EU RISK MANAGEMENT PLAN

EPIDYOLEX (CANNABIDIOL)

Data lock point for this RMP	12 Oct 2023	Version number	4.0
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Rationale for submitting an updated RMP: Removal of the important identified risks of somnolence and sedation, lethargy, pneumonia, rash hypersensitivity reactions and the important potential risks of aggression, euphoria, urinary retention from the list of safety concerns.

Summary of significant changes in this RMP:

Part II
SI – New information added on epidemiology based on updated literature searches and new data
SII – New information added on toxicology
SV – Updated Post-authorisation Experience
SVII – Removal of the important identified risks of somnolence and sedation, lethargy, pneumonia, rash hypersensitivity reactions and the important potential risks of aggression, euphoria, urinary retention from the list of safety concerns

Part III
III.1 – Routine Pharmacovigilance Activities
III.I.A – Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: removal of follow-up forms for pneumonia and rash hypersensitivity
III.I.B – Removal of the section Other Forms of Routine Pharmacovigilance Activities for Safety Concerns

Other RMP versions under evaluation: None

QPPV name[1]: PPD

Deputy QPPV name: PPD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV or deputy QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AML	Angiomyolipoma
ASM	Antiseizure medication
AST	Aspartate aminotransferase
BAC	Blood alcohol concentration
BDS	Botanical drug substance
BMI	Body mass index
CB_1	Cannabinoid receptor type 1
CBD-OS	Cannabidiol oral solution
CBDV	Cannabidivarin
CLB	Clobazam
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
DDD	Defined daily dose
DILI	Drug-induced liver injury
DS	Dravet syndrome
EAP	Expanded access programme
EEA	European Economic Area
EEG	Electroencephalogram
ETC	Electron transport chain
EU	European Union
FDA	United States Food and Drug Administration
GLP	Good Laboratory Practice
H-MD	Healthy subjects multiple dose
H-SD	Healthy subjects single dose
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IV	Intravenous
LGS	Lennox-Gastaut syndrome
MAH	Marketing Authorization Holder
NOAEL	No-observed-adverse-effect level
OLE	Open-label extension
PASS	Post-authorisation Safety Study
PPI-SD	Phase I patients [special populations] single dose
PRAC	Pharmacovigilance Risk Assessment Committee

Abbreviation	Definition
PSUR	Periodic safety update report
PT	Preferred term
PV	Pharmacovigilance
RCT	Randomised controlled trial
RMP	Risk management plan
SAE	Serious adverse event
SD	Single dose
SE	Status epilepticus
SmPC	Summary of product characteristics
SMEI	Severe myoclonic epilepsy in infancy
SUDEP	Sudden unexplained death in epilepsy
TE	Treatment-emergent
THC	Δ^9-tetrahydrocannabinol
TSC	Tuberculosis sclerosis complex
ULN	Upper limit of normal
USA	United States of America
VGB	Vigabatrin
VPA	Valproic acid

PART I PRODUCT(S) OVERVIEW

Table Part I.1: Product Overview

Active substance(s) (INN or common name)	**Cannabidiol**
Pharmacotherapeutic group(s) (ATC Code)	N03AX24
Marketing Authorisation Holder in EU	Jazz Pharmaceuticals Ireland Limited
Medicinal products to which this RMP refers	Cannabidiol Oral Solution (CBD-OS)
Invented name(s) in the European Economic Area (EEA)	Epidyolex
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Cannabinoids
	The precise mechanisms by which cannabidiol exerts its anticonvulsive effects in humans are unknown. Cannabidiol reduces neuronal hyper-excitability and inflammation through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV1) channels, and modulation of adenosine-mediated signalling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1 (ENT-1).
	Important information about its composition: None
Hyperlink to the Product Information	SmPC
Indication(s) in the EEA	Current: 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. Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older.
	Proposed (if applicable): N/A

Table Part I.1: Product Overview (Continued)

<table>
<tr><td>Active substance(s)
(INN or common name)</td><td>Cannabidiol</td></tr>
<tr><td rowspan="2">Dosage in the EEA</td><td>Current:
The dosage recommendations for LGS, DS and TSC are summarised in the following table:
<table>
<tr><td></td><td>LGS and DS</td><td>TSC</td></tr>
<tr><td>Starting dose – first week</td><td colspan="2">2.5 mg/kg taken twice daily (5 mg/kg/day)</td></tr>
<tr><td>Second week</td><td>Maintenance dose – 5 mg/kg twice daily (10 mg/kg/day)</td><td>5 mg/kg twice daily (10 mg/kg/day)</td></tr>
<tr><td>Further titration as applicable (incremental steps)</td><td colspan="2">Weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day)</td></tr>
<tr><td>Maximal recommended dose</td><td>10 mg/kg twice daily (20 mg/kg/day)</td><td>12.5 mg/kg twice daily (25 mg/kg/day)</td></tr>
</table></td></tr>
<tr><td>Proposed (if applicable): NA</td></tr>
<tr><td rowspan="2">Pharmaceutical form(s) and strengths</td><td>Current:
100 mg/mL oral solution</td></tr>
<tr><td>Proposed (if applicable): None</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Indication

Cannabidiol oral solution is indicated for use as adjunctive therapy of seizures associated with LGS or DS in conjunction with clobazam, for patients 2 years of age and older.

Cannabidiol oral solution is indicated for use as adjunctive therapy of seizures associated with TSC for patients 2 years of age and older.

SI.2 Incidence

Dravet syndrome (also known as SMEI) is a rare form of severe epilepsy with onset in early childhood. It has an estimated incidence of approximately 1 per 40,000 (Hurst, 1990; Yakoub, 1992; Durá-Travé, 2007). Birth prevalence (incidence at birth) of DS is estimated as 3.3 per 100,000 persons from recent European data (Orphanet, 2022).

Lennox-Gastaut syndrome accounts for an estimated 3% to 4.3% of childhood epilepsies (Beaumanoir, 1992; Markland, 2003)). Cowan (Cowan, 2002) described a range of < 1% to 6% for LGS as a percentage of cases of epilepsy in children. Incidence of LGS is estimated as 0.1 per 100,000 persons from European data (Orphanet, 2022).

