients who had received CLB previously.

In the pivotal CBD-OS trials, differences in terms of baseline characteristics were observed between the patients not taking clobazam and patients taking CLB (Table 41). The analyses show that the patients not taking concomitant CLB had previously failed more AEDs.

Table 37 Baseline Seizure Rate and Prior AED Use in LGS and DS Trials (ITT Analysis Set)

Baseline Characteristics of Patients with LGS or DS	Taking CLB (N=398)	Not Taking CLB (N=316)
Median number of AEDs used prior to enrolment	5	6
Percentage of patients who failed > 6 AEDs prior to enrolment	29%	43%
Baseline primary seizures/28 days, median	36	54
Baseline total seizures/28 days, median	94	129

- *Stratified meta-analyses of all pivotal studies focused on CBD-OS's anticonvulsant effect independent of clobazam use*

The applicant presented data from stratified meta-analyses that statistically combined estimates of treatment effect from the 10 mg/kg/day CBD-OS groups vs. placebo. Estimates from the 20 mg/kg/day CBD-OS groups vs. placebo combined and 10 + 20 mg/kg/day CBD-OS groups vs. placebo combined were also presented for comparison.

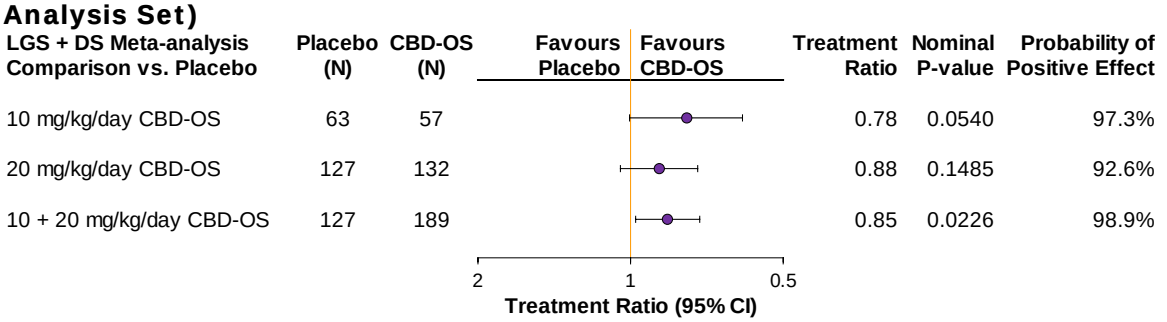
Table 38 Seizure Definitions in LGS and DS Trials

LGS	DS
Primary Seizure: Drop[a]	Primary Seizure: Convulsive
Tonic–clonic seizure Tonic seizure Atonic seizure	Tonic–clonic seizure Tonic seizure Atonic seizure Clonic seizure

A An attack or spell involving the entire body, trunk, or head that led (or could have led) to a fall, injury, slumping in a chair, or hitting the patient's head on a surface.

The meta-analyses for the primary seizure count for patients not taking CLB concomitantly are presented by CBD-OS dose in Figure 27. For patients not taking CLB, 10 mg/kg/day CBD-OS was associated with a 22% greater reduction in primary seizure count over placebo (P=0.054).

Figure 30 Meta-analysis of Negative Binomial Regression Treatment Estimates of Primary Seizure Count by CBD-OS Dose for Patients Not Taking Clobazam (ITT Analysis Set)



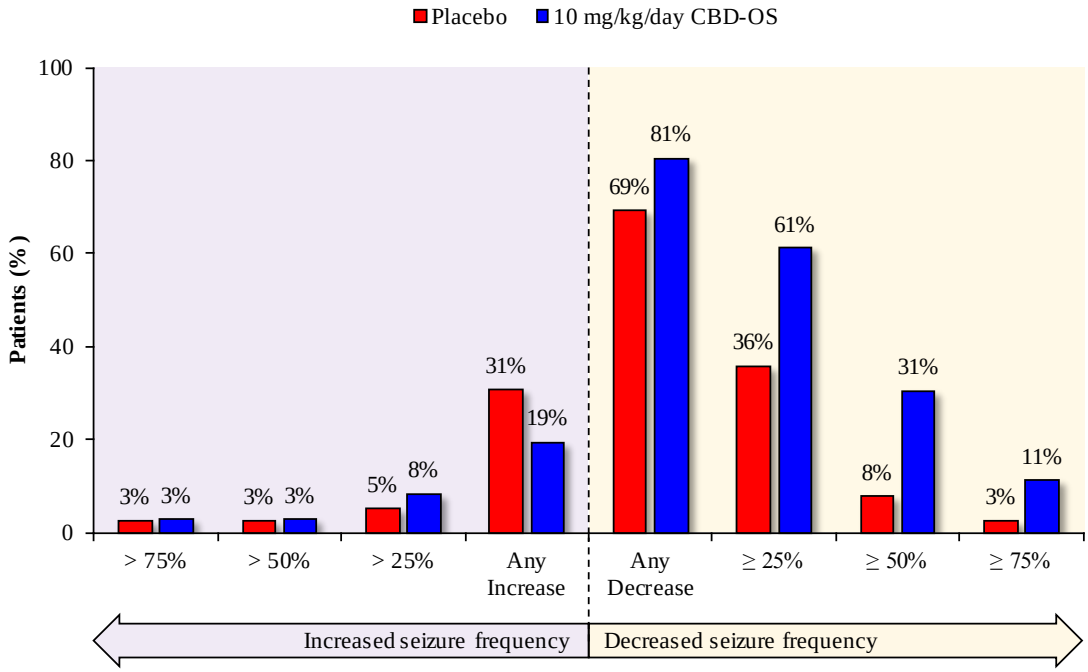
Note: Treatment ratios and 95% confidence intervals are shown graphically using a log2 scale.
Note: Results are based on a fixed effects meta-analysis.

The 20 mg/kg/day CBD-OS dose was associated with a 12% greater reduction in primary seizure count over placebo for patients not taking CLB (P=0.149).

- *Rationale for attenuated response in change in the seizure count analysis in patients not taking clobazam, while having little impact on the responder analyses*

The drop seizure response rates for 10 mg/kg/day CBD-OS patients with LGS not taking CLB concomitantly is presented in Figure 31.

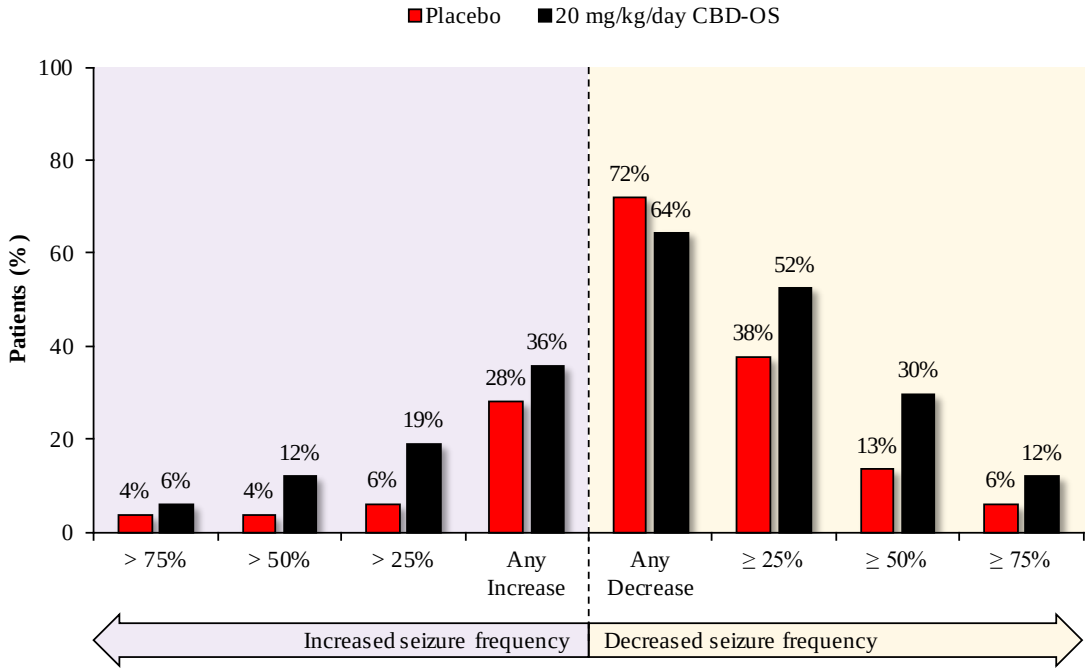
Figure 31 Cumulative Bar Charts of Percentage Change in Drop Seizure Frequency with 10 mg/kg/day CBD OS for Patients Not Taking Concomitant Clobazam in LGS Trial GWEP1414 (ITT Analysis Set)



Note: Each bar can be interpreted independently from other bars in the chart and depicts a dichotomous summary of the proportion of patients meeting the specified criterion on the x-axis.

The 20 mg/kg/day CBD-OS dose also demonstrated benefit over placebo at ≥ 25%, ≥ 50%, and ≥ 75% levels of drop seizure reduction compared with placebo (right side of Figure 31), with 52% of CBD-OS patients attaining a ≥ 25% reduction in drop seizure frequency compared to 38% of placebo patients. However, more 20 mg/kg/day CBD-OS patients experienced a paradoxical increase in drop seizure frequency compared with placebo (left side of Figure 31), most notably at the > 25% level of increase. As a result, the primary endpoint of reduction in drop seizure frequency is attenuated for the 20 mg/kg/day group not taking CLB, but the key secondary endpoint of ≥ 50% reduction in drop seizure frequency is not affected. It should be noted that the degree of seizure increase was no greater with CBD-OS compared with placebo for patients not taking CLB in the pivotal DS trials. This paradoxical seizure increase at the 20 mg/kg/day dose level without CLB was not present at the Epidyolex 10 mg/kg/day dose level and was not seen in the 2 pivotal DS trials at either dose. Increased seizure frequency is a common risk in drug-resistant epilepsies including LGS and DS, and the Epidyolex SmPC contains a warning of this potential risk, similar to other AEDs.

Figure 32 Cumulative Bar Charts of Percentage Change in Drop Seizure Frequency with 20 mg/kg/day CBD OS for Patients Not Taking Concomitant Clobazam in LGS Trials GWEP1414 and GWEP1423 Combined (ITT Analysis Set)

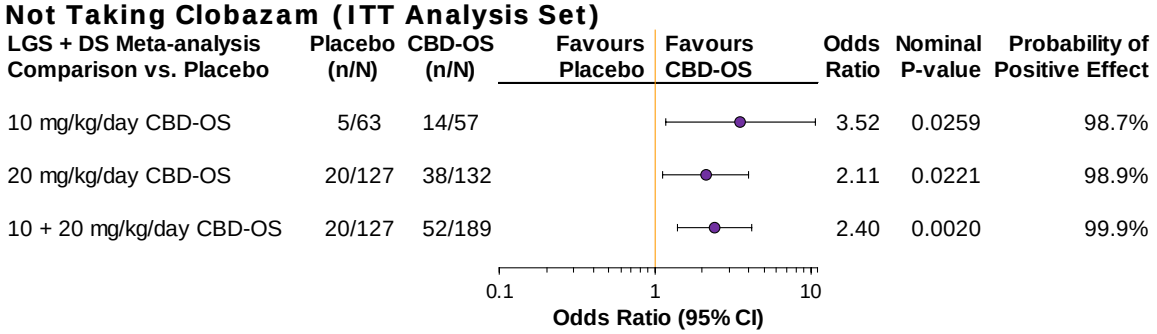


Note: Each bar can be interpreted independently from other bars in the chart and depicts a dichotomous summary of the proportion of patients meeting the specified criterion on the x-axis.

- *Clinical relevance of CBD-OS treatment effect for patients not taking clobazam*

The meta-analyses for the key ≥ 50% response rate for patients not taking CLB concomitantly are presented by CBD-OS dose in Figure 32. For these analyses, a conservative approach addressing missing data was used, whereby any patients who were withdrawn during treatment were considered non-responders. The proportion of patients not taking CLB with a ≥ 50% reduction from their baseline primary seizure frequency was 24.6% across the 10 mg/kg/day CBD-OS groups compared with 7.9% across the placebo groups; this difference in proportions was nominally statistically significant (P=0.026). The ≥ 50% responder rate for patients not taking CLB across the 20 mg/kg/day CBD-OS groups was 28.8% compared with 15.7% across the placebo groups and this difference in proportions was also nominally statistically significant (P=0.022). CBD-OS at both 10 and 20 mg/kg/day increased the likelihood of achieving a ≥ 50% reduction in seizure frequency to a similar degree for patients taking or not taking CLB.

Figure 33 Meta-analysis of Logistic Regression Treatment Estimates of Primary Seizure Responders (≥ 50% Reduction from Baseline) by CBD-OS Dose for Patients Not Taking Clobazam (ITT Analysis Set)



Note: Odds ratios and 95% confidence intervals are shown graphically using a log10 scale.
Note: Patients who withdrew during the treatment period are considered non-responders.
Note: Responders were analysed using logistic regression models with age group, treatment, factor, and factor by treatment interaction as covariates.

Clinical studies in special populations

Only patients between 2 and 55 years of age were included in the pivotal trials. Children below 2 years of age were not included in any of the pivotal trials.

Supportive studies

A Phase 3 Open Label Extension (OLE) trial (GWEP1415) and an expanded access program (EAP) conducted under physician-sponsored investigational new drug (IND) applications in the United States (US), provide supportive efficacy data for CBD-OS as adjunctive therapy for the treatment of seizures associated with LGS and DS. Patients who completed the treatment period of the pivotal trials had the option to enrol in the OLE trial to evaluate the continued safety and efficacy of CBD-OS, which was taken twice daily as adjunctive therapy. The EAP enrolled patients with treatment-resistant epilepsies, including LGS and DS.

Table 39 Overview of Trials Supportive of Efficacy in Patients with LGS or DS

	GWEP1415	EAP
Description	Adjunct to existing AEDs in patients with DS or LGS who completed the treatment period of a randomized controlled trial with CBD-OS	Adjunct to existing AEDs in patients with refractory epilepsies, including DS and LGS
Regions	US, UK, France, Poland, Spain, The Netherlands, Israel	US, Australia[a]
Patient Population	Patients (2–55 years) with a clinical diagnosis of DS or LGS, taking ≥ 1 AED at a stable dose, and who completed GWEP1332 (Part A or B), GWEP1423, GWEP1414 or GWEP1424 (trial ongoing)	Patients with drug resistant epilepsy taking ≥ 1 AEDs at a stable dose
Treatment Group: Number of Patients Treated[b]	CBD-OS: 630	CBD-OS (all patients): 684 CBD-OS (DS/LGS): 161
Treatment	Treatment Period (up to 3 years): • Titration Period (Weeks 1–2): - CBD-OS 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 11 days • Maintenance Period: - CBD-OS up to a maximum of 30 mg/kg/day Taper (10% per day) and follow-up	Baseline Period (4 weeks) Treatment Period (until CBD-OS approved): • Titration Period (5–8 weeks): - CBD-OS 5 mg/kg/day increasing 5 mg/kg every 3–14 days • Maintenance Period: - CBD-OS up to a maximum of 50 mg/kg/day depending on site Taper over 1 month and follow-up
Efficacy Endpoints	• Percentage change from baseline in drop (LGS only), convulsive (DS and combined DS + LGS), and total (DS, LGS, and combined DS + LGS) seizure frequencies • Number of patients seizure free from drop (LGS only), convulsive (DS and combined DS + LGS), and total (DS, LGS, and combined DS + LGS) seizures	• Percentage change from baseline in convulsive and total seizure frequencies for DS, LGS, and combined DS + LGS • Proportions of patients with ≥ 50%, ≥ 75% or 100% reductions from baseline in convulsive and total seizure frequencies for DS, LGS, and combined DS + LGS

	GWEP1415	EAP
Description	Adjunct to existing AEDs in patients with DS or LGS who completed the treatment period of a randomized controlled trial with CBD-OS	Adjunct to existing AEDs in patients with refractory epilepsies, including DS and LGS
Regions	US, UK, France, Poland, Spain, The Netherlands, Israel	US, Australia[a]
Patient Population	Patients (2–55 years) with a clinical diagnosis of DS or LGS, taking ≥ 1 AED at a stable dose, and who completed GWEP1332 (Part A or B), GWEP1423, GWEP1414 or GWEP1424 (trial ongoing)	Patients with drug resistant epilepsy taking ≥ 1 AEDs at a stable dose
Treatment Group: Number of Patients Treated[b]	CBD-OS: 630	CBD-OS (all patients): 684 CBD-OS (DS/LGS): 161
Treatment	Treatment Period (up to 3 years): • Titration Period (Weeks 1–2): - CBD-OS 2.5 mg/kg/day increasing 2.5–5.0 mg/kg QOD over 11 days • Maintenance Period: - CBD-OS up to a maximum of 30 mg/kg/day Taper (10% per day) and follow-up	Baseline Period (4 weeks) Treatment Period (until CBD-OS approved): • Titration Period (5–8 weeks): - CBD-OS 5 mg/kg/day increasing 5 mg/kg every 3–14 days • Maintenance Period: - CBD-OS up to a maximum of 50 mg/kg/day depending on site Taper over 1 month and follow-up
Efficacy Endpoints	• Percentage change from baseline in drop (LGS only), convulsive (DS and combined DS + LGS), and total (DS, LGS, and combined DS + LGS) seizure frequencies • Number of patients seizure free from drop (LGS only), convulsive (DS and combined DS + LGS), and total (DS, LGS, and combined DS + LGS) seizures	• Percentage change from baseline in convulsive and total seizure frequencies for DS, LGS, and combined DS + LGS • Proportions of patients with ≥ 50%, ≥ 75% or 100% reductions from baseline in convulsive and total seizure frequencies for DS, LGS, and combined DS + LGS

Abbreviations: AED, antiepileptic drug; CBD-OS, cannabidiol oral solution; DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome; PBO, placebo; QOD, every other day.