Establishing the incidence of TSC is complicated by changes to the diagnostic criteria which occurred in 2012. Since then, in Europe, the estimated annual incidence rate of definite or possible TSC is approximately 1 in 11,180 (8.9 per 100,000 persons) to 1 in 22,360 (4.5 per 100,000 persons), as has arisen from a German prospective national surveillance study (Ebrahimi-Fakhari , 2018 and correction, 2019). This incidence is for TSC, rather than patients with seizures associated with TSC. Epileptic seizures are estimated to affect > 70% of patients with TSC (Dabora, 2001; Chu-Shore 2010; Vignoli, 2013; Wang, 2014).

SI.3 Prevalence

Dravet syndrome accounts for 1.4% of epilepsies in children aged < 15 years (Hurst, 1990; (Yakoub, 1992; Durá-Travé, 2007). The point prevalence of DS in the EU ranges from 0.11 per 10,000 total population (based on studies in Norway and Spain) (Syvertsen, 2015; Gil-Nagel , 2019) to 0.48 per 10,000 (based on a German study) (Schubert-Bast, 2021). The European-based Orphanet has reported a birth prevalence of DS as 0.33 per 10,000 (Orphanet, 2022). Based on a summary of these findings, the point prevalence of DS in the EU is 0.11-0.48 per 10,000 total population. Since the total population of the EU on 1 Jan 2023 was estimated as 448,387,872 (Eurostat, 2023), a calculated current prevalence of DS in the EU population is approximately 21,523 persons. The reduction in numbers compared to the EU-RMP v3.0 is due to the UK leaving the EU.

Incidence of LGS has been reported as 3% or below among the entire childhood epilepsies and approximately 4% at specialised epilepsy centres (Beaumanoir, 1992; Markland, 2003). The median prevalence of epilepsy in Europe for all ages has been reported as 5.2 per 1000

(Forsgren, 2005). Assuming a conservative estimate of LGS incidence of 4% as a percentage of childhood epilepsies across the EU, the following prevalence estimates of patients were calculated:

Prevalence of epilepsy for all ages in the EU, using a value of 5.2 per 1,000 (1 in 192)

448,387,872/192 = 2,335,354 persons.

Prevalence of LGS among all ages in the EU population

4% of 2,335,354 = 93,414 persons.

Prevalence of LGS per 10,000 among all ages in the EU population

(93,414/448,387,872× 10,000 = 2.08 per 10,000 persons for persons of all ages (or 93,414 persons) in the EU.

The MAH has used the most conservative prevalence estimate for TSC identified in the published literature of 0.9 per 10,000 persons (O'Callaghan, 1998), which is comparable to estimates cited by Orphanet and previously approved EU orphan designation applications. Based on Eurostat population data for the EU on 1 Jan 2023, the MAH estimates the number of persons in the EU affected by TSC is approximately:

(448,387,872/10,000) × 0.9 = 40,355 persons.

Further detailed background information on prevalence is provided in the MAH's report on the maintenance of designation criteria at the time of marketing authorisation or type 2 variation application for a designated orphan medicinal product for DS, LGS and TSC.

SI.4 Demographics of the Population in the Authorised Indication

Dravet syndrome is a severe infantile-onset, genetic, treatment-resistant epilepsy syndrome that is associated with poor outcomes (Caraballo, 2005). Onset usually occurs during the first year of life and manifests typically as a prolonged (> 15 min) clonic, generalised or unilateral convulsive seizure, often triggered by fever, which can evolve into SE (Arzimanoglou, 2009; Dravet, 2011; Dravet, 2013). 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, eg, *PCDH19* (protocadherin-19) (Scheffer, 2012). Dravet syndrome is extremely resistant to treatment during childhood and patients continue to have uncontrolled seizures throughout their lifetime.

Lennox-Gastaut syndrome is a rare epilepsy syndrome with a devastating clinical course. 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 spike and wave on interictal EEG when awake, or bursts of fast rhythmic waves and slow polyspikes, and generalised fast rhythms during sleep (Arzimanoglou, 2009). Generally, LGS is more prevalent in boys; however, with the exception of tuberous sclerosis, genetic factors are regarded to be of minor importance in LGS as approximately 75% of cases are of symptomatic origin with underlying cerebral malformation, hypoxic–ischemic injury or metabolic disease (Dulac, 1993; Camfield, 2011). It may present as infantile spasms in early life and the seizures evolve to multiple seizure types (Morita, 2013). Lennox-Gastaut syndrome 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) (van Rijckevorsel, 2008; Isojarvi, 2016).

Tuberous sclerosis complex is a genetic disorder characterised by the formation of non-malignant tumours (tubers) in multiple organ systems. Two responsible genes, TSC1 and TSC2, were discovered in the 1990s; however, these do not predict for the manifestation of TSC in individuals, and 15% to 20% of TSC patients do not have identified mutations in TSC1 and TSC2 (Jones, 1999; Sancak, 2005). Although many patients show symptoms in the first year of life, subtle presentation can result in unrecognised TSC until later in life. Tumors in TSC patients can occur in any major organ yet develop primarily in the brain, eyes, heart, kidney, skin, and lungs (Crino, 2006). Epileptic seizures are the most common neurological manifestation of TSC. Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80% of TSC patients (Curatolo, 2018; Chu-Shore , 2010).

SI.5 The Main Existing Treatment Options

No formal treatment guidelines are available for DS and LGS.

First-line therapies for DS typically include VPA as well as first- or second-line therapies (fenfluramine, stiripentol or CLB, topiramate, ketogenic diet) or later options (cannabidiol pharmaceutical grade, topiramate, ketogenic diet and others, eg, levetiracetam, bromides, vagus nerve stimulation) (Wirrell, 2002). Stiripentol is approved in the EU and the UK for DS for use in conjunction with CLB and VPA. Fenfluramine is approved in the US, EU and the UK for DS and LGS.