[a] *The efficacy dataset excluded Australia as seizure data were collected only for sites in the US.*

[b] *As per data cutoff dates of 01 May 17 (GWEP1415) and 08 December 2016 (EAP).*

GWEP1415

This is an ongoing open-label extension trial for patients with LGS or DS who previously completed a double-blind, placebo-controlled 'core' trial (GWEP1414, GWEP1423, GWEP1332, or the ongoing GWEP1424 trial). The trial comprises a 2-week dose titration period, a maintenance period, a 10-day taper period, and a 4-week follow-up period. Patients may receive treatment for up to 3 years if in the USA, France or Poland, and for up to 1 year if in UK, Spain, The Netherlands, or Israel. Information on seizures is recorded weekly using an IVRS. All patients titrate CBD-OS to 20 mg/kg/day and continue on this dose. However, the investigator may decrease the dose in case of intolerance or increase the dose in an attempt to achieve better seizure control. The maximum dose is 30 mg/kg/day.

Primary endpoint: AE profile and other safety assessments.

Secondary efficacy endpoints included in the interim analysis (data cut-off 3 November 2016):

For the interim analysis, the primary efficacy dataset included patients from all 4 pivotal trials. Efficacy endpoints using the primary efficacy dataset included the percentage change from the pivotal trial baseline in seizure frequency (average per 28 days), maintenance of seizure frequency reduction, and freedom from seizures for (1) drop seizures in patients with LGS only; (2) convulsive seizures in patients with DS only and in all patients combined; and (3) total seizures in patients with LGS only, DS only, and in all patients combined. S/CGIC at last visit was also included as a secondary endpoint.

A total of 630 patients (366 LGS, 264 DS) enrolled from the preceding core trials, including GWEP1332A and GWEP1424, which was still ongoing by the interim data cut date (03 November 2016). At the data cut date, 34 patients (5%; all DS) had completed treatment, 142 patients (23%; 67 LGS, 75 DS) had withdrawn, and 454 patients (72%; 299 LGS, 155 DS) were continuing with treatment. Overall, the majority of patients White/Caucasian (87%) and from the USA (68%); 53% were male. The mean age was 13.4 years. A total of 284 patients enrolled from the 3 pivotal trials (209 with LGS, 75 with DS) had been treated for at least 37 weeks in the OLE at the time of the interim data cut date.

Patients in the open-label extension study experienced a reduction in seizure frequency compared to pivotal trial baseline values. The median reductions were comparable in magnitude with that observed in the pivotal trial active groups. According to the Applicant, this demonstrates maintenance of efficacy. To account for differences in sample size with increasing time, the Applicant also analysed the subgroups of patients treated for 37-48 weeks, and found similar results.

Expanded Access Program (EAP)

The EAP comprised physician-initiated emergency, individual, intermediate, and State initiated intermediate INDs in the US, and a Compassionate Access Scheme in New South Wales, Australia. These were open-label observational studies for patients with refractory epilepsies, which included those with LGS or DS who were not candidates for the pivotal trials. The efficacy dataset excluded Australia because, per protocol, patients enrolled into the Compassionate Access Scheme in New South Wales had 'uncountable' seizures. Generally, there was a dose titration period lasting 5–8 weeks, a maintenance period, a 1-month taper period, and a 1-month follow-up period. Dose titration commonly started at 5 mg/kg/day CBD-OS, given in 2 divided doses, and increased by 5 mg/kg every 3–14 days up to a maximum of 50 mg/kg/day, depending on the site. Efficacy endpoints discussed here were the percentage change from baseline in convulsive and total seizure frequencies (average per 28 days) in patients with LGS and DS combined. Data received by the cut-off date of 08 December 2016 was used for reporting of results.

A total of 92 patients with LGS and 58 patients with DS were included in the analyses of efficacy. At the interim data cut date (08 December 2016), 24/92 patients with LGS (26%) and 17/58 patients with DS (29%) had withdrawn. In the LGS efficacy analysis set, the mean [SD] age was 12.6 [6.9] years; 66% were male. Forty-eight patients (52%) had been treated for more than 1 year. In the DS efficacy analysis set, the mean [SD] age was 12.4 [7.9] years; 53% were male. Thirty-eight patients (66%) had been treated for more than 1 year.

Patients experienced a median reduction in seizure frequency comparable in magnitude with that observed in the pivotal trial active groups.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal trials were designed as double-blind parallel-group placebo-controlled trials with a baseline period of 4 weeks and a treatment period of 14 weeks (titration phase 2 weeks, maintenance phase 12 weeks), after which the patients either entered an open-label extension study or (upon completion/withdrawal) tapered the dose over a 10-day period with a safety follow-up 4 weeks after final dose.

The pivotal trials were designed to evaluate 10 mg/kg/day or 20 mg/kg/day CBD-OS vs. placebo as adjunctive therapy. This is appropriately reflected in the wording of the approved indication.

The choice of doses was not based on dose-response information since no such information was available for any indication before entering phase 3. In order to inform dosing and treatment decisions, the applicant carried out a post hoc analysis of efficacy by cumulative day during the first 14 days of treatment (titration period) of trials GWEP1423, GWEP1414 and GWEP1332B. Per the titration schedule, all patients started on 2.5 mg/kg/day CBD-OS (or equivalent volume of placebo) and reached 10 mg/kg/day on Days 7 and 8 of the titration period; patients randomised to 20 mg/kg/day reached full dose on Day 11. These data showed that noticeable reductions in seizure frequency can be achieved when CBD OS is titrated to a dose of 7.5 mg/kg/day in both LGS and DS. This is further supported by evidence of a benefit for CBD OS over placebo in the proportions of patients who achieved a $\geq$ 50% reduction from their baseline primary seizure frequency during the first 8 days of treatment, during which time a dose of 10 mg/kg/day had been reached. In addition, the results of study GWEP1424 showed significant improvement compared to placebo treatment for CBD-OS 20 and 10 mg/kg/day on the primary efficacy endpoint and all key secondary efficacy endpoints. Collectively, the data support the applicant's proposal to establish as maintenance dose 10 mg/kg/day CBD-OS for both indications.

The titration regimen used in the studies was different from that proposed in the SmPC. Indeed the proposed titration scheme is a simplified version compared to the one used in pivotal clinical trials. Specifically, the starting does used in the pivotal clinical trials was 2.5mg/kg/day while the SmPC proposes to start the treatment at 5mg/kg/day. In addition, the up titration was done with dose increments of 2.5 mg/kg/day over two days period while the proposed posology indicates that after one week the dose should be increased with 5mg/kg/day to a target maintenance dose of 10mg/kg/day. It is agreed that the proposed posology, in comparison to the one used in clinical trials, is convenient and minimizes dosing errors. In terms of starting dose, it is worth acknowledging that, based on the presented data, 2.5 mg/kg/day is not an effective dose. The proposed titration scheme was designed to benefit patients/caregivers and prescribers, and it was supported by population PK modelling and simulation results submitted by the applicant. These results show little difference in plasma levels of CBD between titration schemes (clinical trials vs proposed posology), particularly at 10 mg/kg/day. In addition, the 10 mg/kg/day dose in LGS trial GWEP1414 demonstrated efficacy paired with better safety profile (see safety section of this report) compared with the 20mg/kg/day dose showing a lower incidence of transaminase elevations and overall AEs. Based on the above considerations the CHMP agreed with the proposed posology (see SmPC section 4.2) with a starting dose of 5 mg/kg/day which can be up titrated with 5 mg/kg/day up to a target maintenance dose of 10 mg/kg/day and in patients who tolerate the 10 mg/kg/day dose but require greater levels of seizure reduction further up titration, with 5 mg/kg/day dose increments, are allowed up to a daily dose of 20 mg/kg.

Another shortcoming of the study designs was the fact that it was not specified in the study protocols whether the investigational product should be taken with food. While it is acknowledged that based on the submitted data it is not possible to define the conditions under which CBD-OS should be administered, the CHMP agreed with the applicant's proposal that prandial status should be the same at each subsequent CBD-OS administration in order to reduce the inter-individual variability. The fact that CBD-OS should be administered consistently either with or without food intake is appropriately reflected in SmPC section 4.2 and PIL.

In very few patients CBD-OS was administered via nasogastric tubes. The applicant presented efficacy data from a total of 8 patients which took IMP via a gastric/gastrostomy tube (G-tube) during the pivotal trials of which only 6 completed the trials. While the percentage change from baseline in total seizure frequency during the treatment period reported in these patients shows a reduction in seizure frequency in patients on CBD-OS, compared with the patients on placebo, the CHMP agrees that no

meaningful conclusions can be drawn due to the small sample size and consequently no PI recommendations can be made in this regard.

During the studies, investigators were allowed to reduce the dose of IMP or a concomitant AED if a patient experienced adverse events (AEs) but if IMP was reduced, they were encouraged to titrate the patient back up to the target dose when possible. Dose reductions due to AEs were not recorded as protocol deviations although dose reductions could potentially compromise blinding. Dose reductions of CLB were necessary in approximately 25% of LGS patients on CBD-OS 20 mg/kg/day as compared to 3-10% of patients on placebo. In patients with DS, dose reductions of CBD-OS were necessary in 18% of patients on CBD-OS 20 mg/kg/day as compared to 0 on placebo. The applicant performed a subgroup analyses on each arm of trials GWEP1414, GWEP1423 and GWEP1332B which showed that treatment differences remained in favour of CBD-OS following the exclusion of patients with IMP and/or CLB or VPA dose reductions during the trial. This doesn't rule out the possibility that dose reductions may in some cases have disclosed the treatment assignment but in the absence of any evidence suggesting that such instances have occurred, the CHMP considers that the potential for unblinding is not a significant concern.

Seizure numbers and types were recorded daily by the caregiver during the baseline and treatment period using an IVRS. At the screening visit, each principal investigator (PI) and the caregiver(s) of the patient discussed the seizure semiology for each seizure type, and they confirmed the different known seizure presentations of the patient. The precise seizure description was recorded on the Epilepsy Diary Reference Sheet and provided to the caregiver for reference, who began calling in to IVRS that same evening. To ensure accuracy of seizure identification and reporting across the pivotal trials, seizure types were verified by members of a committee of independent experts The International League against Epilepsy (ILAE) 1989 seizure classifications were used in the pivotal trials. The ILAE classifications are used routinely in clinical practice; therefore, it is expected that caregivers are accustomed to recording these seizure types and reporting their frequency. The CHMP's view was that the training provided to the care givers seemed brief given the highly demanding task of correctly classifying seizures. However, it was acknowledged that the caregivers are used to identify and report the seizure frequency, on regular basis, outside clinical trials setting and the training provided during the clinical trial would complement the one received in 'clinical practice'. Consequently, the CHMP agreed that the reported seizure frequency can be considered reliable.

CBD-OS was presented as an oral solution containing 100 mg/mL CBD in sesame oil with anhydrous ethanol (79 mg/mL), added sweetener (sucralose), and strawberry flavouring. Placebo was presented as an oral solution of sesame oil containing anhydrous ethanol (79 mg/mL), added sweetener (sucralose), and strawberry flavouring. A palatability questionnaire had to be completed in trials GWEP1423, GWEP1414 and GWEP1332B to assess caregiver's perceived palatability of IMP for product development purposes. A 5-point Likert scale was used in each trial, the results of which were not analysed until after the trial was completed and the blind was broken. According to the results for trial GWEP1332B, there was clearly no preference for like or dislike of CBD-OS taste. Similarly, for trials GWEP1414 and GWEP1423, there was no clear preference for the 20 mg/kg/day CBD-OS group. However, in trial GWEP1414 in the 10 mg/kg/day group, there was a higher proportion of patients who liked the taste of CBD-OS. In the placebo groups, there were similar rates of neutral response (i.e., neither liked it nor disliked it) across the trials. Despite the fact that it cannot be excluded that the taste of CBD-OS would be perceived differently - and less pleasant - than that of placebo as reflected by the caregiver palatability scores, neither the applicant or the patients were aware about these difference during the trial conduct. Based on this the CHMP considers that the possible perceived difference in taste between the active and placebo formulations had no impact on the reliability of the study results.

During the recruitment phase of two of the pivotal studies (GWEP1423 and GWEP1332B), protocol amendments were implemented, during the recruitment period, increasing patient numbers and changing eligibility criteria in particular regarding IVRS compliance. This led to the concern that slightly different patient populations were recruited before and after the protocol amendment's implementation especially in study GWEP1423. In order to assess the impact of the amendment on the treatment effect, the applicant conducted post hoc analyses of the primary outcome in patients randomised before vs. after amendment 4 in study GWEP1423. Treatment differences were in favour of CBD-OS over placebo for both patient populations and were no greater for patients randomised under amendment 4.

Lennox-Gastaut Syndrome (Studies GWEP1414 and GWEP1423)

Patient population

In order to be eligible for the trial, patients had to be aged 2–55 years with a clinical diagnosis of LGS. Patients must have had at least 2 drop seizures each week during the first 28 days of the baseline period and have a history of slow (< 3.0 Hz) spike-and-wave pattern in an EEG prior to their enrolment into the baseline period. A drop seizure was defined as an attack or spell (atonic, tonic, or tonic-clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface. Patients must have been taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening and have documented failures on more than 1 AED. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for 4 weeks prior to screening and the patient was willing to maintain a stable regimen throughout the trial. Patients and/or parent(s)/legal representative had satisfactorily completed the IVRS telephone diary on at least 25 days of the baseline period. Following the screening visit, a committee of independent experts reviewed a list of seizures experienced by the patients and would confirm the seizure types or request further information until an agreement was reached.

Endpoints and analysis

The predefined primary endpoint was the percentage change from baseline in drop seizure frequency. According to the epilepsy guideline (CHMP/EWP/566/98 Rev.2/Corr), the primary endpoint should dichotomise the data into 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). In all pivotal studies, however, a continuous rather than a dichotomised variable was chosen as primary and the ≥ 50% responder rate was key secondary endpoint (in the EU submission). Considering the rarity of the condition, the choice of primary and key secondary endpoints as well as the hierarchical approach to control the type I error is acceptable. The drop seizures are frequent in LGS patients, are associated with high morbidity and mortality in this population, responsible for most injuries associated with falls, and that they are easily identified by parents and caregivers. Based on this it is considered that the drop seizures bear a high burden of disease in LGS patients and the CHMP agreed that measuring the frequency of drop seizure can be considered a clinically relevant endpoint for LGS patients.

There were 3 prospectively defined key secondary endpoints: (1) the proportion of patients who achieved ≥ 50% reduction in drop seizures (responder analysis); (2) the percentage change from baseline in total seizure frequency; and (3) the Subject/Caregiver Global Impression of Change (S/CGIC) at last visit. These endpoints were tested hierarchically in the above order following analysis of the primary endpoint. In trial GWEP1414 (including also a 10 mg/kg/day dose), the primary endpoint was tested first by comparing the 20 mg/kg/day CBD-OS group with the placebo group, then by comparing the 10 mg/kg/day CBD-OS group with the placebo group. Given statistical significance at both doses, the key secondary endpoints were then tested, first by comparing the 20 mg/kg/day CBD-

OS group with the placebo group for each endpoint, and then by comparing the 10 mg/kg/day CBD-OS group with the placebo group for each endpoint.

Dravet Syndrome (Study GWEP1332B and GWEP1424)

Patient population

Patients had to be aged 2-18 years with a clinical diagnosis of Dravet Syndrome confirmed by a committee of independent experts, and had to have experienced 4 or more convulsive seizures during the 4-week baseline period. A convulsive seizure was defined as a tonic, clonic, tonic-clonic, or atonic seizure. Patients must have been taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening. Patients and/or parent(s)/legal representative had satisfactorily completed the IVRS telephone diary on at least 25 days of the baseline period. Following the screening visit, a committee of independent experts reviewed a list of seizures experienced by the patients and would confirm the seizure types or request further information until an agreement was reached.

Children below 2 years of age were not included contrary to advice given by the CHMP (EMEA/H/SA/3106/1/2015/PA/PED/III). Dravet syndrome initiates during the first year of life. Different types of seizures appear soon after disease onset, the seizures are often particularly difficult to control, and a number of anti-epileptic drugs may have been already tried and failed before a child reaches the age of 2 years. Furthermore, in accordance with RMP, data in children < 2 years is identified as missing data to its relevance for Dravet patients. In order to address this concern, the applicant proposed to develop an updated PBPK model which will be available in the first quarter of 2020. The investigation into potential sampling techniques for very young patients has been initiated and when results are available, this will be applied to any trials involving patients under 2 years of age (further details available in the clinical pharmacology discussion section). The CHMP agreed that the proposed plan would appropriately address the need to generate further data in patient under 2 years of age in order to characterize the efficacy and safety profile in this patient population.

The SCN1A genotype was determined in most patients, and most patients tested had a mutation. This finding reflects the available epidemiological data. Moreover, the applicant performed subgroup analyses of the primary and key secondary endpoints which showed that the efficacy of CBD-OS was not influenced by *SCN1A* mutation type.

Endpoints and analysis

The primary endpoint for study GWEP1332B was the percentage change from baseline in convulsive seizure frequency (average per 28 days) during the treatment period for CBD-OS compared with placebo. The primary endpoint for study GWEP1424 was the change in convulsive seizure frequency during the treatment period compared to baseline in patients taking CBD-OS compared with placebo. A convulsive seizure was defined as a tonic, clonic, tonic-clonic, or atonic seizure. Convulsive seizures are accurately identified by caregivers and are the most common observable motor component in DS. The CHMP agreed that measuring the frequency of convulsive seizure can be considered a clinically relevant endpoint for DS patients. A continuous variable rather than a dichotomised variable (responder analysis) was chosen due to the rareness of DS. For the purpose of the EU submission the ≥ 50% responder rate was the key secondary endpoint in Study GWEP1332B which is considered acceptable. For the EU submission only, the secondary endpoints in Study GWEP1332B were tested hierarchically, starting with the key secondary endpoint followed by all other secondary endpoints. For submissions outside the EU, there was no hierarchical testing of secondary endpoints. In Study GWEP1424 (submitted as part of the Day150 responses of the current EU procedure), a hierarchical gate-keeping procedure was used to control the type I error starting with the primary endpoint for the 20 mg/kg/day dose followed by the 10 mg/kg/day dose, then the 1st key secondary endpoint for the 20 mg/kg/day dose etc.