Patients with DS may be prone to seizure exacerbation with sodium channel modulators such as carbamazepine, oxcarbazepine, lamotrigine and phenytoin (Wirrell, 2017). Currently used ASMs are not fully effective for the treatment of DS, and patients are prone to life-long seizures. Patients are also frequently treated with multiple ASMs, sometimes in an off-label manner, in an effort to control their seizures.

Lennox-Gastaut syndrome is one of the most pharmacoresistant forms of epilepsy (Crumrine, 2011), with all seizure types extremely refractory to conventional ASMs. Notably, there is a greater number of currently approved ASMs for LGS, and these include cannabidiol, lamotrigine, fenfluramine, rufinamide and topiramate for the EU and cannabidiol, CLB, felbamate, fenfluramine, lamotrigine, rufinamide and topiramate for the US. Similarly to DS, > 1 ASM in combination with others is usually required to gain any seizure control. The standard ASMs that are available for use as a combination include CLB, VPA, lamotrigine, felbamate, rufinamide, topiramate and fenfluramine. In general, first-line treatment of patients with LGS should be sodium valproate, with lamotrigine and subsequently rufinamide, advised as adjunctive therapy (Cross, 2017). Antiseizure medications known to potentially exacerbate seizures in patients with LGS include carbamazepine, eslicarbazepine, oxcarbazepine, gabapentin, vigabatrin, phenytoin and pregabalin and tiagabine (Cross, 2017; Montouris, 2020).

Other than Epidyolex, the only approved therapy for TSC-associated seizures in the EU is the mTOR inhibitor everolimus. Everolimus (the 40-O-[2-hydroxyethyl] derivative of sirolimus/rapamycin) is a kinase inhibitor that selectively inhibits mTOR activity (Votubia, 2022). Originally approved to treat tumours in patients with TSC, everolimus was subsequently approved in 2017 for adjunctive treatment of adult and paediatric patients aged 2 years and older

with TSC-associated partial-onset seizures (French, 2016; Votubia, 2022). The mTOR inhibitors can lead to adverse reactions including non-infectious pneumonitis, infections, severe hypersensitivity reactions, angioedema, stomatitis, renal failure, impaired wound healing and metabolic disorders. Serious infections occur more frequently in patients under 6 years of age (Votubia, 2022). With long-term use of everolimus, stomatitis and mouth ulceration remained the most common adverse reactions and were associated with dose interruptions or reductions (Franz, 2001).

Seizures associated with TSC are also frequently treated with non-pharmacological therapies such as surgery, vagus nerve stimulation or the ketogenic diet (Krueger, 2013; Wang, 2014; Nabbout, 2018). Most frequently, a combination of ASMs is used to reduce the frequency of infantile spasms and seizures in this patient population.

Vigabatrin was most recently approved in the EU in 2018 (as Kigabeq, 2023) and is used for treatment of infantile spasms that are secondary to TSC but is not indicated specifically for treatment of seizures associated with TSC. Long-term treatment with VGB is associated with irreversible peripheral visual field defects, the risk of which increases with increasing dose and cumulative exposure (Willmore, 2009). Additional warnings and precautions include MRI abnormalities and neurotoxicity, including intramyelinic edema (Kigabeq, 2023). Furthermore, there is evidence that spasms may relapse and become refractory to VGB following discontinuation of treatment in children with focal cortical dysplasia/TSC (Kröll-Seger, 2007).

Corticotropin or the corticotropin analogue tetracosactide approved in 1998 (as Synacthen ampoules), has been demonstrated as effective in the treatment of infantile spasms, although many studies do not provide TSC-specific infantile spasm data (Hancock , 2013; Wang, 2014). Corticotropin treatment and long-term exposure is associated with serious AEs, including fulminant infections secondary to immunosuppression, hypertension, glucosuria and metabolic abnormalities (Riikonen, 1980; Pellock, 2010). Corticotropin may contribute to the enlargement of cardiac rhabdomyoma in TSC patients (Hishitani, 1997; Hiraishi , 2000). Due to risk of AEs, corticotropin treatment is therefore generally short-term (~2 weeks followed by taper) and close monitoring is required in TSC patients with cardiac rhabdomyoma. Relapse rates following effective corticotropin treatment range from 15% to 60% (Hancock, 2013).

Additional ASMs that have been reported in the literature as second-line therapies for partial-onset seizures associated with TSC include lamotrigine, levetiracetam, carbamazepine, felbamate and clobazam (Franz, 2001; Collins, 2006; Jennesson, 2013; Curatolo, 2018; van der Poest Clement, 2020).

SI.6 Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity

SI.6.1 Dravet Syndrome

Following the initial onset of DS, after a typical period of 2 weeks to 2 months, further febrile seizures occur and afebrile seizures also appear. In addition to convulsive seizures, other seizure types appear between the ages of 1 and 4 years, including myoclonic seizures, focal seizures, atypical absences and obtundation statuses (in which consciousness is impaired). Significant developmental delay becomes apparent from the second year onward, and associated neuropsychological disturbances, such as attention deficit/hyperactivity disorder, are common.

Beyond 5 years of age, convulsive seizures decrease but persist and occur mainly in sleep. Myoclonic and absence seizures tend to disappear and focal seizures either persist or decrease (Wirrell, 2017).

Although psychomotor development and behaviour tend to improve over time, cognitive impairment persists throughout the patient's lifetime (Arzimanoglou, 2009; Dravet, 2011; Dravet, 2013). Myoclonic seizures are a defining characteristic of DS and can be massive, predominantly involving axial muscles or erratic/segmental, which are mainly limited to the distal limbs and face. Massive myoclonic seizures are often associated with EEG paroxysms and can be variable in intensity, with outcomes ranging from falling (drop attack) to causing only small, saccadic movements of the head, shoulders or trunk (Arzimanoglou, 2009; Dravet, 2011; Dravet, 2013). Erratic myoclonic seizures do not have an EEG correlate and are typically mild in intensity, although they can affect fine motor coordination. Some patients with DS experience both massive and erratic myoclonic seizures, yet these seizures can be absent in some DS patients. Such cases are defined as "borderline" SMEI and may have different EEG features to typical SMEI, although the course and outcome of the disease remain the same (Kanazawa, 1992; Yakoub, 1992; Dravet, 2013).