Efficacy data and additional analyses

The primary endpoint was met in all four studies with an approximately 40-50% median reduction in the active groups as compared to approximately 15-25% in the placebo groups. Whereas it is questionable whether a median treatment difference of 20-25% may in itself be considered clinically relevant, in the LGS studies the primary analysis was supported by key secondary analyses including responder analyses and global impression of change. In terms of drop seizure free days, the treatment difference in LGS corresponded to 3-5 drop seizure free days per 28 days. In Dravet Syndrome, the key secondary endpoint (responder analysis) was not met in Study GWEP1332B. In Study GWEP1424, the key secondary endpoint analyses supported the primary analyses.

The two syndromes LGS and DS are both considered epileptic encephalopathies, are high frequency seizure disorders comprised of multiple seizure types, share many of the same seizure types, are highly treatment refractory and they are to some degree treated with same medications. Morbidity and mortality are high in both disorders, and SUDEP is a common cause of death at a young age. However, the syndromes differ in age of onset and aetiology: Dravet Syndrome is usually associated with SCN1A mutations, and may likely be considered a sodium channel disorder, whereas SCN1A mutations are usually not seen in LGS. Thus, there is not a clear biological rationale for expecting rather similar effect sizes in the two indications. While the finding of rather similar effect sizes may be a consequence of CBD-OS having unspecific anticonvulsive properties the methodological and pharmacokinetic issues discussed in this report may also play a role.

In all pivotal studies, the efficacy analyses relied on the caregiver's judgment and correct entry of seizure information in the IVRS. Dealing with missing data in seizure frequency trials is challenging due to the average over a given period being used. Furthermore, as seizure 'rater', the caregiver was not blinded to other clinical information regarding e.g. adverse events, dose reductions, behaviour, and the general well-being of the patient, meaning that rating might be influenced by these factors. During the procedure the applicant submitted the results of several analyses investigating the correlation between the occurrence of AE (such as somnolence, sedation, lethargy or fatigue Decreased appetite or diarrhoea) and treatment effects. The presented results suggested that there is no association to a modest association between seizure reduction and occurrence of AEs which are representative for CBD-OS safety profile. Based on the provided analyse the CHMP concluded that while it cannot be excluded that the unblinding occurred in few cases, the underreporting of seizures by the caregiver and the patient’s behaviour were unlikely to be impacted by unblinding. Overall the impact of any potential unblinding cases on the robustness of the presented data is not considered relevant.

At least some of the treatment difference may likely be ascribed to the bi-directional pharmacokinetic interaction with clobazam (leading to increased clobazam active metabolite N-CLB concentrations and to increased CBD active metabolite 7-OH-CBD concentrations). CBD-OS and clobazam have a complex 2-way metabolic interaction. CBD-OS inhibits CYP2C19 which is required to metabolise the active clobazam metabolite N-CLB. This leads to 2 to 4 fold increase in N-CLB and an approximate 1.5-fold increase in 7-OH-CBD concentrations, which may partially explain the treatment difference. In the pivotal trials there was substantial clobazam concomitant treatment at baseline (approximately 50% in LGS and 65% in DS). The Applicant performed various analyses intended to demonstrate independent efficacy of CBD-OS. However, in the 20 mg/kg/day dose level in both LGS studies, in one DS study at the 20 mg/kg/day and in the other DS study at the 10 mg/kg/day, performing the primary analysis on the subgroup of patients on CLB and the subgroup of patients not on CLB consistently revealed much larger treatment difference point estimates in the CLB subgroups than in the non-CLB subgroups.

At the CHMP’s request the applicant was invited to discuss the clinical relevance of the efficacy of CBD-OS independent of clobazam with particular focus on results obtained with the intended maintenance dose (10 mg/kg/day). This dose level was only investigated in two studies: GWEP1414 (LGS) and

GWEP1424 (DS). In DS, a marked difference (primary endpoint) between the on-CLB (treatment ratio 0.63) and off-CLB (treatment ratio 0.91) subgroups was observed for the 10 mg/kg/day dose in accordance with what was observed in DS study GWEP1332B for the 20 mg/kg/day dose (In DS study GWEP1424, the 20 mg/kg/day dose off-CLB showed a treatment ratio of 0.80). In LGS, such a difference was not observed for the 10 mg/kg/day dose in study GWEP1414 (treatment ratio on-CLB 0.70, treatment ratio off-CLB 0.71), whereas a marked difference was observed for the 20 mg/kg/day dose in both LGS studies. The overall impression when looking across both dose levels and both diseases is that the treatment effect (seizure frequency reduction, primary endpoint) is far larger in the on-CLB subgroups (treatment ratios of 0.46-0.70) than in the off-CLB subgroups (treatment ratios of 0.71-0.92) with the confidence intervals for the off-CLB subgroups generally overlapping unity (a treatment ratio of 1, indicating no effect).

In order to demonstrate that the treatment effect off-CLB is different from zero, the applicant performed meta-analyses across diseases and doses. The meta-analyses were stratified by trial, which is agreed. For patients not taking clobazam (10 mg/kg/day dose), the meta-analyses suggest a reduction, albeit not statistically significant, in seizure counts of approximately 22 % (95 % CI 0 % - 40 %). The meta-analyses are considered helpful although several strong assumptions are made. The diseases are not as such comparable, the primary endpoints are different (addressing different seizure types), and efficacy of the 10 mg/kg/day and 20 mg/kg/day doses - although of comparable magnitude - cannot be considered identical. Despite these limitations, the meta-analyses do indicate that the treatment effect off-CLB is smaller than the treatment effect in patients on clobazam.

In order to explain the lack of - or smaller magnitude of - treatment effect in patients not taking clobazam, the applicant noted that there are likely multiple factors involved, one being that these patients have previously tried clobazam without success and may therefore as a group be considered more difficult to treat. However, this explanation was developed after seeing the results and is therefore prone to bias. In addition, while there are differences in baseline clinical characteristics between these subgroups the two patient subpopulations do not appear to be fundamentally different. Furthermore, the fact that patients off CLB in LGS have a higher risk of experiencing an *increase* in seizures at 20 mg/kg/day may merely be interpreted as lack of efficacy. It is neither meaningful nor methodologically valid to consider a decrease on a scale as proof of efficacy but an increase on the same scale as an adverse event (rather than a lack of efficacy).

Thus, while a small favourable effect of CBD-OS independent of clobazam cannot be excluded, its clinical relevance was not established. The Applicant argued that clinical relevance of CBD treatment, in these rare and severe treatment resistant epileptic encephalopathies can be gleaned from the results of the 50% responder analyses, however based on the discussion of the SAG (see Additional expert consultation section), the view from CHMP is that the primary efficacy analyses should be used to determine clinical relevance.

In the CHMP's view the pharmacokinetic interaction between CBD-OS and CLB remains the most likely explanation for the observed difference in efficacy between the ON-CLB and OFF-CLB subgroups. Therefore, the CHMP concluded that based on the available data CBD-OS efficacy appears to be driven by results obtained in patients on clobazam although CBD-OS may have some small efficacy independent of clobazam.

The clinical relevance of this smaller effect in patients not receiving clobazam was subject of discussion in a Scientific Advisory Group (see the minutes under the heading Additional expert consultation). Overall, the SAG was not convinced that efficacy of clobazam had been reliably demonstrated in statistical terms. Notwithstanding this, the group consisting of experts in the field, were split in the interpretation of the clinical relevance of the observed effect of CBD-OS without clobazam. Approximately half of the group did not consider the observed effect clinically relevant whereas the

other half did indeed consider the effect clinically relevant. The experts who considered the effect clinically relevant also considered results from responder analyses as supportive of the clinical relevance. The SAG did not consider that data supported the company's claim that the observed smaller effect of CBD-OS in patients off clobazam was due to these patients constituting a particularly treatment-resistant subgroup.

Whereas the presented study results demonstrated that CBD-OS had a statistically significant effect in the studied LGS and DS populations, the effect size appeared mainly driven by the effect size observed in clobazam-treated patients whereas in patients off clobazam the effect size was small. Given these concerns which were partly shared by the SAG members, the CHMP does not consider that it has been convincingly demonstrated that the effect size in patients off clobazam is statistically and clinically relevant.

Patients in the open-label extension (OLE) study experienced a reduction in seizure frequency compared to pivotal trial baseline values. The median reductions were comparable in magnitude with that observed in the pivotal trial active groups. According to the Applicant, this demonstrates maintenance of efficacy. To account for differences in sample size with increasing time, the Applicant also analysed the subgroups of patients treated for 37-48 weeks, and found similar results. However, both analyses are subject to selection bias and thus in the CHMP's view do not necessarily reflect maintenance of efficacy.

Patients included in the Expanded Access Program (EAP) experienced a median reduction in seizure frequency comparable in magnitude with that observed in the pivotal trial active groups. Given the uncontrolled nature of the programme and the high likelihood of selection bias, CHMP considers that no firm conclusions can be drawn based on these data.

Additional expert consultation

In the course of the procedure, the CHMP identified the need for expert input and thus a scientific advisory group expert meeting was convened, which included the participation of patient representatives, on the following questions:

1. The results of all four pivotal studies conducted in LGS and DS patients indicate a smaller magnitude of the effect in patients not treated with clobazam. The SAG is asked to discuss the importance of these findings, in particular:

a. Please discuss if the results observed in the subgroup of patients off clobazam treatment show a clinically relevant effect

Overall, SAG experts expressed doubts about the validity of the efficacy data and were not fully convinced that they are reliably demonstrating an effect in patients OFF-clobazam treatment, mainly, from a statistical point of view.

However, experts were split in their interpretation of the clinical relevance of the effect.

Some considered that for both LGS and DS patients the clinical relevance of the demonstrated effect in PEP and responder analysis was not sufficiently shown in patients off clobazam.

Others clearly stated that despite the size of the observed effect some consistency of the effect across available studies should be acknowledged, indicating some clinical relevance. For these experts, if data were to be considered reliable, the observed effect in patients OFF-clobazam would be considered clinically important (a 30% reduction of seizure numbers in LGS for example and a 1/3 of patients achieving more than 50% reduction is clearly clinically relevant).

Some experts made a statement that in the field of paediatric rare epilepsies, the type of trial as performed for this application may not be fully suited to register all the aspects that would constitute clinically meaningful efficacy in real life. They insisted that in this specific type of situation, registration of seizure numbers or other "standard" endpoints often fail to reflect the full range of benefits that could be important to the patients and caregivers.

b. Please discuss the apparent discrepancy between the results of the primary efficacy analysis (reduction in seizure frequency) and the results of the 50% responder analysis. In that respect, the SAG experts are asked to discuss which endpoint can be considered of primary interest in terms of establishing the clinical relevance of the effect.

It was pointed out that the Applicant made the choice to use the reduction of seizure frequency as primary endpoint, instead of responder analysis. The SAG experts were once again split, with majority (including patient representatives) favoring the clinical importance of reduction of seizure frequency, while others commented that the >50% response rate is more clinically relevant in these specific conditions. However, some experts questioned the relevance of a ≥50% reduction of a single type of seizure, when both LGS and DS patients present with many other types of seizures.

c. Please discuss the claim (based on the presented data for previous use of clobazam in a significant proportion of the patients not receiving clobazam in the trials) that patients off clobazam represent a specific treatment resistant subgroup, explaining at least partly the apparent smaller efficacy observed in this subgroup of patients.

The SAG experts considered that there are not enough data to support the claim that patients OFF-clobazam represent a specific treatment resistant subgroup.

2. The results observed in patients not taking clobazam may have been impacted by the effects observed in a subset of patients experiencing worsening of seizure frequency which to some extent decrease the positive effect on seizure frequency observed in the majority of patients. The applicant has proposed that in clinical practice this can be managed by early discontinuation of CBD-OS in patients experiencing worsening of seizure frequency and continuing CBD-OS treatment in patients with a favorable response, only. In that respect, the SAG experts are asked to discuss the feasibility and clinical utility of such an approach taking into consideration the known risks associated with CBD-OS treatment.

The experts were convinced that these patients are managed by a highly specialized group of physicians, and normally a warning will be introduced in any new anti-epileptic drug, so any worsening will be registered and can be managed in clinical practice by withdrawing the patient from the treatment.

The patient representatives supported adding a clear warning about the potential worsening while on treatment with the product, since there is the perception in the patient community that this is a "natural" product and hence should not be expected to have any negative effects. This perception will potentially affect the reports of worsening that may come from the parents and caregivers.

3. The SAG experts are asked to discuss which precautions (if any) are considered necessary in order to minimize the treatment risks taking into consideration not only the risk of worsening of seizure frequency but also the other identified risks associated with CBD-OS (in particular sedation and hepatotoxicity).

The SAG expressed concerns about the small proportion of patients that will experience status epilepticus and will have to be treated for that. It is not clear how the observed toxicological effects of CBD may interact with the known toxicity of the drugs used to manage status epilepticus.

Another concern expressed was related to the rescue use of midazolam and the potential effect on respiratory depression in these patients. The applicant should clarify whether such interaction has been observed.

4. The SAG experts are asked to comment on the clinical utility and the effect in practice of a potential restriction of use of CBD-OS only to patients already receiving clobazam as part of their therapy.

SAG experts were split in their position about an indication that clearly excludes OFF clobazam patients. Although it was considered that data in OFF-clobazam patients could indicate efficacy, no consensus could be reached regarding a restricted indication to this specific group.

Some members supported this restricted indication, which should be based on the evidence provided by the trials. Additionally, they expressed concerns that a different approach will increase the use of CBD instead of clobazam. However, the argument that CBD will then be prescribed off-label, even if the current level of evidence does not support this, was not considered a valid argument to have an indication for patients OFF-clobazam in the absence of proven efficacy.

Other experts, including the patient representatives, were against a restriction, stating the following reasons:

- Such an indication will require the use of clobazam in order to prescribe CBD, thus patients who cannot tolerate clobazam (often observed in children) will not be given the option to use CBD for treatment. This situation was highlighted by the patient representatives as undesirable.
- It is likely that a restricted indication may not be followed in practice – it will potentiate off-label use
- Individual patients may still exist that will show clinically relevant benefit and having an additional effective treatment option is appreciated.

2.5.4. Conclusions on the clinical efficacy

Clinical efficacy in Lennox-Gastaut Syndrome and Dravet Syndrome, two serious, rare, treatment resistant epileptic encephalopathies, was evaluated in four pivotal trials in which the primary outcome measure was reduction in drop seizure frequency and convulsive seizure frequency, respectively. These are considered clinically relevant endpoints. The primary endpoint was met in all four studies with an approximately 40-50% median reduction of seizure frequency in the active groups as compared to approximately median 15-25% in the placebo groups. In Lennox-Gastaut syndrome, the primary analysis was supported by the statistically significant results of key secondary endpoints including responder analyses and global impression of change. In terms of drop seizure free days, the treatment difference in LGS corresponded to 3-5 drop seizure free days per 28 days. In Dravet Syndrome, the key secondary endpoint (responder analysis) was not met in one study (GWEP1332B) whereas in the other study (GWEP1424) the key secondary analyses reached the statistical significance, supporting the results of the primary analyses.

Whereas the presented studies demonstrated that CBD-OS had an effect in both LGS and DS, the effect appeared mainly driven by the effect observed in clobazam treated patients whereas the effect in patients off clobazam was smaller or not detectable. The CHMP does not consider that it has been

convincingly demonstrated that the effect size in off clobazam LGS and DS patients treated with other combined treatments is statistically and clinically relevant, hence that it does not support the indication initially claimed with any kind of drug combination.

Therefore, the CHMP considers that the presented efficacy data supports the application for Epidyolex in the treatment of use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in conjunction with clobazam only, for patients 2 years of age and older.

2.6. Clinical safety

Safety data to support the use of CBD-OS in patients with LGS or DS has been collected from 8 completed Phase 1 trials, 4 completed double-blind, placebo-controlled trials in target indications (2 trials in LGS and 2 trials in DS), and 1 ongoing Phase 3 OLE trial. Supportive data was also collected from the EAP (investigator-initiated IND applications [US]) and other compassionate use programs (i.e., State INDs [US] and CAS [Australia]) in patients with DREs. Supportive safety data from additional Phase 1 clinical pharmacology trials, trials in other patient populations with epilepsy, and trials in other exploratory indications are presented by trial in CSRs/interim synoptic reports (ISRs) only.

Patient exposure

The 2 target patient populations for this marketing application (LGS and DS) are complex, with both having seizures that are inadequately controlled despite their current AED regimen (multiple adjunctive AEDs combined for treatment).

The data from the LGS and DS RCTs and open-label trials have been pooled and presented together to provide a larger safety dataset to aid risk identification. In the Pool DS/LGS, 456 patients were exposed to CBD-OS and 292 patients were exposed to placebo, representing 113.55 and 78.34 patient-years on treatment, respectively. In OLE trial, GWEP1415, a total of 278 patients in GWEP1415-DS and 366 patients in GWEP1415-LGS received CBD-OS, which represented 252.76 and 385.39 patient years on treatment, respectively.

Additional supportive safety data are available from 322 patients exposed to CBD-OS in a dose range of 200 mg to 6000 mg in phase I studies in healthy subjects and patients with renal or hepatic impairment. Further safety data are available from an expanded access and compassionate use programs among patient with a serious or life-threatening condition with no other comparable or satisfactory therapeutic options and from smaller studies in other patient groups.

Overall as of the cut-off dates, 1928 unique subjects have been exposed to CBD-OS in GW-sponsored development programs. An additional 68 unique subjects have been exposed to CBD capsules and 12 unique subjects have been exposed to CBD i.v. solution.

Table 40 Overall Summary of CBD-OS exposures in the clinical development and supportive programs

Population Source	Total CBD-OS exposures	Number of Unique CBD-OS exposures
Controlled trials in the target indications (DS and LGS)		
Pool DS/LGS	456	
Pool DS	221	221
Pool LGS	235	235
Long-term open-label trial in the target indications (DS and LGS)		
GWEP1415-DS/LGS[a]	644	
GWEP1415-DS[a]	278	112
GWEP1415-LGS[a]	366	157
Phase 1 clinical pharmacology trials (healthy subjects and special patient populations)		
Pool H-SD	197[b]	110
Pool H-MD	125	125
Pool PP1-SD	163[b]	87
EAP and other compassionate use programs (drug-resistant epilepsy)		
Pool EAP	684	523[c]
Pool EAP-DS	64	64
Pool EAP-LGS	97	97
Trials in other patient populations with epilepsy[d]		
GWEP1521 OLE (Patients with TSC)	11	11
GWEP1428 (Placebo-controlled DDI trial in patients with epilepsy)	16	16
GWEP1428 OLE	18	4
GWEP1447 VPA arm	17	17
Trials in other exploratory indications[d]		
GWAP1241 (schizophrenia or related psychotic disorders)	43	43
Additional Phase 1 clinical pharmacology trials[d]		
GWEP1446 Part B	12	12
GWEP17028	14	14
GWEP17075	32	32
GWEP17077	48	48
	Total	1928

[a] Unique exposures in GWEP1415 includes patients treated with placebo in a blinded core study but transitioned to CBD-OS in the OLE.