Long-term seizure outcomes in DS are extremely poor, with 2 long-term studies reporting 92% and 84% of DS patients still having seizures in adulthood, respectively (Akiyama, 2010; Takayama, 2014). Death during childhood is common in DS. Sudden unexplained death in epilepsy and SE are the most common causes of death in DS, with drowning and accidental death following seizures also common causes (Shmuely, 2016). Risk factors for SUDEP include frequent generalised tonic–clonic seizures, early seizure onset, polytherapy and developmental delay (Sillanpää, 2010; Hesdorffer, 2011), all of which are common in DS. A review of 177 unique cases of death in DS reported in the literature highlighted that 73% of the deaths occurred before the patient reached 10 years of age, with the cause being SUDEP in 49% of cases and SE in 32% of cases (Shmuely, 2016). Longitudinal follow-up (median 17 years) of 100 unrelated DS patients enrolled into the Epilepsy Genetics Research Program reported 17 deaths with a median patient age of 7 years, equating to a DS-specific mortality rate of 15.84 per 1000 patient-years (Cooper, 2016). Sudden unexplained death in epilepsy was the most common cause of death (59%), equating to a DS-specific SUDEP rate of 9.32 per 1000 patient-years, which is nearly twice the rate for adults with refractory epilepsy.

SI.6.2. Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome 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 leading to increased morbidity and mortality (van Rijckevorsel, 2008; Isojarvi, 2016). In a number of cases, LGS follows the onset of infantile spasms (Morita, 2013).

Cognitive impairment is apparent in 75% to 95% of all LGS patients by 5 years post-onset (Arzimanoglou, 2009). Developmental delays (20%-60% of patients) and behavioural disturbances are very common and often profound (Arzimanoglou, 2009; Crumrine, 2011).

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 (Autry, 2010). Neurological comorbidity including prolonged seizures and SE are correlated with mortality and, in particular, SUDEP (Autry, 2010).

SI.6.3. Tuberous Sclerosis Complex

Epileptic seizures are the most common neurological manifestation of TSC, affecting > 70% of patients (Dabora, 2001; Chu-Shore, 2010; (Vignoli, 2013) ; Wang, 2014). Seizure onset occurs within the first year of life in approximately two-thirds of TSC patients and occurs within the first 3 years of life in 80% of TSC patients (Curatolo, 2018; Curatolo, 2018). The onset of epilepsy in TSC commonly manifests as focal motor seizures, which in approximately one-third of TSC patients coexist with infantile spasms (Chu-Shore, 2010).

Cognitive impairment (intelligence/developmental quotient < 70) is observed in around 60% of all TSC patients with a history of seizures and in approximately three-quarters of all TSC patients with a history of refractory epilepsy (Chu-Shore, 2010). Early management of seizures is therefore important in preventing subsequent epileptic encephalopathy and in reducing the associated cognitive and neuropsychiatric consequences (Bombardieri, 2010; Wang, 2014).

SI.6.4 Important Comorbidities

Non-epileptic co-morbidities appear with age in DS, including intellectual disability, ataxia and crouching gait. In adults, progressive worsening includes levodopa (L-DOPA)-responsive Parkinsonism. The incidence of SUDEP is high, regardless of age (Gataullina, 2017).

The diagnostic clinical and EEG features of LGS may not be present at the time of onset of LGS and it sometimes evolves from other early-onset epileptic encephalopathies. It is suggested that approximately 20% of LGS cases are preceded by West syndrome (also known as infantile spasms) with a peak onset between 4 and 7 months, which itself can evolve from Ohtahara syndrome (onset within 1 month of birth) (Camfield, 2011). Due to this aetiology, 20 to 60% of LGS patients already have delayed cognitive development at onset of LGS (Arzimanoglou, 2009). In cryptogenic cases of LGS (25% to 30% of all cases) development appears normal prior to the onset of the first seizures, yet cognitive impairment is apparent in 75% to 95% of all LGS patients by 5 years post-onset (Arzimanoglou, 2009). Various behavioural and psychiatric comorbidities are often seen in LGS patients, including attention deficit/hyperactivity disorder, anxiety, aggressive behaviour, psychosis and depression (Arzimanoglou, 2009; Camfield, 2011).

In relation to TSC, the most serious comorbidity is caused by lesions in the central nervous system, renal, pulmonary, cardiac and endocrine systems. Renal disease is a major cause of mortality in patients with TSC and leads to a higher risk for developing anaemia caused by renal lesions, otherwise known as AML (Amin, 2017). Angiomyolipomas have been reported in 34% to 80% of TSC patients overall (Rakowski, 2006). Eijkemans et al (Eijkemans, 2015) reported that 244 of the 351 subjects (69.5%) with TSC had confirmed AML. Renal AMLs may lead to secondary anaemia and was reported in 60.7% of patients with TSC in 1 study ((Eijkemans, 2015). Renal AML is also associated with the development of pulmonary lymphangioleiomyomatosis, a cystic disease of the lungs, which occurs almost exclusively in female patients (Amin, 2017). Approximately half of the patients with TSC have learning disabilities, which have been associated with higher mortality (Amin, 2017).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage (for each safety finding) are summarised below.

SII.1 Toxicity

The toxicity profile of CBD (as either CBD-OS, purified CBD or CBD BDS) was evaluated in a comprehensive toxicology programme, consistent with ICH requirements and in compliance with the Organisation for Economic Co-operation and Development and FDA principles of GLP regulations. The programme consisted of a series of in vitro and in vivo genetic toxicology studies, exploratory and pivotal repeat-dose oral toxicology studies in rats (up to 26 weeks) and in dogs (up to 39 weeks), IV toxicology studies (up to 28 days) in adult animals, and a battery of reproductive toxicology studies conducted in rats and/or rabbits. Additional studies examined neonatal/juvenile toxicity in rats and dogs because the intended target population includes infants and young adults. Finally, 13-week oral dose range-finding studies followed by a 104-week lifetime carcinogenicity study in the mouse were performed with CBD-OS.

As part of a series of post-marketing requirements, a 104-week rat carcinogenicity bioassay with CBD-OS and a series of studies intended to qualify a disproportionate human metabolite of CBD (7-COOH-CBD) are currently being completed.

SII.1.1 Acute and Repeat-dose Toxicity Studies

No acute toxicology studies of CBD were performed in this programme. However, it has been reported that CBD has low acute IV toxicity, with lethal dose for 50% of the exposed animal population (LD_{50}) values of 50, 242, > 254 or 212 mg/kg in mice, rats, dogs and monkeys, respectively (Rosenkrantz, 1977; Rosenkrantz and Esber 1980; ChemIDplus Lite, 2023).

In the repeat-dose oral (gavage) studies, CBD-OS was well tolerated when administered in the mouse for 13 weeks (NOAEL: 300 mg/kg/day [GWTX1503]), in the rat for 26 weeks (NOAEL: 150 mg/kg/day [GWTX1412]) or in the dog for 39 weeks (NOAEL: 100 mg/kg/day [GWTX1413]). Daily administration of purified CBD to juvenile rats (subcutaneous post-natal day 4 to 6/oral gavage post-natal day 7 to 77) was also well tolerated following 10 weeks of dosing up to a NOAEL of 15/150 mg/kg/day (GWTX1408).

In these studies, the liver was identified as the main target organ, with changes characterised by increased circulating levels of ALP and/or ALT activities (in adult animals), centrilobular hypertrophy, increased liver weight, and/or macroscopic enlargement. These findings were not adverse since there was an absence of concurrent inflammatory, necrotic or fibrotic changes, the animals were healthy and uncompromised, and the findings were generally absent or showed a tendency for reversal at the end of the recovery period. Thyroid hypertrophy and adrenocortical vacuolation were also noted in adult and juvenile rats. Similar changes were noted in adult rats given oral doses of the impurity CBDV for 26 weeks (NOAEL: 80 mg/kg/day [GWTX1429]) and in adult rats given oral doses of the impurities CBD-C4 (NOAEL: 100 mg/kg/day [GWTX1599]) or CBD-C1 (NOAEL: 10 mg/kg/day [GWTX1637]). Similar histopathological findings in the liver were reported in the 13-week oral study with the impurity THC (as Sativex)

at doses up to 150 mg/kg/day THC (NOAEL: 15 mg/kg/day THC [GWTX10124]). As with the rat and dog studies with CBD, these findings were not adverse and demonstrated a tendency for reversal at the end of the recovery period.

SII.1.2 Genotoxicity

There was no evidence of genotoxic potential in a battery of in vitro bacterial mutation assays and in vivo micronucleus and/or COMET assays performed with CBD-OS (GWTX1510), purified CBD (GWOR0910 and GWOR0903) or CBD BDS (GWOR0909, BRW003/004838 and GWOR0908). Similarly, negative results were obtained following in vitro and in vivo genotoxicity assays performed on the impurities CBDV (GWOR0963, GWOR0965 and GWOR1206), CBDC4 (GWTX1597 and GWTX1598), CBDC1 (GWTX1625 and GWTX1624) and THC (as THC BDS in Sativex [GWTX0603 and GWTX1355]), and the major metabolites 7-OH-CBD (GWTX21028) or 7-COOH-CBD (GWTX21068 and GWTX18015).

SII.1.3 Carcinogenicity

There was no evidence of carcinogenic potential in the oral mouse carcinogenicity study with CBD-OS at doses up to 300 mg/kg/day (GWTX1504). Furthermore, CBD is not structurally related to known carcinogens and does not produce any relevant structural alerts.

SII.1.4 Reproductive/Developmental Toxicity

In a battery of reproductive studies using purified CBD, there were no effects on male or female fertility in rats at oral doses up to 250 mg/kg/day (NOAEL) (GWTX1456). In addition, there was no evidence of embryo-foetal developmental toxicity (teratogenic activity) in rats or rabbits at oral doses up to 150 or 80 mg/kg/day (NOAELs), respectively (GWTX1454 and GWTX1452). In the pivotal prenatal and postnatal study in rats with purified CBD at oral dosages up to 250 mg/kg/day (GWTX1532), the NOAEL for maternal toxicity was considered to be 250 mg/kg/day and the NOAEL for F_1 developmental toxicity for both sexes was considered to be 75 mg/kg/day, based on reduced pup body weight, delayed developmental landmarks, delayed sexual maturation in both sexes and macroscopic observations of small testes.

There was no evidence of embryo-foetal developmental toxicity in rats given oral doses of the impurities, CBDV (GWTX1462), CBD-C4 (GWTX15109), CBD-C1 (GWTX1622) or THC (in Sativex) (JJG0015), at doses up to 200, 100, 100 or 12.5 mg/kg/day (the NOAELs), respectively.

In the 26-week repeated dose oral toxicology study in rats treated with CBD-OS (GWTX1412), there was an incidence of minor interstitial cell hyperplasia of the ovary at CBD-OS $\geq$ 50 mg/kg/day CBD. There was a similar finding in rats given CBDV orally at $\geq$ 40 mg/kg/day for 26 weeks (GWTX1429). These findings were reported to represent a subtle change confounded by normal age-related increases in interstitial cells in the rat ovary, which has also been noted following hormonal disruption (Greaves, 2012; Vidal, 2013). However, based on the minor nature of this finding in both studies, it was suggested to be an indirect effect of treatment of unlikely toxicological significance. It should be noted that female rhesus monkeys given CBD at up to 300 mg/kg/day for 90 days showed no effect on oestrous cycle and their pituitary and steroid hormones were essentially unchanged (Rosenkrantz, 1978; Rosenkrantz and Esber, 1980; Rosenkrantz, 1981).