[b] Pool H-SD and Pool PP1-SD include subjects from crossover trials (GWEP1544, GWEP1448, GWEP1541, GWEP1431) having multiple treatment periods separated by washout periods. Therefore, subjects from these trials can be counted more than once such that the total exposures in Pool H-SD or Pool PP1-SD are larger than the sum of the actual number of subjects who participated in the trials.

[c] Patients are unique non-DS non-LGS patients.

[d] Patients from these trials are not included in ISS pools. Safety data from these trials are provided in the respective CSRs.

Since the indications of LGS and DS are early onset epilepsies, the patient populations were predominantly aged ≤ 18 years old. In the LGS trials, approximately 30% of the patients were aged ≥

18 years old. In the DS trials, approximately 30% of the patients were < 6 years old, and all patients were ≤ 18 years old. The mean age and mean weight of patients in the All CBD-OS group of Pool LGS (15.6 years; 42.7 kg) was older and heavier than that in Pool DS (9.2 years; 32.7 kg), which is reflective of the age differences in the overall patient populations included in the trials.

Table 41 - Disposition by Age in controlled DS and LGS trials (Pool DS/LGS)

Age Group	Number of Patients:	All CBD-OS n (%)	Placebo n (%)
2–5 years	Treated	90 (100.0)	56 (100.0)
	Completed	77 (85.6)	54 (96.4)
	Discontinued	13 (14.4)	2 (3.6)
	Adverse Event	10 (11.1)	1 (1.8)
6–11 years	Treated	172 (100.0)	104 (100.0)
	Completed	154 (89.5)	101 (97.1)
	Discontinued	18 (10.5)	3 (2.9)
	Adverse Event	10 (5.8)	0
12–17 years	Treated	117 (100.0)	78 (100.0)
	Completed	108 (92.3)	75 (96.2)
	Discontinued	9 (7.7)	3 (3.8)
	Adverse Event	5 (4.3)	1 (1.3)
≥ 18 years	Treated	77 (100.0)	54 (100.0)
	Completed	71 (92.2)	52 (96.3)
	Discontinued	6 (7.8)	2 (3.7)
	Adverse Event	2 (2.6)	1 (1.9)

Note: Percentages are based on the number of patients in the subgroup.
Note: Enrolled analysis set.

Adverse events

Treatment-emergent Adverse Events (TEAS):

- In the phase II and phase III controlled clinical trials

There were more TEAS in the CBD-OS treated groups than in the placebo groups. There were more TEAS in the 20 mg/kg/day than the 10 mg/kg/day CBD-OS groups. The TEAS in the DS and LGS pools were similar except for a few SOCs mentioned below.

Most commonly reported adverse events were within:

- The SOC 'Nervous system disorders', including somnolence, lethargy, sedation, drooling and tremor.

- The SOC 'Gastrointestinal disorders', including diarrhoea, vomiting.

- The SOC 'Metabolism', including decreased appetite.

-The SOC 'Investigations', including changes in the levels of hepatic enzymes.

In the CBD-OS treated LGS group four subjects had recorded cardiac disorders of tachycardia (II), arrhythmia (I) and bradycardia (I) as compared to one subject in the placebo group. As no CBD-OS treated subjects with DS had similar changes of rhythm, and as the reported incidence/prevalence is fairly comparable to the background prevalence, it is less likely to be related to CBD.

The following table summarises the most frequently reported AEs during controlled DS and LGS trials:

Table 42 - Incidence of common TEAEs (≥3% of patients in all CBD-OS group) in controlled DS and LGS trials (Pool DS/LGS)

SOC PT	CBD-OS 5 mg/kg/day (N=10) n (%)	CBD-OS 10 mg/kg/day (N=139) n (%)	CBD-OS 20 mg/kg/day (N=307) n (%)	All CBD-OS (N=456) n (%)	Placebo (N=292) n (%)
Patients with at least 1 TEAE	**8 (80.0)**	**117 (84.2)**	**277 (90.2)**	**402 (88.2)**	**222 (76.0)**
Gastrointestinal disorders	**1 (10.0)**	**30 (21.6)**	**118 (38.4)**	**149 (32.7)**	**73 (25.0)**
Diarrhoea	0	18 (12.9)	65 (21.2)	83 (18.2)	28 (9.6)
Vomiting	1 (10.0)	0 9 (6.5)	40 (13.0)	50 (11.0)	30 (10.3)
Constipation	1 (10.0)	5 (3.6)	12 (3.9)	18 (3.9)	12 (4.1)
General disorders and administration site conditions	**3 (30.0)**	**36 (25.9)**	**86 (28.0)**	**125 (27.4)**	**52 (17.8)**
Pyrexia	3 (30.0)	24 (17.3)	45 (14.7)	72 (15.8)	35 (12.0)
Fatigue	0	10 (7.2)	41 (13.4)	51 (11.2)	15 (5.1)
Infections and infestations	**4 (40.0)**	**59 (42.4)**	**130 (42.3)**	**193 (42.3)**	**96 (32.9)**
Upper respiratory tract infection	1 (10.0)	14 (10.1)	24 (7.8)	39 (8.6)	25 (8.6)
Nasopharyngitis	0	8 (5.8)	25 (8.1)	33 (7.2)	18 (6.2)
Pneumonia	0	10 (7.2)	12 (3.9)	22 (4.8)	2 (0.7)
Ear infection	0	5 (3.6)	8 (2.6)	13 (2.9)	7 (2.4)
Bronchitis	0	2 (1.4)	10 (3.3)	12 (2.6)	6 (2.1)
Sinusitis	0	4 (2.9)	8 (2.6)	12 (2.6)	7 (2.4)
Investigations	**2 (20.0)**	**29 (20.9)**	**85 (27.7)**	**116 (25.4)**	**42 (14.4)**
ALT increased	0	6 (4.3)	21 (6.8)	27 (5.9)	3 (1.0)
AST increased	0	5 (3.6)	20 (6.5)	25 (5.5)	2 (0.7)
Weight decreased	0	2 (1.4)	13 (4.2)	15 (3.3)	4 (1.4)
GGT increased	0	6 (4.3)	14 (4.6)	20 (4.4)	6 (2.1)
Liver function test abnormal	0	0	12 (3.9)	12 (2.6)	1 (0.3)
Metabolism and nutrition disorders	**1 (10.0)**	**27 (19.4)**	**84 (27.4)**	**112 (24.6)**	**28 (9.6)**
Decreased appetite	0	23 (16.5)	73 (23.8)	96 (21.1)	22 (7.5)
Increased appetite	0	4 (2.9)	8 (2.6)	12 (2.6)	3 (1.0)
Nervous system disorders	**6 (60.0)**	**59 (42.4)**	**151 (49.2)**	**216 (47.4)**	**97 (33.2)**
Somnolence	2 (20.0)	33 (23.7)	76 (24.8)	111 (24.3)	28 (9.6)
Convulsion	0	9 (6.5)	23 (7.5)	32 (7.0)	22 (7.5)
Status epilepticus	1 (10.0)	12 (8.6)	16 (5.2)	29 (6.4)	16 (5.5)
Lethargy	0	4 (2.9)	19 (6.2)	23 (5.0)	7 (2.4)
Sedation	2 (20.0)	3 (2.2)	16 (5.2)	21 (4.6)	2 (0.7)
Psychiatric disorders	**3 (30.0)**	**23 (16.5)**	**66 (21.5)**	**92 (20.2)**	**33 (11.3)**
Irritability	0	10 (7.2)	15 (4.9)	25 (5.5)	5 (1.7)
Aggression	0	3 (2.2)	15 (4.9)	18 (3.9)	3 (1.0)
Insomnia	0	5 (3.6)	10 (3.3)	15 (3.3)	6 (2.1)
Respiratory, thoracic and mediastinal disorders	**0**	**14 (10.1)**	**46 (15.0)**	**60 (13.2)**	**34 (11.6)**
Cough	0	6 (4.3)	13 (4.2)	19 (4.2)	9 (3.1)
Skin and subcutaneous tissue disorders	**1 (10.0)**	**18 (12.9)**	**35 (11.4)**	**54 (11.8)**	**18 (6.2)**
Rash[a]	0	3 (2.2)	16 (5.2)	19 (4.2)	3 (1.0)

a One additional patient in Pool DS (R-1187-004) randomized to 20 mg/kg/day CBD-OS had a non-serious TEAE of rash on Day 28 that resolved on Day 58 with no action taken regarding IMP. The event was of mild intensity and was not considered treatment-related by the investigator. The CRF AE page for this event was not provided to the sponsor until after database lock and was therefore not entered into the clinical database for this trial. Further details are provided in GWEP1424 CSR Section 5.6.4 and Section 9.3.1.4.3.

Note: Safety analysis set.

Source: ISS Table DSLGS.9.3.1.

- In the open-label extension study (OLE)

In general, the adverse event profile in the OLE study resembled the adverse events profile observed in the clinical phase II and phase III trials. Hence, somnolence, lethargy, sedation, decreased appetite

and increasing levels of hepatic enzymes were also noted in the OLE study. Decreased weight, which may be caused by reduced appetite or gastrointestinal adverse events, was also noted. Further, diarrhoea, vomiting, and constipation are frequently reported adverse events. There were also four reports of changed cardiac rhythm, as also noted in the CBD-OS treated LGS group in the phase III trials.

Table 43 - Incidence of common TAEs (≥3% of patients in the all CBD-OS group) in OLE extension trial GWEP1415 (GWEP1415-DS/LGS by modal dose)

SOC PT	CBD-OS ≤ 20 mg/kg/day (N=352) n (%)	CBD-OS > 20 mg/kg/day (N=292) n (%)	All CBD-OS (N=644) n (%)
Patients with at least 1 TEAE	**329 (93.5)**	**283 (96.9)**	**612 (95.0)**
Gastrointestinal disorders	**174 (49.4)**	**178 (61.0)**	**352 (54.7)**
Diarrhoea	104 (29.5)	116 (39.7)	220 (34.2)
Vomiting	63 (17.9)	65 (22.3)	128 (19.9)
Constipation	25 (7.1)	28 (9.6)	53 (8.2)
Nausea	19 (5.4)	15 (5.1)	34 (5.3)
Abdominal pain upper	8 (2.3)	8 (2.7)	16 (2.5)
General disorders and administration site conditions	**123 (34.9)**	**138 (47.3)**	**261 (40.5)**
Pyrexia	84 (23.9)	99 (33.9)	183 (28.4)
Fatigue	32 (9.1)	28 (9.6)	60 (9.3)
Gait disturbance	8 (2.3)	12 (4.1)	20 (3.1)
Infections and infestations	**195 (55.4)**	**208 (71.2)**	**403 (62.6)**
Upper respiratory tract infection	64 (18.2)	53 (18.2)	117 (18.2)
Nasopharyngitis	51 (14.5)	52 (17.8)	103 (16.0)
Ear infection	23 (6.5)	35 (12.0)	58 (9.0)
Sinusitis	23 (6.5)	31 (10.6)	54 (8.4)
Pneumonia	19 (5.4)	30 (10.3)	49 (7.6)
Influenza	25 (7.1)	20 (6.8)	45 (7.0)
Urinary tract infection	19 (5.4)	25 (8.6)	44 (6.8)
Pharyngitis streptococcal	14 (4.0)	17 (5.8)	31 (4.8)
Gastroenteritis viral	10 (2.8)	17 (5.8)	27 (4.2)
Otitis media	10 (2.8)	16 (5.5)	26 (4.0)
Bronchitis	12 (3.4)	13 (4.5)	25 (3.9)
Viral infection	13 (3.7)	8 (2.7)	21 (3.3)
Viral upper respiratory tract infection	7 (2.0)	14 (4.8)	21 (3.3)
Pharyngitis	11 (3.1)	6 (2.1)	17 (2.6)
Injury, poisoning and procedural complications	**77 (21.9)**	**77 (26.4)**	**154 (23.9)**
Laceration	9 (2.6)	19 (6.5)	28 (4.3)
Contusion	12 (3.4)	15 (5.1)	27 (4.2)
Fall	11 (3.1)	9 (3.1)	20 (3.1)

1. Liver related adverse events:

When combining the patient populations in Pool DS/LGS, the incidence of TEAEs meeting the search criteria for AESI abnormal liver TEAEs was 14.9% in the All CBD-OS group (N=456) compared with 3.1% in the placebo group (N=292). The overall AESI incidence was higher in the CBD-OS 20 mg/kg/day group (17.6%; N=307) than the 10 mg/kg/day dose group (9.4%; N=139). The 3 most common AESI PTs were ALT increased, AST increased, and GGT increased.

Overall, the incidence of AESI abnormal liver TEAEs in the OLE trial was similar to that seen in the controlled trials (18.6% vs. 14.9%, respectively), with no evidence of new patterns of AEs (the 3 most common AESI PTs were ALT increased, AST increased, and GGT increased)

A. Transaminase elevations and levels of bilirubin + INR:

CBD-OS dose dependently increased the risk of liver enzyme primarily related to transaminase elevations.

The majority of the increases were below 3 x ULN. However, patients with greater than 3 x ULN elevation in transaminases showed a clear dose-response relationship with clearly increased risk for 20 mg/kg/day whereas the risk for 10 mg/kg/day was comparable to that of placebo.

The risk of elevations of transaminases was increased in patients with elevated transaminases before treatment and particularly in that receiving valproic acid. In patients not receiving valproic acid, there was a small increase in risk of any elevation of transaminases. However, there were no changes greater than 5xULN although the number of patients with elevated transaminases and no concomitant valproic acid treatment was too low to allow a definite conclusion but did not suggest and increased risk. Baseline transaminase use and concomitant valproate treatment synergistically increased the risk of CBD-OS to induce post-baseline hepatocellular injury. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a much lesser extent than valproate.

In controlled trials, 27 patients were reported with ALT-elevations > 5 x ULN. The majority of these patients received 20 mg/kg/day of CBD-OS (22/27) and were concomitantly treated with valproate (23/27). Ten participants had SAE or AE leading to discontinuation of the study while seventeen patients with ALT-elevations > 5 x ULN remained on the study. During the OLE phase, 19 patients were reported with ALT-elevations > 5 x ULN, most of them treated with Placebo during the controlled phase but at high-doses (20-30mg/kg/d) during OLE phase and receiving VPA (16/19).

Most cases of ALT elevation occurred within the first 30 days of use. However, there were also a number of cases commencing more than 30 days after initiation of treatment stressing the need for continuous monitoring of liver enzymes throughout treatment. Some cases, particularly those also treated with VPA occurred as late as after 6 to 18 months after treatment initiation in controlled trials. Similar pattern was found on the OLE group.

Table 44 - Frequency of ALT elevations by baseline ALT in patients with or without concomitant valproate in pool DS/LGS (Pivotal DS and LGS)

Peak ALT (× ULN)	No Concomitant Valproate Baseline ALT ≤ ULN	No Concomitant Valproate Baseline ALT > ULN	Concomitant Valproate Baseline ALT ≤ ULN	Concomitant Valproate Baseline ALT > ULN
	CBD-OS 20 mg/kg/day (N=106) *n / N* (%)	CBD-OS 20 mg/kg/day (N=38) *n / N* (%)	CBD-OS 20 mg/kg/day (N=129) *n / N* (%)	CBD-OS 20 mg/kg/day (N=25) *n / N* (%)
> 2 ×	5/106 (4.7)	8/35 (22.9)	45/129 (34.9)	18/23 (78.3)
> 3 ×	3/106 (2.8)	3/35 (8.6)	25/129 (19.4)	16/25 (64.0)
> 5 ×	3/106 (2.8)	0/38	8/129 (6.2)	9/25 (36.0)
> 8 ×	0/106	0/38	3/129 (2.3)	4/25 (16.0)
> 10 ×	0/106	0/38	1/129 (0.8)	3/25 (12.0)
> 20 ×	0/106	0/38	0/129	1/25 (4.0)
	CBD-OS 10 mg/kg/day (N=52) *n / N* (%)	CBD-OS 10 mg/kg/day (N=12) *n / N* (%)	CBD-OS 10 mg/kg/day (N=58) *n / N* (%)	CBD-OS 10 mg/kg/day (N=9) *n / N* (%)
> 2 ×	4/52 (7.7)	0/12	7/58 (12.1)	1/8 (12.5)
> 3 ×	1/52 (1.9)	0/12	3/58 (5.2)	1/9 (11.1)
> 5 ×	0/52	0/12	1/58 (1.7)	1/9 (11.1)
> 8 ×	0/52	0/12	1/58 (1.7)	0/9
> 10 ×	0/52	0/12	0/58	0/9
> 20 ×	0/52	0/12	0/58	0/9
	Placebo (N=108) *n / N* (%)	Placebo (N=32) *n / N* (%)	Placebo (N=123) *n / N* (%)	Placebo (N=22) *n / N* (%)
> 2 ×	2/108 (1.9)	3/28 (10.7)	3/123 (2.4)	4/19 (21.1)
> 3 ×	1/108 (0.9)	0/31	1/123 (0.8)	0/22
> 5 ×	1/108 (0.9)	0/32	1/123 (0.8)	0/22
> 8 ×	0/108	0/32	1/123 (0.8)	0/22
> 10 ×	0/108	0/32	1/123 (0.8)	0/22
> 20 ×	0/108	0/32	1/123 (0.8)	0/22

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.

Table 45 Frequency of ALT elevation by baseline ALT in patients with or without concomitant valproate in pool LT-DS/LGS

Peak ALT (× ULN)	No Concomitant Valproate Baseline ALT ≤ ULN	No Concomitant Valproate Baseline ALT > ULN	Concomitant Valproate Baseline ALT ≤ ULN	Concomitant Valproate Baseline ALT > ULN
	CBD-OS (N=245) *n / N* (%)	CBD-OS (N=80) *n / N* (%)	CBD-OS (N=293) *n / N* (%)	CBD-OS (N=55) *n / N* (%)
> 2 ×	21/245 (8.6)	18/77 (23.4)	104/293 (35.5)	33/51 (64.7)
> 3 ×	9/245 (3.7)	9/78 (11.5)	63/293 (21.5)	25/55 (45.5)
> 5 ×	3/245 (1.2)	2/80 (2.5)	21/293 (7.2)	12/55 (21.8)
> 8 ×	0/245	2/80 (2.5)	9/293 (3.1)	5/55 (9.1)
> 10 ×	0/245	2/80 (2.5)	5/293 (1.7)	4/55 (7.3)
> 20 ×	0/245	1/80 (1.3)	0/293	1/55 (1.8)

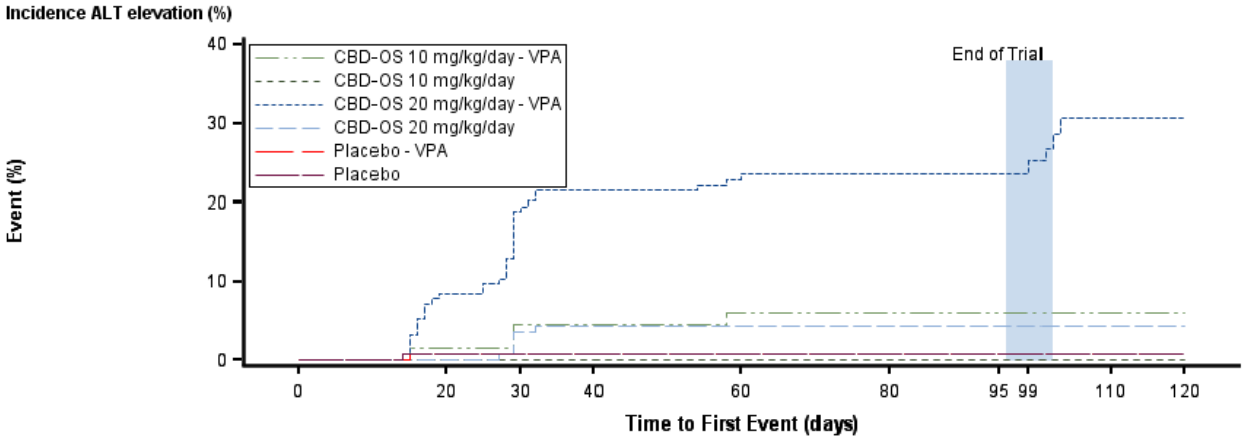
N corresponds to the total number of patients in the treatment group.
n / N: *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at at baseline.

Table 46 Frequency of liver-related adverse events (AE), SAE, and AEs resulting in discontinuation (AE DC) in CBD-OS patients taking concomitant clobazam ot no concomitant clobazam inpool DS/LGS (pivotal DS and LGS)

SOC	20 mg/kg/day CBD-OS and Concomitant Clobazam (n=161)			20 mg/kg/day CBD-OS and No Concomitant Clobazam (n=137)		
PT	AE	SAE	AE DC	AE	SAE	AE DC
Investigations (liver-related)	**31 (19.3)**	**9 (5.6)**	**12 (7.5)**	**17 (12.4)**	**2 (1.5)**	**3 (2.2)**
AST Increased	13 (8.1)	5 (3.1)	7 (4.3)	6 (4.4)	2 (1.5)	2 (1.5)
ALT Increased	11 (6.8)	4 (2.5)	6 (3.7)	10 (7.3)	2 (1.5)	2 (1.5)
GGT Increased	9 (5.6)	2 (1.2)	2 (1.2)	5 (3.6)	2 (1.5)	2 (1.5)
Liver Function Test Abnormal	8 (5.0)	3 (1.9)	2 (1.2)	3 (2.2)	0	0
Transaminases Increased	6 (3.7)	1 (0.6)	2 (1.2)	2 (1.5)	0	1 (0.7)
Blood Bilirubin Increased	1 (0.6)	0	0	0	0	0
Hepatic Enzyme Increased	0	0	0	1 (0.7%)	0	0

Figure 34 Liver analysis

7.Liver analyses: KM analyses for Time to Event
DSLGS.7.1.10 KM Plot for Time to first ALT > 3X ULN by Treatment Group with and without Concomitant Valproate
Pool DS/LGS (controlled DS/LGS) - Safety Analysis Set



Patients without events/censoring before or at the corresponding timepoint (Patients with events on or before the corresponding timepoint)

CBD-OS 10 mg/kg/day - VPA	67(0)	66(1)	64(3)	64(3)	63(4)	63(4)	60(4)	4(4)	0(4)
CBD-OS 10 mg/kg/day	64(0)	64(0)	64(0)	64(0)	64(0)	64(0)	63(0)	2(0)	0(0)
CBD-OS 20 mg/kg/day - VPA	154(0)	141(13)	123(30)	118(33)	111(36)	108(36)	103(36)	19(41)	0(41)
CBD-OS 20 mg/kg/day	142(0)	140(0)	133(5)	132(6)	129(6)	129(6)	124(6)	11(6)	0(6)
Placebo - VPA	145(0)	144(1)	144(1)	144(1)	143(1)	143(1)	142(1)	8(1)	0(1)
Placebo	139(0)	138(1)	138(1)	138(1)	136(1)	136(1)	132(1)	11(1)	0(1)

Valproate=VPA
Subjects from study GWEP1332 Part A are excluded.
Censoring is done at last known date or Day 120, whichever comes first.
Output ID: f-livkmf-alt3-valproate-dslgs 06MAR19
X:\GWPHARMA\ISS_ADDITIONAL_REQUEST\REQUEST11\BIOSTATISTICS\PRODUCTION\FIGURES\PGM\F-LIVKMF.sas

Figure 35 Kaplan-Meier plot of incidence of ALT elevations to>5 x ULN for patients taking or not taking valproate in pool LT-DS/LGS

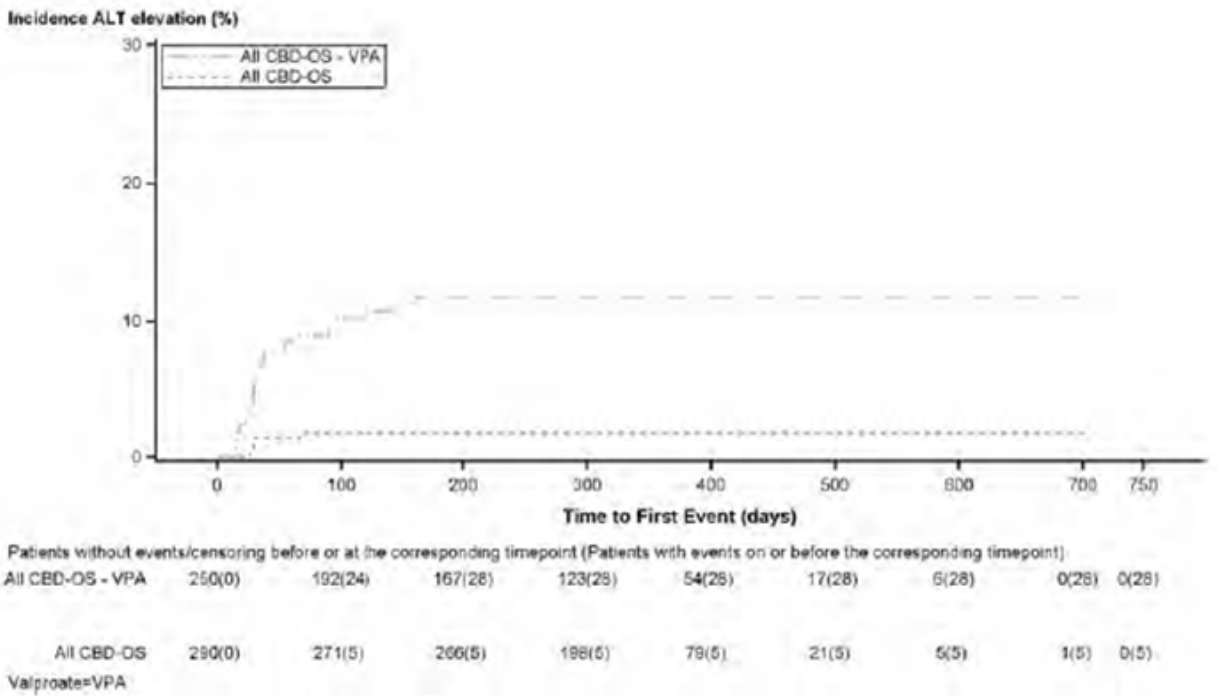
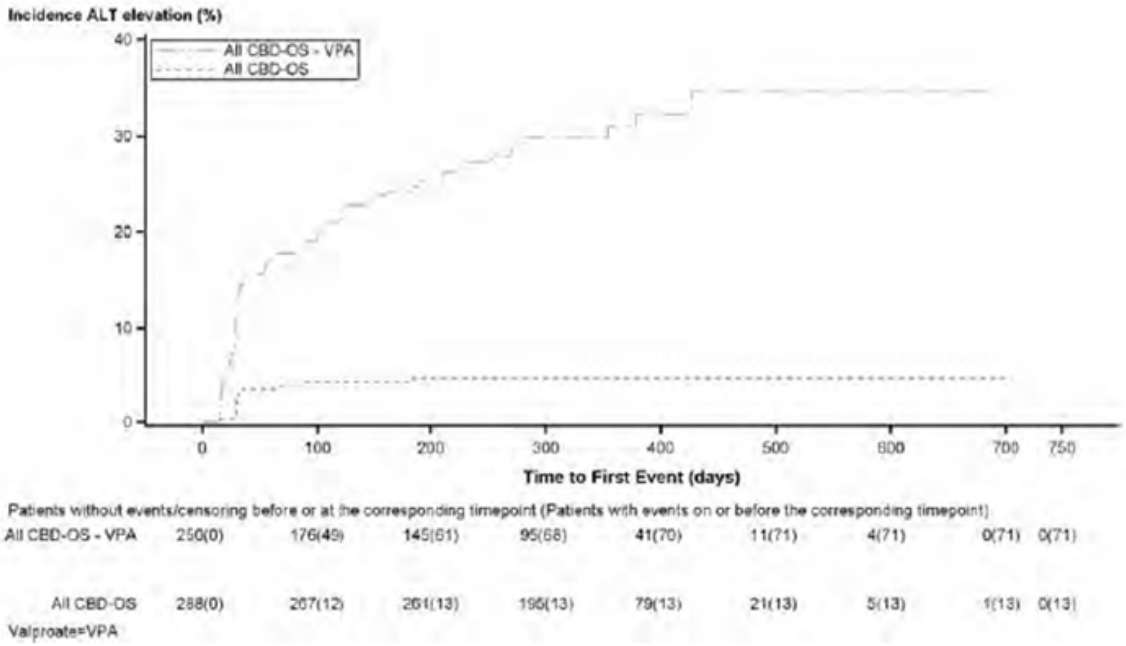


Figure 36 Kaplan-Meier plot of incidence of ALT elevations to >3 x ULN for patients taking or not taking valproate in pool LT-DS/LGS



B. Frequencies of liver-related AEs, SAEs, and discontinuations:

CBD-OS dose dependently increased the risk of liver related adverse events. In controlled studies there was one case of acute hepatic failure (SAE), one case of hepatic failure (non-serious per investigator) and one case of hepatotoxicity. All liver related AEs occurred in patients taking CBD-OS at 20mg/kg/day as add-on therapy to VPA (hepatic failures) or clobazam (hepatotoxicity). Acute hepatic failures lead to discontinuation.

The patient reported to have an SAE of 'acute hepatic failure' had an AST elevation preceded by fever and vomiting and experienced abdominal pain during the elevation. The lab values of peak AST of 4.6 × ULN, ALT of 1.6 × ULN, bilirubin of 1.1 × ULN, and INR = 1.09.

The patient was reported to have recovered from this event. The other patient for whom an AE of 'hepatic failure' was reported had no related symptoms and had results for peak ALT (3.1 × ULN), AST (1.4 × ULN), normal bilirubin (0.5 × ULN) and INR = 0.98. The patient was reported to have recovered from this event.

2. CNS related adverse events:

A. Somnolence, lethargy, sedation

In the controlled studies, The CBD-OS treatment led to somnolence, lethargy, and sedation in a substantial number of participants (First table in Safety). The potential mode of action causing was not clarified by the applicant. At request, the applicant presented results that provide evidence that these AEs were mostly transient and unrelated with age. Less than 2% of cases were classified as SAE, serious AE or AE leading to treatment discontinuation.

B. Psychiatric Disorders

In the controlled studies, an increase in irritability (5.5%) and aggression (3.9%) as non-serious non-severe AE was noted in a non-dose dependency pattern (First table in Safety). These adverse events occurred mainly within the two first weeks in CBD-OS treated patients. Patients experienced agitation and abnormal behaviour but no hallucination or psychosis. More importantly, there was not a dose-response relationship between CBD and the occurrence of these AE, and no patients discontinued due to these AE.

C. Cognition

As patients with DS and LGS often have reduced cognitive abilities, cognitive tests were performed in a relatively small proportion of the entire safety population and no firm conclusion could be drawn about the possible negative impact of CBD-OS on cognition.

D. Suicidality

No TEAEs related to suicidality (ideation or actual attempts) were reported in the 456 patients exposed to CBD-OS in the controlled DS or LGS trials or in the 644 patients exposed to CBD-OS in the OLE trial GWEP1415. In EAP (N=684), 2 patients had TEAEs meeting the search criteria for AESI suicidality: 1 patient (0.3%) in the CBD-OS > 20–30 mg/kg/day group (N=379) had TEAEs of suicidal ideation and suicidal behaviour and 1 patient (1.3%) in the CBD-OS > 40 mg/kg/day group (N=75) had a TEAE of suicidal ideation. Both patients had TEAEs after 14 weeks on treatment (). Both patients had TEAEs that were considered severe and serious

E. Abuse liability

At request, the Applicant provided results supporting that the CNS concentrations were likely not enough to induce euphoria, even in the case of concomitant use of cannabis for therapeutic or recreational purposes. Moreover, there was no difference in placebo vs. CBD-OS in reported AE-related abuse liability.

F. Seizure worsening

The percentage of patients who experienced seizure worsening may have been slightly higher in the CBD-OS groups (57.54 cases per 100 PY) than in the placebo group (better 53.30 cases per 100PY). There was not an increased risk of statues epilepticus in patients treated with CBD-OS as compared to placebo group (First table in Safety).

3. Adverse events of other organ systems

A. Diarrhoea, decreased appetite, body weight and BMI

The incidence of AESI diarrhea in Pool DS/LGS was 18.2% in the All CBD-OS group compared with 9.6% in the placebo group. The incidence in the CBD-OS 20 mg/kg/day group (21.2%) was higher than that in the 10 mg/kg/day group (12.9%) The incidence of AESI decreased appetite in Pool DS/LGS was 21.1% in the All CBD-OS group compared with 7.5% in the placebo group (First table in Safety). Compared to placebo, CBD-OS was associated with a smaller increase in mean body weight suggesting a slight impairment of weight gain in these growing children. However, no clear differences between CBD-OS and placebo were observed as regards BMI or Z-score during the relatively short phase 3 trials with regards to these measures. In the controlled studies, the incidences of both AE were higher for patients treated with VPA in placebo and particularly in the all CBD-OS group.

Table 47 Incidence of TEAEs proposed as ADRs by valproic acid use in controlled DS and LGS trials (Pool DS/LGS)

SOC PT VPA Use	All CBD-OS n (%)	Placebo n (%)
Total number of patients		
With VPA	149	99
Without VPA	174	128
Number of patients with any TEAE		
With VPA	132 (88.6)	70 (70.7)
Without VPA	152 (87.4)	94 (73.4)
Gastrointestinal disorders		
Diarrhoea		
With VPA	37 (24.8)	10 (10.1)
Without VPA	17 (9.8)	10 (7.8)
Metabolism and nutrition disorders		
Decreased appetite		
With VPA	44 (29.5)	7 (7.1)
Without VPA	21 (12.1)	4 (3.1)

B. Rash and DRESS syndrome

In the controlled trials, rash was noted as AE in 5.2% of patients in in the 20 mg/kg/day group and 2.2% in the 10 mg/kg/day group while those in placebo had 1%. Although the mechanism is not fully understood, there CBD-OS treatment may lead to rash. At request, the Applicant clarified that DRESS did not occur.

C. Urinary retention

In controlled trials, urinary retention was reported as AE in 3.0% and 2.1% of patients treated with 10mg/kg/day and 20 mg/kg/day, respectively, whereas no patient treated with placebo reported this AE.

D. Vital signs

Blood pressure, heart rate and body temperature showed no clinically relevant differences between the CBD-OS and placebo groups

Serious adverse event / deaths / other significant events

Fatal events in the phase III clinical trials

During GWEP1423, patient GWEP1423-V031 (CBD-OS 20 mg/kg/day) experienced convulsive status epilepticus, acute respiratory distress syndrome, aspiration pneumonia, acute respiratory failure with hypoxia and hypercapnia, left renal calculus, deep vein thrombosis, pneumothorax (left and right) and subsequently died. Medical conditions at screening included global developmental delays, spastic quadriplegia, pain related to feeding, and G-tube use, and had a history of acute respiratory distress syndrome and pneumonia (resolved at screening).

Fatal events in the OLE

During the OLE phase, there were six fatal TEAEs.

Patient narratives:

• Patient in group CBD-OS ≤ 20 mg/kg/day modal dose with medical history of DS, lack of normal physiological development, autism spectrum disorder, and low energy. On OLE Day 230, the patient was found face down, apneic, and unresponsive in bed. It was reported that the patient had a normal day and ate lunch before going to bed for a rest. The working diagnosis was SUDEP.

• Patient in group CBD-OS ≤ 20 mg/kg/day modal dose with medical history of DS, developmental delay. On OLE Day 91, the patient had attended a routine study visit and appeared well. In the morning of OLE Day 94, the patient was found dead in bed due to SUDEP (as per the death certificate).