In the repeat-dose toxicology studies conducted in this programme, no treatment-related histopathological findings were reported in the testes of rats or dogs given CBD-OS, CBD BDS or the impurities. Furthermore, semen analysis (sperm count, motility and abnormalities) revealed no adverse effects in the 26-week oral rat study with CBDOS (150 mg/kg/day) (GWTX1412) or CBDV (80 mg/kg/day) (GWTX1429) or in the 13-week dietary rat study with CBD as CBD BDS (225 mg/kg/day) (JJG0002) or in the 4-week IV rat study with CBD as CBD BDS (25 mg/kg/day) (GPA 003/013834).

SII.2 Safety Pharmacology

The safety pharmacology programme included a series of studies to evaluate the effects in the CNS, cardiovascular system and respiratory system.

In the rat primary observation Irwin test of CNS function, no behavioural, physiological, or body temperature changes were observed following administration of CBD BDS at 10 to 100 mg/kg (GWOR10109).

In the cardiovascular system, CBD BDS inhibited human ether-à-go-go-related gene (hERG) tail current in a concentration-dependent manner and had no effect on Purkinje fibre action potentials (GWOR10120) or QT interval changes (GWOR1101). Changes in cardiovascular parameters (heart rate, blood pressure and electrocardiogram) in the conscious dog were not considered to be adverse (GWOR10111).

In the respiratory system, CBD BDS had no biologically significant effect on respiratory parameters in conscious rats (GWOR10110).

SII.3 Other Toxicity-related Information or Data

SII.3.1 Abuse Potential/Dependence

The abuse and dependence/withdrawal potential of purified CBD was investigated in the following in vivo models: (1) drug discrimination, (2) non-precipitated withdrawal, (3) IV self-administration and (4) in vitro abuse liability studies and in vivo Tetrad test.

SII.3.1.1 Drug Discrimination Studies

Drug discrimination is a well-established model to compare the subjective effect associated with a known drug of abuse with a test compound, usually of the same class. Two studies conducted by the MAH were designed to determine whether the subjective effect experienced following either THC (GWTX1554) or midazolam (GWTX15110) training was similar to that of CBD-OS. Rats trained to distinguish between the psychoactive effects of either THC or midazolam and vehicle, subsequently generalised to the saline cue following oral (gavage) administration of CBD-OS at all doses (20, 75 and 150 mg/kg). Furthermore, CBD-OS evoked no psychoactive effects at any of the doses tested. In conclusion, the findings demonstrate that CBD-OS did not produce THC- or midazolam-like psychoactive effects at any dose tested. These data predict that CBD-OS will not produce benzodiazepine- or THC-like psychoactive effects in humans, which could lead to it becoming a recreational drug of abuse.

SII.3.1.2 Physical Dependence and Non-precipitated Withdrawal Test

CBD-OS was assessed in the non-precipitated withdrawal test in juvenile and adult male (GWTX1555) and female (GWTX15114) rats, at oral (gavage) doses of up to 100 mg/kg twice daily for 19 days and once on Day 20. Comparisons were made with vehicle control, comparator (diazepam) and positive control (morphine). Symptoms of physical withdrawal were assessed over an 8-day period, following cessation of dosing. There were no clear withdrawal effects of CBD-OS observed in juvenile or adult rats of either sex. In contrast, diazepam and morphine induced moderate and marked signs of dependence, respectively, in male and female rats of both age groups.

SII.3.1.3 Self-administration Studies

In self-administration studies, the positive reinforcing properties of purified CBD were assessed in rats trained to intravenously self-administer cocaine (GWTX1551) or heroin (GWTX1663). Doses of purified CBD examined were selected to deliver plasma exposures equal to or greater than that expected in man. While no positive reinforcement was observed in rats trained to the stimulant cocaine, weak positive reinforcement was observed in those trained to the sedative euphoriant heroin. Upon substitution to training drug, reinstatement of responding was observed in all dose groups. A third IV self-administration study was conducted in the midazolam-trained rhesus macaque (GWTX1664). Here, no positive reinforcement was observed with purified CBD at any of the 3 doses examined (1.0, 3.2 and 5.6 mg/kg). As previously described, doses were selected to deliver plasma exposure equal to or greater than those observed in man. Therefore, irrespective of training drug class (stimulant, sedative euphoriant and benzodiazepine), CBD was not perceived to be a rewarding stimulus and as such is unlikely to be a potential drug of abuse in man.

SII.3.1.4 In Vitro Abuse Liability Studies and In Vivo Tetrad Test

In vitro affinity diversity screens revealed that neither purified CBD nor the major human metabolites (7-hydroxy-cannabidiol [7-OH-CBD] and 7-carboxy-cannabidiol [7-COOH-CBD]) bind to abuse liability-associated molecular targets. Furthermore, CBD and 7-OH-CBD do not exhibit CB_1 receptor agonist-like activity on the Tetrad test (GWOR1211 and GWPP1370).

SII.4 Impurities

Since analysis of the active pharmaceutical ingredient revealed impurities at levels greater than the qualification thresholds specified in ICH guidance documents, a battery of in vitro and in vivo genetic toxicology, repeat-dose toxicology and reproductive toxicology studies were conducted to qualify the major impurities present in CBD-OS, namely, CBDV, CBD-C4, CBD-C1 and THC. All pivotal studies were performed in accordance with GLP. None of these impurities were mutagenic or clastogenic, or demonstrated reproductive effects at the maximum doses tested. The NOAEL reported in repeat-dose studies provided satisfactory multiples of human exposure when compared to exposures associated with the maximum recommended therapeutic dose of 25 mg/kg/day CBD.

More recently, 2 oxidative isomeric degradants, GWP04205136 and GWP04205137, were identified as semi stable precursors formed during the oxidation of CBD to CBE I and CBE II in the finished oral product of CBD-OS. An initial in silico quantitative structure-activity

relationship analysis followed by a GLP-compliant miniaturised bacterial mutagenicity (Ames) assay (GWTX21173) confirmed the positive mutagenicity of the isomers. Since the limited quantities of degradants that can be obtained from chemical synthesis preclude conducting follow-up in vivo studies using the currently recommended ICH M7 protocols, a retrospective qualification of these oxidative degradants was conducted based on a review of experimental batches utilised in the completed genetic toxicology and mouse carcinogenicity studies with CBD. This risk assessment was further complemented with a detailed weight-of-evidence analysis based on a read-across methodology using a validated and regulatory-compliant in silico programme (OECD QSAR Toolbox). Both assessments concluded that the presence of degradants GWP04205136 and GWP04205137 at the levels documented in CBDOS is not anticipated to pose an incremental carcinogenic risk to the exposed patient population Module 4, Toxicology Risk Assessment of Degradants GWP04205136 and GWP04205137 report; Expert Review and Weight-of-Evidence and Read-Across Analysis on the Mutagenicity and Carcinogenicity of GWP04205136 and GWP04205137).