• Patient in group CBD-OS ≤ 20 mg/kg/day modal dose with medical history of LGS, gastrostomy, anoxic brain damage, cerebral palsy, gastroesophageal reflux disease, failure to thrive, feeding difficulties, and obstructive sleep apnoea syndrome. On OLE Day 29 the patient had vomiting; open-label IMP was discontinued on this day. The patient subsequently developed difficulty breathing on OLE Day 30 with acute respiratory distress and shock. The patient was intubated due to acute respiratory failure and treated for pneumonia. The patient started to wean from BiPAP on OLE Day 42, and completed a course of antibiotics on OLE Day 43. On OLE Day 45, the patient vomited and had progressive respiratory distress during the evening. The patient died on OLE Day 47 due to respiratory failure, a complication of aspiration pneumonia.

• Patient in group CBD-OS ≤ 20 mg/kg/day modal dose with medical history of LGS, chronic lung disease, aspiration pneumonia, microcephaly, cortical injury, cerebral palsy, global developmental delay, gastroesophageal reflux disease, Nissen fundoplication and repair, gastrostomy, vagal nerve

stimulator implantation, and obstructive sleep apnoea syndrome. On OLE Day 144, the patient was found to have severe bowel obstruction, sepsis, and fever. Emergency surgery found necrotic dead small bowel. The patient was unstable after surgery and subsequently died on OLE Day 145.

• Patient in groupCBD-OS > 20 mg/kg/day modal dose with medical history of LGS, attention deficit hyperactivity disorder, gastroesophageal reflux disease, developmental delay, MRSA, right craniotomy and complete corpus callosotomy, respiratory distress syndrome in the newborn, apnoea of prematurity, and incontinence of faeces and urine. On OLE Day 98, the patient had 4 seizures in the morning before being taken to the emergency room, and was diagnosed with respiratory syncytial virus, reactive airway disease and decreased urinary output. On OLE Day 99, the patient was found in the morning to have passed away during sleep.

• Patient in group CBD-OS > 20 mg/kg/day modal dose with medical history of LGS, congenital right temporal haemorrhage, encephalopathy, global developmental delay, spastic quadriparesis, gastrostomy tube placement, uncontrolled myoclonic seizures, uncontrolled tonic seizures, unwitnessed seizures when alone, and was microcephalic. Viral respiratory infection on OLE Day 54 and bronchiolitis on OLE Day 56. They recovered from the viral respiratory infection on OLE Day 58. On the morning of OLE Day 78, the patient was found dead. The cause of death was reported as complications of seizure disorder due to perinatal hypoxic ischemic encephalopathy. The death was classified as natural.

EAP:

Overall in Pool EAP, 12 patients (1.8%) died. The highest incidence of fatal TEAEs in Pool EAP was in the Respiratory, thoracic and mediastinal disorders SOC (0.9%), followed by the Nervous system disorders SOC (0.6%) and then the General disorders and administration site conditions SOC (0.4%).

Serious adverse events

Serious adverse events occurred more commonly in the CBD-OS groups than in the placebo groups. The serious adverse events were increased within the CNS-SOC, infections- and infestations-SOC, investigations (including liver-related parameters), respiratory- and general disorders SOCs, gastrointestinal- and metabolism and nutrition-SOC. The pattern of serious adverse events reflects the pattern of reported adverse events.

Phase II/III:

Table 48 Serious TEAEs reported in >1 patient in the all CBD-OS group in controlled DS and LGS trials (Pool DS/LGS)

SOC PT	CBD-OS 5 mg/kg/day (N=10) n (%)	CBD-OS 10 mg/kg/day (N=139) n (%)	CBD-OS 20 mg/kg/day (N=307) n (%)	All CBD-OS (N=456) n (%)	Placebo (N=292) n (%)
Patients with at least 1 serious TEAE	**1 (10.0)**	**28 (20.1)**	**61 (19.9)**	**90 (19.7)**	**26 (8.9)**
Gastrointestinal disorders	**0**	**1 (0.7)**	**7 (2.3)**	**8 (1.8)**	**1 (0.3)**
Constipation	0	0	3 (1.0)	3 (0.7)	0
General disorders and administration site conditions	**0**	**3 (2.2)**	**6 (2.0)**	**9 (2.0)**	**1 (0.3)**
Pyrexia	0	3 (2.2)	2 (0.7)	5 (1.1)	1 (0.3)
Fatigue	0	0	2 (0.7)	2 (0.4)	0
Infections and infestations	**0**	**10 (7.2)**	**22 (7.2)**	**32 (7.0)**	**5 (1.7)**
Pneumonia	0	6 (4.3)	8 (2.6)	14 (3.1)	0
Viral infection	0	1 (0.7)	3 (1.0)	4 (0.9)	1 (0.3)
Adenovirus infection	0	1 (0.7)	1 (0.3)	2 (0.4)	0
Sepsis	0	0	2 (0.7)	2 (0.4)	0
Injury, poisoning and procedural complications	**0**	**1 (0.7)**	**2 (0.7)**	**3 (0.7)**	**0**
Toxicity to various agents	0	1 (0.7)	1 (0.3)	2 (0.4)	0
Investigations	**0**	**2 (1.4)**	**13 (4.2)**	**15 (3.3)**	**2 (0.7)**
Aspartate aminotransferase increased	0	1 (0.7)	7 (2.3)	8 (1.8)	0
Alanine aminotransferase increased	0	0	6 (2.0)	6 (1.3)	0
Gamma-glutamyltransferase increased	0	0	4 (1.3)	4 (0.9)	0
Liver function test abnormal	0	0	3 (1.0)	3 (0.7)	0
Transaminases increased	0	1 (0.7)	1 (0.3)	2 (0.4)	0
Metabolism and nutrition disorders	**0**	**2 (1.4)**	**3 (1.0)**	**5 (1.1)**	**2 (0.7)**
Decreased appetite	0	1 (0.7)	2 (0.7)	3 (0.7)	0
Nervous system disorders	**1 (10.0)**	**16 (11.5)**	**26 (8.5)**	**43 (9.4)**	**19 (6.5)**
Status epilepticus	1 (10.0)	12 (8.6)	15 (4.9)	28 (6.1)	15 (5.1)
Convulsion	0	4 (2.9)	6 (2.0)	10 (2.2)	3 (1.0)
Somnolence	0	2 (1.4)	5 (1.6)	7 (1.5)	0
Lethargy	0	0	3 (1.0)	3 (0.7)	0
Seizure cluster	0	1 (0.7)	1 (0.3)	2 (0.4)	3 (1.0)
Patients with at least 1 serious TEAE	**1 (10.0)**	**28 (20.1)**	**61 (19.9)**	**90 (19.7)**	**26 (8.9)**
Respiratory, thoracic and mediastinal disorders	**0**	**2 (1.4)**	**11 (3.6)**	**13 (2.9)**	**4 (1.4)**
Pneumonia aspiration	0	1 (0.7)	3 (1.0)	4 (0.9)	1 (0.3)
Acute respiratory failure	0	0	3 (1.0)	3 (0.7)	0
Hypoxia	0	1 (0.7)	2 (0.7)	3 (0.7)	1 (0.3)
Sleep apnoea syndrome	0	1 (0.7)	1 (0.3)	2 (0.4)	0

Note: Safety analysis set.

Laboratory findings

In the RCT and the OLE trial, mean decreases in haematology laboratory values over time were observed across the LGS and DS patient populations. However, they were not determined to be of clinical significance.

The increase in hepatic enzymes has been previously discussed together with liver-related AE.

For all other biochemistry laboratory such as creatinine levels values, mean changes over time and potentially clinically significant laboratory abnormalities over time were similar for all treatment groups and across the LGS and DS patient populations observed in Pool DS/LGS

Safety in special populations

Age

Adverse events according to age:

Table 49 Incidence of serious TEAEs and TEAEs leading to discontinuation by age group in controlled DS andLGS trials (pool DS/LGS)

Type of TEAE Age Group	All CBD-OS n (%)	Placebo n (%)
Total number of patients		
2–5 years	51	38
6–11 years	117	79
12–17 years	80	57
≥ 18 years	75	53
Number of patients with any serious TEAE		
2–5 years	12 (23.5)	3 (7.9)
6–11 years	22 (18.8)	3 (3.8)
12–17 years	14 (17.5)	5 (8.8)
≥ 18 years	12 (16.0)	5 (9.4)
Number of patients with any TEAE leading to discontinuation		
2–5 years	10 (19.6)	1 (2.6)
6–11 years	9 (7.7)	0
12–17 years	7 (8.8)	1 (1.8)
≥ 18 years	4 (5.3)	1 (1.9)

Note: Percentages are based on the number of patients in the subgroup.
Note: Safety analysis set.

The risk of any TEAE and any TEAE leading to discontinuation of was higher for CBD-OS than for placebo in all age groups. The risk was higher in the younger age groups than in the older age groups

Gender

The population of each trial comprised between 52% and 57% male and 43%–48% female patients. There were no marked differences in outcome between male and female patients.

Weight

CBD-OS is dosed according to weight, i.e. 10 mg/kg/day or 20 mg/kg/day. Hence, there were no differences between treatment groups due to weight of patients.

DS and LGS

Overall, there were no differences in the CBD-OS safety profile between DS and LGS patients.

Race or region

Mainly Caucasians were included, i.e. White/Caucasian 88–90%. Differences according to race and genetic polymorphism are unknown.

Use in Pregnancy and Lactation

No studies have been conducted in pregnant or lactating women

Impaired renal or liver function

A phase I study was conducted in patients with impaired renal (mild, moderate, severe) or impaired liver (mild, moderate, severe) function. No safety issues were observed in this study. However, from the phase II/III studies it is evident that CBD is hepatotoxic and that the severity of the hepatotoxic effect is increased in patients with impaired liver function at baseline (please refer to the section of liver-related adverse events).

Immunological events

Rash, presumably a Type IV hypersensitivity reaction, was observed in approx. 1% of the CBD-OS treated population as compared to none in the placebo group.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions have been investigated in the PK-section of this AR. Further, valproate increased the hepatotoxicity of CBD (please refer to assessment of liver-related adverse events)

Discontinuation due to adverse events

TEAEs leading to discontinuation were more common among CBD-OS treated patients compared to placebo treated patients. Elevated liver enzymes were the leading cause of discontinuation but gastrointestinal disorders and nervous system disorders were also common reasons for discontinuation.

Phase II/III:

Table 50 TEAEs leading to discontinuation reported in >1 patient in all CBD-OS group in controlled DS and LGS trials (pool DS/LGS)

SOC PT	CBD-OS 5 mg/kg/day (N=10) n (%)	CBD-OS 10 mg/kg/day (N=139) n (%)	CBD-OS 20 mg/kg/day (N=307) n (%)	All CBD-OS (N=456) n (%)	Placebo (N=292) n (%)
Patients with at least 1 TEAE leading to discontinuation	**0**	**2 (1.4)**	**33 (10.7)**	**35 (7.7)**	**3 (1.0)**
Gastrointestinal disorders	**0**	**0**	**7 (2.3)**	**7 (1.5)**	**0**
Diarrhoea	0	0	2 (0.7)	2 (0.4)	0
Vomiting	0	0	2 (0.7)	2 (0.4)	0
General disorders and administration site conditions	**0**	**1 (0.7)**	**7 (2.3)**	**8 (1.8)**	**0**
Fatigue	0	0	5 (1.6)	5 (1.1)	0
Pyrexia	0	1 (0.7)	2 (0.7)	3 (0.7)	0
Investigations	**0**	**1 (0.7)**	**17 (5.5)**	**18 (3.9)**	**1 (0.3)**
AST increased	0	1 (0.7)	9 (2.9)	10 (2.2)	0
ALT increased	0	1 (0.7)	8 (2.6)	9 (2.0)	0
GGT increased	0	0	4 (1.3)	4 (0.9)	0
Liver function test abnormal	0	0	3 (1.0)	3 (0.7)	1 (0.3)
Transaminases increased	0	0	3 (1.0)	3 (0.7)	0
Metabolism and nutrition disorders	**0**	**0**	**7 (2.3)**	**7 (1.5)**	**0**
Decreased appetite	0	0	6 (2.0)	6 (1.3)	0
Nervous system disorders	**0**	**0**	**12 (3.9)**	**12 (2.6)**	**2 (0.7)**
Somnolence	0	0	7 (2.3)	7 (1.5)	0
Convulsion	0	0	5 (1.6)	5 (1.1)	1 (0.3)
Hypotonia	0	0	2 (0.7)	2 (0.4)	0
Lethargy	0	0	2 (0.7)	2 (0.4)	0
Psychiatric disorders	**0**	**0**	**3 (1.0)**	**3 (0.7)**	**1 (0.3)**
Aggression	0	0	2 (0.7)	2 (0.4)	0
Skin and subcutaneous tissue disorders	**0**	**1 (0.7)**	**2 (0.7)**	**3 (0.7)**	**0**
Rash	0	0	2 (0.7)	2 (0.4)	0

Note: Safety analysis set.

2.6.1. Discussion on clinical safety

The safety database is considered sufficiently large considering that DS and LGS are orphan diseases. It includes 456 DS and LGS patients (DS;N=221 and LGS;N=235) patients from four pivotal Phase III

studies. Additionally, 27 DS patients from a phase II study and 630 patients in the open-label extension, OLE, study. Of the 630 patients in the OLE, 353 had not previously been exposed to CBD-OS.

In the phase 3 clinical trials the patient years of exposure to CBD-OS 10 mg/kg/day were 36.26 PY while exposure to 20 mg/kg/day was 76.45 PY. Additional supportive safety data are available from 322 patients exposed to CBD-OS in a dose range of 200 mg to 6000 mg in phase I studies in healthy subjects and patients with renal or hepatic impairment. Further safety data are available from an expanded access and compassionate use programs among patient with a serious or life-threatening condition with no other comparable or satisfactory therapeutic options and from smaller studies in other patient groups. In total, 1928 patients have been exposed to CBD-OS.

However, exact exposure to CBD-OS in patients is unknown, since the uptake of CBD-OS is increased by a factor of four, if administered with food. Yet, the study protocols did not instruct the caregivers/patients to take CBD-OS with meals. Consequently, the participants may have been exposed to different amounts of CBD-OS depending on whether they administered CBD-OS with food or not. Nevertheless, the available data show an overall positive relationship between the administered dose and observed number and severity of adverse events. This supports that in individual children a gradual increase of CBD-OS will lead to a gradually increasing risk of emerging safety events or of the severity of safety events. Hence, under conditions of a sufficient safety-monitoring schedule and a gradual increase of CBD-OS dose given consistently with or without a meal, specific emerging safety issues appear manageable. The SmPC and the PIL emphasizes that CBD-OS should be taken consistently either with or without food to assure that children are not accidently exposed to several fold higher doses of CBD.

Comparing CBD-OS to placebo, the discontinuation rate was higher in the CBD-OS group (8%) than in the placebo group (1%). The number of patients who experienced a serious adverse event was also higher in the CBD-OS group (20%) than in the placebo group (11%). Adverse events were reported by 88% in the CBD-OS group as compared to 76% in the placebo group. When comparing the CBD-OS 20 mg/kg/day group to the CBD-OS 10 mg/kg/day group, the incidences of discontinuations, serious adverse events, and common adverse events were higher in the CBD-OS 20 mg/kg/day group. Adverse event such as somnolence, decreased appetite, diarrhoea, and increased hepatic transaminase were common in the CBD-OS groups and occurred more frequently than in the placebo group. Analysis of safety in subgroups with different underlying disease, DS or LGS, did not show any clear differences across the different adverse events. Hence, CBD-OS may be used in both DS and LGS patients while adhering to similar precautions as specified in section 4.3 and 4.4 in the SmPC.

The main safety issue with the use of CBD-OS is hepatotoxicity. The incidence of TEAEs meeting the search criteria for AESI abnormal liver TEAEs was 14.9% in the All CBD-OS group (N=456) compared with 3.1% in the placebo group (N=292). The overall AESI incidence was higher in the CBD-OS 20 mg/kg/day group (17.6%; N=307) than the 10 mg/kg/day dose group (9.4%; N=139).

A very clear dose-response relationship with more cases in the 20 mg/kg/day group than in the 10 mg/kg/day group further supports the hepatotoxicity of CBD-OS. The Applicant has provided sufficient additional information to document that no patients in the clinical studies or in the EAP died due to a hepatotoxic effect of CBD-OS.

Some information on hepatic synthesis function have been provided, e.g. INR was elevated in approx. 10% of the population in the OLE trials, whereas the frequencies of abnormal INR levels were comparable between the CBD-OS and placebo groups in the phase II/III trials. However, the Applicant provided additional information regarding transaminases levels and the corresponding levels of INR, bilirubin, and albumin in individual patients. This has clarified that in some patients the level of bilirubin increased along with transaminase increases even though bilirubin did not increase above the

upper limit of normal. In addition, it has been clarified that among a few of the patients, who experienced transaminase increases, the INR rose to levels slightly above the upper limit of normal. Unfortunately, measurements of INR and bilirubin were not always made at a relevant time point. The schedule for liver related blood tests comprised four time points after baseline; at 2 weeks, 4 weeks, 8 weeks, and 14 weeks after start of the treatment. Nevertheless, the Applicant has provided sufficient additional information to conclude that the synthesis function was only affected in a few patients with ALT > 5 x ULN. Furthermore, the Applicant has provided an overview of the actual data on recovery from ALT/AST level > 5 x ULN. Hereby, the Applicant has clarified that the CBD-induced liver injury, as assessed by transaminase elevations, was transient if CBD was discontinued/reduced in due time Additionally, the Applicant has provided more information on the patients, who experienced transaminase elevations more than three months after initiation of CBD-OS. Although there were no IgG measurements conducted, it was clarified that these patients did not suffer from a CBD induced "autoimmune-like-DILI". Liver toxicity is primarily hepatocellular and not directed at the biliary system. However, in an uncontrolled study in patients in a different non-epilepsy indication, 2 elderly patients experienced elevations of alkaline phosphatase levels above 2 times the ULN in combination with transaminase elevations. The elevations resolved after discontinuation of Epidyolex.

The hepatotoxicity of CBD-OS is aggravated in patients with an affected liver function at baseline and particularly in patients concomitantly treated with valproate. Patients who did not have an increase in ALT at baseline and were not concomitantly treated with valproate had only a slight increase in ALT when treated with CBD-OS 20 mg/kg/day (3% with ALT > 3x ULN) as compared to placebo (1% with ALT > 3x ULN). This is unlike patients who did have an increase in ALT at baseline and were not treated with valproate (9% with ALT > 3x ULN). In the placebo group it was 0%. However these estimations were based on low numbers. At the same time, there is little doubt that the combination of valproate and CBD-OS (20% with ALT > 3x ULN) substantially increases the risk of hepatotoxicity as compared to CBD-OS without concomitant valproate (9% as noted above). Finally, it is also clear that the combination of CBD-OS and valproate in patients with signs of an affected liver function at baseline, significantly increases the risk of hepatotoxicity, even if the numbers of patients in this category is low: In the CBD-OS 20 mg/kg/day concomitantly treated with valproate and with baseline ALT > ULN, 64% of the population developed ALT > 3x ULN. The toxicity of CBD-OS in doses of 10 mg/kg/day is significantly lower. Consequently, the SmPC recommends targeted dose maintenance of 10 mg/kg/day. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a much lesser extent than valproate.

The liver related adverse events occurred mainly in the weeks 2-7 after the start of the treatment with CBD-OS. However, some liver related adverse events occurred earlier and some events, especially in patients concomitantly treated with valproate, occurred as late as six month or more after the start of the treatment. The Applicant has provided additional information to document that only a minority of the patients experienced two peaks of elevated transaminases over the duration of the phase III + OLE trials. Especially in patients concomitantly treated with valproate, the onset, the duration, and the possible reoccurrence of liver injury varied considerably. A standard monitoring of hepatocellular function at 1 month, 3 months and 6 months after treatment initiation is proposed for patients treated with 10 mg/kg/day without baseline transaminase elevations and not using valproate. Some patients are subject to an intensified monitoring schedule (2 weeks, 1 month, 2 months, 3 months and 6 month) as they are at increased risk of hepatocellular injury during treatment with Epidyolex. The intensified monitoring schedule applies to patients concomitantly treated with valproate and patients with baseline transaminase elevations. Upon increase of their Epidyolex dose greater than 10 mg/kg/day, serum transaminases and total bilirubin levels should also be obtained according to the same intensified monitoring schedule Further, the use of CBD is contraindicated in patients with baseline transaminase elevations > 3 X ULN and bilirubin > 2 X ULN.

The Applicant has discussed the pathophysiological reason for the interaction between CBD-OS and valproate. Although investigations are still ongoing, it appears that both valproate and CBD have an inhibitory effect on mitochondrial respiration. However, the Applicant is conducting a follow-up study on the interaction between CBD-OS and valproate and has agreed to provide the results from this study when available. Finally, the CBD oral solution contains alcohol that will lead to an alcohol intake above the upper limit of acceptance for children up to six years of age at the 20 mg/kg/day dose. The long-term effect of this is unknown but upon request the Applicant has agreed to provide additional data if available.

In comparison, the age of the patients or the underlying disease (healthy individuals vs. DS vs. LGS vs. other conditions tested in the EAP) did not appear to influence the degree of hepatotoxicity of CBD-OS treatment. However, it cannot be excluded that other AEDs than valproate and to a lesser extent clobazam, may also increase the hepatotoxic effect of CBD-OS but this could not be assessed due to the low number of subjects in strata of different combinations of other AEDs.

Another safety issue is the influence of CBD-OS on the CNS. Somnolence, sedation, and lethargy are frequently recorded, especially in combination with clobazam. At least one of these events occurred in approx. 40% of patients treated with the combination of Epidyolex and clobazam regardless of whether Epidyolex was administered as 10 or 20 mg/kg/day. In phase II/III trials, 3% discontinued for this reason. Aggression and/or irritability occurred in 9% of the CBD-OS treated population, whereas agitation and abnormal behaviour occurred in approx. 5% of the CBD-OS treated population. However, only three patients (1%) discontinued due to aggression and none discontinued due to agitation and abnormal behaviour. Psychosis with hallucinations was not reported. The cases of these adverse events occurred mainly within the two first weeks in CBD-OS treated patients in the phase II/III trials. The sudden occurrence in the CBD-OS group after onset of CBD-treatment indicates a casual relation to the treatment. The Applicant has provided an additional discussion to clarify that somnolence, sedation and lethargy appear transient. In comparison, it is not fully clarified if aggression and abnormal behaviour are transient. However, the Applicant has included the risk of aggression and abnormal behaviour to the section 4.8 On the other hand, regarding the SAE status epilepticus, high number of patients reported this serious event in both the Epidyolex group and placebo group. It should be conveyed to the treating physicians that although there may be a reduction in seizures frequency, no change in frequency of status epilepticus occurrence was observed in clinical trials. Based on these results, a warning regarding similar risk of Status epilepticus in the Epidyolex and placebo groups is included in Section 4.4 in SmPC.

It is uncertain whether CBD-OS has an effect on cognition and behavioural pattern others than those mentioned above. Currently accepted test especially for cognition can only be conducted in patients with normal levels of cognition and normal pattern of behaviour. As patients with DS and LGS often have reduced cognitive abilities, the tests were performed in a relatively small proportion of the entire safety population and no firm conclusion could be drawn. However, the Applicant has discussed the possibility of a decrease in cognitive function, which with the currently available data cannot be clarified. Therefore, the possible influence on cognitive development has been added to the RMP as a potential risk. Considering the very limited data regarding later development of children with LGS and in particular with DS and associated unknown long-term impact of CBD-OS on cognitive and endocrine functions, potential undesirable effects of CBD-OS on psychological development and endocrine system in later childhood may occur.

There are three reports on suicidal ideation/behaviour, two in the EAP and one in the RCT. However, the applicant has provided additional information to clarify a false report of a completed suicide in the RCT. Thus, CBD-OS might increase the risk of suicidal ideation/behaviour, which is a known class effect, but the patients in the EAP have competing risks for developing suicidal ideation/behaviour. This is reflected in the SmPC section 4.4.

CBD-OS contains a small amount of THC. The applicant has provided an additional discussion the concentrations of THC and CBD in CNS to address the risk of abuse. A warning regarding the abuse potential is currently not warranted.
The applicant has provided an additional discussion on how the amount of THC probably is too low to affect the developing brain. Although chronic cannabis use possibly leads to neuropsychological decline in some individuals, the effect of CBD on the developing brain in the amounts administered in the treatment of DS and LGS is not possible to determine.
Regarding hypersensitivity, it appears that CBD-OS treatment may lead to (a mainly T cell mediated) hypersensitivity reaction in approx. 1% of the population. However, in some studies rash was recorded in up to 23% of the CBD-OS treated population as compared to none in other studies. The Applicant provided additional information regarding this difference of rash incidences. Since rash and the risk of hypersensitivity reactions are already mentioned in the SmPC and the RMP, the issue is not pursued any further. In specific patients, the Applicant has clarified that DRESS did not occur.

In total, there were seven deaths. There was one death in the phase III trials, the CBD-OS 20 mg/kg/day group, and there were six deaths in the OLE. The causes of deaths were sudden death in epilepsy (N=2), bowel obstruction with necrotic bowel and septic shock (N=1), seizure disorder with cerebral oedema and pulmonary oedema (N=1) and respiratory distress and aspiration pneumonia (N=3). The respiratory distress and aspiration pneumonia in three patients followed an episode of vomiting, an episode of status epilepticus, and as a consequence of seizure disorder due to perinatal hypoxic ischemic encephalopathy, respectively. The applicant has provided narratives and laboratory data to justify that none of the deaths were related to CBD-OS treatment.

The applicant has provided additional information and discussed additional issues such as an imbalance between CBD-OS groups and placebo with regard to diarrhoea, decreased appetite, urinary retention. The risk of urinary retention as well as of decreased appetite and a related loss of weight cannot be excluded and have been included in the RMP as a potential risk (urinary retention) and described further in the SmPC (weight loss, risk of reduced height gain). Small decreases of red blood cell counts, red blood cell volume, and haematocrit were observed over a year of treatment. However, the decreases did not continue and were considered not clinically relevant. Changes of creatinine levels and occurrence of pyrexia were noted but were considered not to be of significant clinical relevance.
Additional long-term safety data have been provided. In the original submission, the long term data of study GWEP1415 were not included. Comparing the incidence of adverse events in the placebo-controlled trials with the long term data, the incidence of adverse events per time on study remained unchanged throughout the studies.

Conclusions on the clinical safety

The safety database is considered adequate since DS and LGS are orphan diseases. It includes 456 DS and LGS patients (DS;N=221 and LGS;N=235) patients from four pivotal Phase III studies. Additionally, 27 DS patients from a phase II study and 630 patients in the open-label extension, OLE, study. Of the 630 patients in the OLE, 353 had not previously been exposed to CBD-OS. In the phase 3 clinical trials, the patient years of exposure to CBD-OS 10 mg/kg/day were 36.26 py while exposure to 20 mg/kg/day was 76.45 py. The most common adverse events comprise nervous system disorders in 42% (10 mg/kg/day), including somnolence, sedation, lethargy, and convulsion, changed laboratory parameters related to liver function in 21% (10 mg/kg/day), and psychiatric disorders in 17% (10 mg/kg/day), including aggression and abnormal behaviour. The size of the safety database makes it likely that rare adverse events or adverse events occurring after longer exposure have not been captured.

There is a pronounced effect of food on the bioavailability (and consequently plasma concentration) of CBD, which is addressed by instructing caregiver that CBD-OS is taken consistently either with or without meals. The main safety issue with CBD-OS is hepatotoxicity, which in some instances was severe and serious, resulting in hospitalisation. The risk of hepatotoxicity is increased in patients taking Valproate and to a lesser extent in patients taking clobazam, especially if the baseline liver function is affected.

The CHMP considers the following measures necessary to address issues related to safety:

There are restrictions to the use of CBD-OS for patients at increased risk of adverse reactions; patients concomitantly treated with valproate acid, patients with concomitant transaminase elevations, and patients with signs of DILI. These patients are subject to an intensified monitoring schedule. Further, the risk of somnolence and sedation in approx. 40% of the treated population is emphasised.

A follow-up study on the interaction between CBD-OS and valproate is on-going and the final study report should be provided once available.

2.7. Risk Management Plan

Table 48 – Summary table of the 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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
	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		December 2019 Annually June 2026
	Collect data on pregnancy and lactation	Pregnancy and lactation		Ongoing - will be discussed in Periodic Safety Update Reports

Risk minimisation measures

Table 49 - Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatocellular injury	Routine Risk Minimisation: SmPC Section 4.4: Special warnings and precautions for use SmPC Section 4.8: Undesirable effects Package Leaflet Section 2 Available by prescription only	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 - June 2026
Somnolence and sedation	Routine Risk Minimisation: SmPC Section 4.4: Special warnings and precautions for use SmPC Section 4.8: Undesirable effects Package Leaflet Section 2 Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Lethargy	Routine Risk Minimisation: SmPC Section 4.8: Undesirable effects Package Leaflet Section 2 Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Pneumonia	Routine Risk Minimisation: SmPC Section 4.8: Undesirable effects Available by prescription only	Routine activities including: Specific detailed adverse reaction follow-up for pneumonia reports. Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Rash hypersensitivity reactions	Routine Risk Minimisation: SmPC Section 4.8: Undesirable effects Available by prescription only	Routine activities including: Specific detailed adverse reaction follow-up for rash hypersensitivity reactions. Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Suicidality	Routine Risk Minimisation: SmPC Section 4.4: Special warnings and precautions for use Package Leaflet Section 2 Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Seizure worsening	Routine Risk Minimisation: 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	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Aggression	Routine Risk Minimisation: SmPC Section 4.8: Undesirable effects Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Euphoria	Routine Risk Minimisation: SmPC Section 5.1: Pharmacodynamic properties Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Impact on cognitive development	Routine Risk Minimisation: Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026
Urinary retention	Routine Risk Minimisation: Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Exposure during pregnancy and lactation	Routine Risk Minimisation: SmPC Section 4.6: Fertility, Pregnancy and Lactation Available by prescription only	Routine activities Additional activities including: Participation in AED Pregnancy Registries including: • European and International Registry of Antiepileptic Drugs and Pregnancy • North American Antiepileptic Drug Pregnancy Registry
Long-term safety	Routine Risk Minimisation: Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing observational cohort study – final CSR June 2026

Conclusion

The CHMP and PRAC considered that the RMP version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant requested alignment of the PSUR cycle with the international birth date (IBD). The IBD is 25.06.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

With the responses to the 2nd D180 List of Outstanding Issues the applicant has withdrawn the claim that cannabidiol is a NAS. A NAS status was no longer applied for during the evaluation.

At the time of the withdrawal of the NAS claim, it was the CHMP's view that based on the review of the data, the active substance cannabidiol contained in the medicinal product Epidyolex is not to be

qualified as a new active substance in itself or in comparison to cannabidiol (herbal extract of Cannabis sativa L.), which is contained in the medicinal product, Sativex oromucosal spray, previously authorized in the European Union. The CHMP concluded that cannabidiol in both products are structurally identical, hence the patients are exposed to the same therapeutic moiety, i.e. cannabidiol

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Lennox–Gastaut Syndrome (LGS) is a rare epileptic encephalopathy. The onset of LGS usually occurs between 3 and 5 years of age and is characterised by the presence of multiple seizure types (predominantly tonic, atonic, and atypical absence seizures), slow electroencephalogram spike-waves with abnormal background activity when awake, and fast polyspikes during sleep. Other seizure types can occur in LGS, including generalised tonic–clonic, focal, and myoclonic seizures. These seizure types have onset in childhood, and many persist into adulthood. Status epilepticus (SE) may occur in some patients with LGS. LGS can be subdivided into cases of known origin (genetic, structural, metabolic, immune and infectious) and idiopathic cases, in which the first clinical sign is often the occurrence of abrupt falls (commonly referred to as drop attacks/seizures). Drop seizures are common in LGS and can lead to physical injury. Cognitive impairment is apparent in ≥ 75% of all LGS patients by 5 years post onset, and behavioural and psychiatric comorbidities (including attention deficit/hyperactivity disorder and aggressive behaviour) are common. Children and adolescents with LGS have an increased risk of death. Neurological comorbidity including prolonged seizures and SE are correlated with mortality and, in particular, sudden unexpected death in epilepsy (SUDEP). While there are 4 approved treatments for LGS in the European Union (EU), most patients with LGS continue to experience drug-resistant epilepsy (DRE).

Dravet Syndrome (DS), also known as severe myoclonic epilepsy in infancy, is a rare form of severe DRE with onset in early childhood. DS is characterised by a variety of treatment-resistant seizures (febrile and afebrile, generalized and unilateral, clonic or tonic–clonic) that occur in the first year of life. Onset usually occurs between 4 and 8 months of age in an apparently normal infant and is often triggered by fever. In addition to convulsive seizures, other seizure types appear between the ages of 1 and 4 years, including myoclonic seizures, focal seizures, and atypical absences. Status epilepticus may occur at initial presentation or later in the clinical course. By late childhood, the seizure profile will often have stabilised. Significant developmental delay becomes apparent from the second year onwards and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common. Intellectual impairment affects nearly all patients and is severe in 50% of cases. Dependency in adulthood is common. Approximately 75% of patients with DS have mutations in

the voltage-gated sodium channel α1 subunit gene (SCN1A); mutations in other genes have been reported in the remaining 25% of SCN1A-negative DS patients, e.g., PCDH19 (protocadherin-19). Long-term seizure outcomes in DS are poor, with many patients still having seizures in adulthood. Death during childhood is common in DS. SUDEP and SE are the most common causes of death in DS, with drowning and accidental death following seizures also common causes. Risk factors for SUDEP include frequent generalized tonic–clonic seizures, early seizure onset, polytherapy, and developmental delay, all of which are common in DS.

3.1.2. Available therapies and unmet medical need

Felbamate, lamotrigine (LTG), topiramate and rufinamide are approved in the EU as adjunctive therapy for treatment of LGS. Only stiripentol (STP), when taken in conjunction with sodium valproate (VPA) and clobazam (CLB), is currently approved in the EU for the treatment of DS; neither VPA nor CLB are approved for LGS or DS specifically, but both are approved for use in epilepsy in the EU, and widely used in both indications. In both indications, VPA is often used to prevent the initial recurrence of convulsive seizures, and benzodiazepines (e.g., diazepam, midazolam, clonazepam, or CLB) are frequently coadministered to limit the duration of long-lasting seizures. Second-line and later options in DS typically include STP, topiramate, ketogenic diet, levetiracetam (LEV), bromides, and vagus nerve stimulation (VNS), while LTG, rufinamide, lacosamide, and felbamate are also used in LGS. Polytherapy is common in both indications. Of note, patients with DS may be prone to seizure exacerbation with sodium channel modulators such as carbamazepine, oxcarbazepine, LTG, phenytoin, and vigabatrin.

In both indications, sufficient seizure control may be difficult to achieve, and thus there is a need for new therapies with a different mode of action.

3.1.3. Main clinical studies

The clinical development program supporting the efficacy of CBD-OS comprises 2 randomised, placebo-controlled trials in LGS; 1 investigating 10 and 20 mg/kg/day CBD-OS (GWEP1414) and 1 investigating 20 mg/kg/day CBD-OS (GWEP1423), and 2 randomised, placebo-controlled trials in DS; 1 investigating 10 and 20 mg/kg/day CBD-OS (GWEP1424) and 1 investigating 20 mg/kg/day CBD-OS (GWEP1332 Part B).

The pivotal trials consisted of a 4-week baseline period, followed by a 14-week treatment period comprising a 2-week titration (dose escalation) period and a 12-week maintenance (stable dosing) period. Patients who discontinued the investigational medicinal product (IMP) were to taper the dose over a 10-day period, with a safety follow-up 4 weeks after final dose.

All pivotal trials included male and female patients who were taking 1 or more AEDs which had been maintained at a stable dose for at least 4 weeks prior to screening. All medications or nonpharmacological interventions for epilepsy (including ketogenic diet and VNS) were to remain stable throughout the trial. For enrolment in the LGS trials, patients had to be aged 2–55 years (inclusive), with a clinical diagnosis of LGS. This included written documentation of having met electroencephalographic diagnostic criteria (slow < 3.0 Hz] spike-and-wave pattern) during the patient's history and evidence of more than 1 type of generalized seizure, including drop seizures, for at least 6 months. Patients had to have documented failures on more than 1 AED and had to have experienced at least 2 drop seizures each week of the 4-week baseline period. A drop seizure was defined as an attack or spell (atonic, tonic, or tonic–clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface. For enrolment in the DS trials, patients had to be aged 2–18 years (inclusive), with a clinical diagnosis of DS confirmed by a committee of independent experts and had to have experienced 4 or more

convulsive seizures during the 4-week baseline period. A convulsive seizure was defined as a tonic, clonic, tonic–clonic, or atonic seizure.