SII.5 Multiples of Human Exposure

The multiples of human exposure (or margins of safety) calculated for the pivotal toxicology studies using the exposure associated with the maximum recommended therapeutic dose of 25 mg/kg/day is presented inTable Part II: Module SII.1. Multiples of human exposure values are generally > 1, indicating an absence of immediate safety concerns for the various endpoints associated with the reported NOAELs.

Table Part II: Module SII.1: Multiples of Human Exposure for CBD

Study Duration, Species/Strain	NOAEL (mg/kg)	Mean $AUC_{(0-t)}$ at NOAEL (ng/mL)[a]	Multiples of Human Exposure[b] Calculated Using AUC[a]	Report Number
Repeat-Dose Toxicology Studies				
13-Week Mouse (CD-1)[c]	300	45350	9	GWTX1503
26-Week Rat (Wistar)[d]	150	63750	13	GWTX1412
39-Week Dog (Beagle)[e]	100	21450	4	GWTX1413
Carcinogenicity Studies				
104-Week Carcinogenicity (Mouse) (CD-1)[f]	300	33400	7	GWTX1504
Reproductive and Developmental Toxicology				
Embryo Foetal Development in the Rat (Wistar)[g]	150	149000	30	GWTX1454
Embryo Foetal Development in the Rabbit (New Zealand White)[h]	80	2030	0.4	GWTX1452
Juvenile Toxicology Studies				
10-Week Juvenile Rat with 6-Week Recovery (Subcutaneous/Oral) (Wistar)[i]	15/150	68350	14	GWTX1408 (TK reported under GWTX18001)

Abbreviations: AUC = area under the concentration-time curve; CBD = cannabidiol; GD = gestation day; NOAEL = no-observed-adverse-effect-level; PND = post-natal day; TK = toxicokinetic.

[a] AUC values indicate combined male and female exposure values.

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

[c] Exposure data from GWTX1503 measured in Week 13 (44300 ng h/mL for males and 46400 ng·h/mL for females).

[d] Exposure data from GWTX1412 measured in Week 26 (60000 ng h/mL for males and 67500 ng·h/mL for females).

[e] Exposure data from GWTX1413 measured in Week 39 (20500 ng h/mL for males and 22400 ng·h/mL for females).

[f] Exposure data from GWTX1504 measured in Week 26 (40600 ng·h/mL for males and 26200 ng·h/mL for females).

[g] Exposure data from GWTX1454 measured on GD 17 (149000 ng h/mL).

[h] Exposure data from GWTX1452 measured on GD 19 (2030 ng h/mL).

[i] Exposure data from GWTX1408 (reported under GWTX18001) measured on PND 70 (75500 ng·h/mL for males and 61200 ng·h/mL for females).

Note: All studies describe adult animals except where stated.

PART II: MODULE SIII CLINICAL STUDY EXPOSURE

The overall extent of exposure in the CBD OS clinical development programme is summarised in MAA Module 2.7.4 Section 1.4 by pooled and non-pooled sources.

A total of 1521 unique subjects have been exposed to CBD OS in the JPI-sponsored development programme. An additional 68 unique subjects have been exposed to cannabidiol capsules, and 12 unique patients have been exposed to CBD IV solution.

There have been 1067 patients with refractory epilepsy who have received CBD-OS as part of the EAP/Compassionate Access Scheme, which included 88 patients with DS and 146 patients with LGS and 37 patients with TSC.

SIII.1 Cumulative Exposure (by Duration) for All Indications

Cumulative exposure by duration of exposure is provided in Table Part II: Module SIII.1 .

Data from single dose studies (Pool H-SD and Pool Phase 1 patients [special populations] single dose [PP1-SD]) are not included in this presentation of exposure by duration of exposure. Total CBD-OS exposures and number of unique CBD-OS exposures are provided in Table Part II: Module SIII.1. Data from legacy Study GWAP1241 in CCI [redacted] are also not included due to availability; however, exposure information is summarised in Table Part II: Module SIII.1, as well as in the GWAP1241 CSR.

Table Part II: Module SIII.1: Cumulative Duration of Exposure to CBD-OS

Duration of Exposure	Patients (Total CBD-OS Exposures)	Person-time (Patient-years)
1-14 days	86	2.16
15-28 days	132	8.37
29-42 days	108	10.49
43-84 days	86	13.99
85-182 days	213	75.28
183-364 days	327	238.92
365-729 days	472	670.95
> 730 days	839	2368.62
Total person-time		**3388.78**

Abbreviation: CBD-OS = cannabidiol oral solution.

SIII.2 Exposure (by Duration) in Studies in Target Indications: Dravet Syndrome, Lennox-Gastaut Syndrome and Tuberous Sclerosis Complex

Cumulative exposure by duration of exposure in patients with DS, LGS or TSC is provided in Table Part II: Module SIII.2.

This consists of exposure from the following:

- Pool LT-DS/LGS/TSC
- Pool EAP-DS
- Pool EAP-LGS
- Pool EAP-TSC

Table Part II: Module SIII.2: Exposure by Duration of Exposure in Patients with DS, LGS or TSC

Duration of Exposure	Patients (N)	Person-time (Patient-years)
1-14 days	12	0.37
15-28 days	25	1.52
29-42 days	35	3.22
43-84 days	57	9.02
85-182 days	105	37.00
183-364 days	189	142.12
365-729 days	296	400.38
> 730 days	513	1504.58
Total person-time		**2098.21**

Abbreviations: DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; TSC = tuberculosis sclerosis complex.