All pivotal trials were double-blind. Randomisation was stratified by 4 age groups for the LGS trials (2 to < 6, 6 to < 12, 12 to < 18, and 18 to < 56 years) and 3 age groups for the DS trials (2 to < 6, 6 to < 13, and 13 to < 19 years). Primary and key secondary endpoints centred primarily on changes in seizure frequency, and were based on daily seizure reports. The number and type of seizures experienced by a patient were reported daily using a telephone-based IVRS. The primary endpoints were percentage change from baseline in drop seizure frequency for the LGS trials, and convulsive seizure frequency for the DS trials during the treatment period, for CBD-OS compared with placebo. All pivotal trials included as a key secondary endpoint the proportion of CBD-OS vs. placebo patients who achieved at least a 50% reduction from baseline in either drop seizure frequency (LGS) or convulsive seizure frequency (DS). Other key secondary endpoints in the trials included the percentage change from baseline in total seizure frequency during the treatment period, and the Subject/Caregiver Global Impression of Change (S/CGIC) at last visit, for CBD-OS compared with placebo.

3.2. Favourable effects

The primary endpoint was met in all four studies with an approximately 40-50% median seizure reduction (drop seizures in LGS, convulsive seizures in DS) in the active groups as compared to approximately 15-25% in the placebo groups:

Study GWEP1414 (Lennox-Gastaut Syndrome): A greater median reduction in drop seizure frequency during the treatment period was seen in the both the 20 mg/kg/day CBD-OS (-41.86) and the 10 mg/kg/day CBD-OS (-37.16) groups, compared with the placebo group (-17.17). The estimated median difference was in favour of CBD-OS treatment over placebo for both 20 mg/kg/day CBD-OS (-21.57; 95% CI: -34.79, -6.67) and 10 mg/kg/day CBD-OS (-19.19; 95% CI: -31.24, -7.69); the difference between each CBD-OS group and placebo was statistically significant (p=0.0047 and p=0.0016, respectively).

Study GWEP1423 (Lennox-Gastaut Syndrome): A greater median reduction in drop seizure frequency during the treatment period was seen in the CBD-OS group (-43.90), compared with the placebo group (-21.80). The estimated median difference was in favour of CBD-OS treatment over placebo (-17.21; 95% CI: -30.32, -4.09), and the difference between treatment groups was statistically significant (p=0.0135).

Study GWEP1332B (Dravet Syndrome): The median percentage change from baseline in total convulsive seizure frequency during the treatment period was −38.94 in the CBD-OS group compared with −13.29 in the placebo group. The estimated median difference was in favour of CBD-OS treatment over placebo (−22.79; 95% CI: −41.06, −5.43) and the difference between treatments was statistically significant (p=0.0123).

Study GWEP1424 (Dravet Syndrome): The median percentage change from baseline in total convulsive seizure frequency during the treatment period was -48.7 in the 10 mg/kg/day CBD-OS group, -45.7 in the 20 mg/kg/day CBD-OS group, and -26.9 in the placebo group. The estimated median difference was in favour of CBD-OS treatment over placebo for both10 mg/kg/day CBD-OS and 20 mg/kg/day CBD-OS; the difference between each CBD-OS group and placebo was statistically significant (p=0.0095 and p=0.0299, respectively).

Similar degrees of reduction were seen in total seizures as well as across seizure types.

In the LGS studies the primary analysis was supported by key secondary analyses including responder analyses and global impression of change. In terms of drop seizure free days, the treatment difference in LGS corresponded to 3-5 drop seizure free days per 28 days.

In Dravet Syndrome, the key secondary endpoint (responder analysis) was not met in Study GWEP1332B. In Study GWEP1424, the key secondary analyses supported the primary analyses.

3.3. Uncertainties and limitations about favourable effects

Prandial state was not specified in the pivotal studies although exposure is highly dependent on whether CBD-OS is taken with food or not. Exposure could therefore not be accurately related to efficacy and safety. Considering that dose is always titrated according to both efficacy and safety, this uncertainty can be considered manageable provided the CBD-OS is consistently taken either with or without food. The SmPC clearly reflects this.

CBD-OS was presented as an oral solution containing 100 mg/ml CBD in sesame oil with anhydrous ethanol (79 mg/ml), added sweetener (sucralose), and strawberry flavouring). Placebo was presented as an oral solution of sesame oil containing anhydrous ethanol (79 mg/ml), added sweetener (sucralose), and strawberry flavouring . It is likely that the taste of CBD-OS was different - and less pleasant - than that of placebo as reflected by the caregiver palatability scores. However, there is no evidence that this fact was commonly known during the course of the pivotal studies.

The two syndromes LGS and DS are both considered epileptic encephalopathies, are high frequency seizure disorders comprised of multiple seizure types, share many of the same seizure types, are highly treatment refractory and they are to some degree treated with same medications. Morbidity and mortality are high in both disorders, and SUDEP is a common cause of death at a young age. However, the syndromes differ in age of onset and etiology: Dravet Syndrome is usually associated with SCN1A mutations, and may likely be considered a sodium channel disorder, whereas SCN1A mutations are usually not seen in LGS. Thus, there is not a clear biological rationale for expecting rather similar effect sizes in the two indications. While the finding of rather similar effect sizes may be a consequence of CBD-OS having unspecific anticonvulsive properties, the methodological and pharmacokinetic issues discussed in this report may also play a role.

Some of the difference in apparent effect size, between patients treated with and without clobazam, may be ascribed to the bi-directional pharmacokinetic interaction with clobazam (leading to increased clobazam active metabolite N-CLB concentrations and increased CBD active metabolite 7-OH-CBD concentrations). CBD-OS and clobazam have a complex 2-way metabolic interaction. CBD-OS inhibits CYP2C19 which is required to metabolise the active clobazam metabolite N-CLB. This leads to a 2 to 4 fold increase in N-CLB and an approximate 1.5-fold increase in 7-OH-CBD concentrations which may partially explain the treatment difference. In the pivotal trials a substantial proportion of patients received clobazam concomitant treatment at baseline (approximately 50% in LGS and 65% in DS). The Applicant performed various analyses intended to demonstrate independent efficacy of CBD-OS. However, in all pivotal trials, performing the primary analysis on the subgroup of patients on CLB and the subgroup of patients not on CLB consistently revealed larger treatment effect sizes in the CLB subgroups than in the non-CLB subgroups. The CHMP considers that the clinical relevance of the observed effect of CBD-OS in patients not on clobazam has not been established.

3.4. Unfavourable effects

CBD-OS can cause hepatocellular injury. Two patients concomitantly treated with valproate experienced toxic hepatocellular injury in combination with metabolic acidosis and encephalopathy, respectively. The incidence of TEAEs meeting the search criteria for AESI abnormal liver TEAEs was 14.9% in the All CBD-OS group (N=456) compared with 3.1% in the placebo group (N=292). However, the number of liver-related adverse events was strongly dose-dependent. In the phase II/III 20 mg/kg/day CBD-OS groups 16% of the population developed transaminases elevations > 3 x ULN whereas in the 10 mg/kg/day CBD-OS groups 3% developed transaminases elevations > 3 x ULN as compared to 1% in the placebo group. Overall, approx. 4% of the CBD-OS population in the phase II/III study discontinued due to liver related AE/SAEs, mainly transaminases elevation.

The hepatotoxicity of CBD-OS is aggravated in patients with an affected liver function, i.e. ALT > ULN at baseline, and in patients concomitantly treated with valproate. Patients who did not have an increase in ALT at baseline and were not concomitantly treated with valproate had only a slight increase in ALT when treated with CBD-OS 20 mg/kg/day (3% with ALT > 3x ULN) as compared to placebo (1% with ALT > 3x ULN). This is unlike patients who did have an increase in ALT at baseline and were not treated with valproate (12% of patients with ALT > ULN at baseline, and 9% of patients with ALT > 3x ULN at baseline).

At the same time, the combination of valproate and CBD-OS (20% with ALT > 3x ULN) substantially increases the risk of hepatotoxicity as compared to CBD-OS without concomitant valproate (5% with ALT > 3x ULN) regardless of baseline ALT. In correspondent placebo groups it was 0%.

Finally, the combination of CBD-OS and valproate in patients with an affected liver function at baseline, increases the risk of hepatotoxicity as compared to the risk of hepatotoxicity if the patients had only had one risk factor (i.e. only baseline ALT > ULN or concomitant treatment with valproate). In the CBD-OS 20 mg/kg/day treated with valproate and with baseline ALT > ULN, 64% of the population developed ALT > 3x ULN. In the study, GWEP1424, all patients who experienced transaminase levels following CBD-OS treatment were concomitantly treated with valproate.

The CBD-OS treatment increased the risk of somnolence and sedation, especially when used in combination with clobazam. Approximately 40% of the patients concomitantly treated with Epidyolex and clobazam experienced clinically significant somnolence and/or sedation regardless of whether Epidyolex was administered as 10 or 20 mg/kg/day. Further, lethargy (9 % in CBD 10mg/kg/day groups vs. 2% in the placebo group) and aggression (2% in CBD 10 mg/kg/day groups vs. 1% in the placebo group) were observed.

The risk of status epilepticus was not reduced by CBD treatment; the frequency of status epilepticus was similar in the CBD and placebo groups during the clinical trials.

A dose-dependent decrease of appetite (22% in CBD 20 mg/kg/day groups), which in some patients translated into a weight loss (11% in CBD 20mg/kg/day groups) was observed.

3.5. Uncertainties and limitations about unfavourable effects

In the placebo-controlled phase 3 clinical trials, the patient years of exposure to CBD-OS 10 mg/kg/day were 36.26 py while exposure to 20 mg/kg/day was 76.45 py. The size of the safety database makes it likely that rare adverse events or adverse events occurring after longer exposure have not been yet captured.

3.6. Effects Table

Table 51 Effects Table for Cannabidiol in Lennox-Gastaut Syndrome.

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
% change in drop seizure frequency	GWEP1414: GWEP1423:	Median % change during treatment	10 mg/kg/d: -37.16 20 mg/kg/d: -41.86 20 mg/kg/d: -43.90	-17.17 -21.80	Comparable results, 2 studies. Handling of missing data insufficient.	
% change in total seizure frequency	GWEP1414: GWEP1423:	Median % change during treatment	10 mg/kg/d: -36.44 20 mg/kg/d: -38.40 20 mg/kg/d: -41.24	-18.47 -13.70	Comparable results, 2 studies. Handling of missing data insufficient.	
Proportion of patients with 50% reduction in drop seizures	GWEP1414: GWEP1423:	OR [95% CI]	10 mg/kg/d: 3.27 [1.47;7.26] 20 mg/kg/d: 3.85 [1.75;8.47] 20 mg/kg/d: 2.57 [1.33;4.97]	- -	Comparable results, 2 studies. Handling of missing data insufficient.	
Unfavourable Effects						
LIVER	Hepatocellular injury with metabolic acidosis or encephalopathy	Number of patients concomitantly treated with valproate	2	0		Pool DS/LGS
LIVER	ALT elevation > 5 x ULN	%	11	0.5	20 mg/kg/day CBD-group	Pool DS/LGS
LIVER	ALT elevation > 3 x ULN	%	15	1	20 mg/kg/day CBD-group	Pool DS/LGS
LIVER	**Without** VPA ALT elevation > 3 x ULN	%	5	1	20 mg/kg/day CBD-group	Pool DS/LGS
LIVER	**With** VPA ALT elevation > 3 x ULN	%	29	1	20 mg/kg/day CBD-group	Pool DS/LGS

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
LIVER	**Without** liver impairment at baseline ALT elevation > 3 x ULN	%	12	1	20 mg/kg/day CBD-group	Pool DS/LGS
LIVER	**With** liver impairment at baseline ALT elevation > 3 x ULN	%	30	0	20 mg/kg/day CBD-group	Pool DS/LGS
LIVER	**With** liver impairment at baseline + VPA ALT elevation > 3 x ULN	%	63	0	20 mg/kg/day CBD-group	Pool DS/LGS
CNS	Somnolence	%	25	8	20 mg/kg/day CBD-group	Pool DS/LGS
CNS	Lethargy	%	8	2	20 mg/kg/day CBD-group	Pool DS/LGS
CNS	Sedation	%	6	1	20 mg/kg/day CBD-group	Pool DS/LGS
CNS	Aggression	%	4	0	20 mg/kg/day CBD-group	Pool DS/LGS
CNS	Seizure worsening Total TEAE	%	14	12	All CBD-groups	Pool DS/LGS
CNS	Seizure worsening Serious TEAE	%	7	4	All CBD-groups	Pool DS/LGS
CNS	Seizure worsening TEAE leading to DC	%	2	0	All CBD-groups	Pool DS/LGS

Abbreviations: ALT; alanine aminotransferase. VPA; valproate. Liver impairment at baseline; ALT > ULN at baseline. CNS; central nervous system. TEAE; treatment emergent adverse event. DC; discontinuation

Table 52Effects Table for Cannabidiol in Dravet Syndrome.

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
% change in convulsive seizure frequency	GWEP1332B: GWEP1424*:	Median % change during treatment	20 mg/kg/d: -38.94 10 mg/kg/d: -48.7 20 mg/kg/d: -45.7	-13.29 -26.9	GWEP1332B: Primary analysis not supported by key secondary endpoint. Handling of missing data insufficient.	
Proportion of patients with 50% reduction in convulsive seizures	GWEP1332B: GWEP1424:	OR [95% CI]	20 mg/kg/d: 2.00 [0.93;4.30] 10 mg/kg/d: 2.21 [1.06;4.62] 20 mg/kg/d: 2.74 [1.32;5.70]	-	GWEP1332B: No significant reduction in proportion of 50% responders.	
Unfavourable Effects – See Effects table above where unfavourable effects are pooled for DS/LGS						

Notes: *****-48.7 in the 10 mg/kg/day CBD-OS group, -45.7 in the 20 mg/kg/day CBD-OS group, and -26.9 in the placebo group. The estimated median difference was in favour of CBD-OS treatment over placebo for both 10 mg/kg/day CBD-OS and 20 mg/kg/day CBD-OS; the difference between each CBD-OS group and placebo was statistically significant (p=0.0095 and p=0.0299, respectively).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Both LGS and DS are serious debilitating conditions affecting children early in life. Both conditions are associated with seizures as well as a high risk of impaired cognition and/or severe neuropsychological disturbances. Currently available antiepileptic treatment rarely succeeds in keeping the children free of seizures and the risk of sudden unexpected death in epilepsy (SUDEP) remains high. Thus, there is a clear unmet medical need. In that respect, the statistically significant reduction in seizure frequency offered by CBD-OS constitutes a favourable effect in this difficult to treat population. In the LGS and one of the DS studies, the clinical relevance of the observed relative reduction in primary seizure frequency is supported by a responder analysis demonstration that CBD-OS (at doses of both 20 mg/kg/day and 10 mg/kg/day), compared to placebo, significantly increases the number of patients achieving a 50 % reduction in primary seizure frequency. A reduction of 50% in the frequency of seizures is considered a clinically relevant effect. However, some notable uncertainties about the favourable effect of CBD-OS remain. In particular, the favourable effect of CBD-OS appears to be linked to co-administration of clobazam whereas the effect of CBD-OS without concomitant clobazam

was smaller and it was considered that clinical relevance has not been established. A Scientific Advisory Group (SAG) convened to discuss the issue of the clinical relevance of effect of CBD-OS in patients not receiving clobazam "were not fully convinced that they (the efficacy data) are reliably demonstrating an effect in patients OFF -clobazam treatment, mainly, from a statistical point of view."

Notwithstanding this, the SAG was split in terms of whether a clinical relevant effect off clobazam had been demonstrated. Thus, the CHMP considers that efficacy of CBD-OS in combination with other AEDs and not clobazam is smaller and clinical relevance has not been established. At the SAG, the clinical utility of limiting the indication to patients receiving concomitant clobazam was discussed. The SAG was split in that respect, some experts confirmed that they supported an indication restricting the use of CBD-OS to patients already receiving clobazam whereas others were against such a restriction.

Treatment with CBD-OS is clearly associated with an increased risk of hepatotoxicity, primarily in terms of elevations of transaminases. In particular, patients with concomitant treatment with valproate and pre-existing elevated transaminases are prone to experience additional elevation of transaminases. Provided that adequate measures are taken to monitor liver function/damage and provided that adequate measures are mandated in case of significant toxicity, as recommended in the SmPC, this risk is considered manageable and acceptable taking into consideration the seriousness of the conditions intended to be treated, including the grave prognosis for these children. The SAG confirmed that these patients are cared for in a setting and by physicians that are capable of and experienced in handling these safety issues.

There is a pronounced effect of food on the bioavailability of the CBS-OS. Unfortunately, in the presented clinical studies, CBD-OS was not systematically administered either with or without food. This results in uncertainty about the relationship between exposure and clinical safety and efficacy. However, as the dose of CBD-OS is gradually titrated according to efficacy and safety, this uncertainty is considered manageable, provided that CBD-OS in the individual patients is systematically administered either with or without food.

3.7.2. Balance of benefits and risks

Whereas a clinically relevant effect of CBD-OS in patients receiving clobazam appears well-documented, a clinically relevant effect of CBD-OS in patients not receiving clobazam remains unproven. Available data from subgroup analyses clearly indicates that the effect off clobazam is smaller and clinical relevance has not been established.

In contrast, clinically relevant efficacy for CBD-OS in combination with clobazam was clearly demonstrated. Furthermore, the safety in these patients is considered acceptable provided that the precautions outlined in the SmPC are adhered to. As at least part of the SAG group considered a restricted indication clinically relevant, the CHMP concluded that the benefit risk is positive for a restricted indication for the use of CBD-OS in conjunction with clobazam.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Epidyolex is positive for the indication "adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in conjunction with clobazam, for patients 2 years of age and older".

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Epidyolex is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0136/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.