Exposure by duration, specific to patients with TSC, from Study GWEP1521 and its OLE, and the EAP is provided in Table Part II: Module SIII.3.

Table Part II: Module SIII.3: Exposure by Duration of Exposure in Patients with TSC

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

Abbreviation: TSC = tuberculosis sclerosis complex.

SIII.3 Exposure by Age and Sex in Studies in Target Indications: Dravet Syndrome, Lennox-Gastaut Syndrome and Tuberous Sclerosis Complex

Exposure by age and sex in patients with DS or LGS or TSC is provided in Table Part II: Module SIII.4. This consists of exposure from the following:

- Pool LT-DS/LGS/TSC
- Pool EAP-DS
- Pool EAP-LGS
- Pool EAP-TSC

Table Part II: Module SIII.4: Exposure by Age and Sex in Patients with DS, LGS or TSC

Age Range	Number of Patients (N)		Person-time (Patient-years)	
	Male	Female	Male	Female
< 2	6	6	6.46	5.88
2-5	147	97	240.31	166.87
6-11	226	191	402.07	330.89
12-17	169	152	262.93	247.94
> 18-55	126	111	212.21	222.28
Total	**674**	**557**	**1123.98**	**973.86**

Abbreviations: DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; TSC = tuberculosis sclerosis complex.

Exposure by age and sex, specific to patients with TSC, from Study GWEP1521 and its OLE, and the EAP is provided in Table Part II: Module SIII.5.

Table Part II: Module SIII.5: Exposure by Age and Sex in Patients with TSC

Age Range	Number of Patients (N)		Person-time (Patient-years)	
	Male	Female	Male	Female
< 2	4	5	3.11	5.37
2-5	39	18	48.3	19.23
6-11	38	32	36.57	36.23
12-17	26	32	25.76	36.06
> 18-55	41	24	35.22	22.96
Total	148	111	148.96	119.85

Abbreviation: TSC = tuberculosis sclerosis complex.

SIII.4 Exposure by Dose in Studies in Target Indications: Dravet Syndrome, Lennox-Gastaut Syndrome or Tuberous Sclerosis Complex

Information on exposure by dose varies according to the source and the way dosing was stratified in each source. For example:

- In the pivotal studies (Pool DS/LGS/TSC), exposure is presented by treatment arm in Table Part II: Module SIII.6 and Table Part II: Module SIII.7.
- In the OLEs (Pools GWEP1415-DS/LGS and OLE-TSC), exposure by modal dose is presented in Table Part II: Module SIII.8 and Table Part II: Module SIII.9.
- In the EAP (Pool EAP-DS, Pool EAP-LGS and Pool EAP-TSC), exposure by the maximum reported dose achieved by the patient is presented in Table Part II: Module SIII.10 and Table Part II: Module SIII.11**Error! Reference source not found.**.

Table Part II: Module SIII.6: Exposure by Dose in the Pivotal Studies (Pool DS/LGS/TSC)

Dose (mg/kg/day)	Patients (N)	Person-time (Patient-years)
5	10	0.84
10	139	36.26
20	307	76.45
25	75	21.11
50	73	20.34
Total	**604**	**155.00**

Abbreviations: DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; TSC = tuberculosis sclerosis complex.

Table Part II: Module SIII.7: Exposure by Dose in the Pivotal TSC Study

Dose (mg/kg/day)	Patients (N)	Person-time (Patient-years)
25	75	21.11
50	73	20.34
Total	**148**	**41.45**

Abbreviation: TSC = tuberculosis sclerosis complex.

Table Part II: Module SIII.8: Exposure by Dose in the DS and LGS OLE (GWEP1415) and the TSC OLE (GWEP1521 OLE)

Modal Dose (mg/kg/day)	Patients (N)	Person-time (Patient-years)
≤ 20	350	521.19
> 20-30	500	895.16
>30	30	30.9
Total	**880**	**1447.25**

Abbreviations: DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; OLE = open-label extension; TSC = tuberculosis sclerosis complex.

Table Part II: Module SIII.9: Exposure by Dose in the TSC OLE (GWEP1521 OLE)

Modal Dose (mg/kg/day)	Patients (N)	Person-time (Patient-years)
≤ 25	156	110.47
> 25	43	42.44
Total	**199**	**152.91**

Abbreviations: OLE = open-label extension; TSC = tuberculosis sclerosis complex.

Table Part II: Module SIII.10: Exposure by Dose in the EAP (Pool EAP-DS, Pool EAP-LGS and Pool EAP-TSC Combined)

Maximum Dose (mg/kg/day)	Patients (N)	Person-time (Patient-years)
0 to ≤ 10	9	7.50
> 10 to ≤ 20	34	42.94
> 20 to ≤ 30	161	291.28
> 30 to ≤ 40	27	61.43
> 40	40	94.05
Total	**271**	**497.20**

Abbreviations: DS = Dravet syndrome; EAP = expanded access programme; LGS = Lennox-Gastaut syndrome; TSC = tuberculosis sclerosis complex.

Table Part II: Module SIII.11: Exposure by Dose in the Pool EAP-TSC

Maximum Dose (mg/kg/day)	Patients (N)	Person-time (Patient-years)
0 to ≤ 10	1	0.67
> 10 to ≤ 20	4	4.58
> 20 to ≤ 30	12	18.74
> 30 to ≤ 40	3	8.11
> 40	17	43.03
Total	37	75.13

Abbreviations: EAP = expanded access programme; TSC = tuberculosis sclerosis complex.

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Important exclusion criteria across the 5 pivotal CBD-OS studies (GWEP1521, GWEP1424, GWEP1414, GWEP1423 and GWEP1332B) for the indications of DS, LGS and TSC are presented in Table Part II: Module SIV.1.

Table Part II: Module SIV.1: Important Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion Criterion	Reason for Exclusion	Missing Information?	Rationale (If Not Included as Missing Information)
Patient has any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil	Standard warning	No	Will be included in SmPC warnings and precautions section
Patient has significantly impaired hepatic function at screening (Visit 1) or randomisation (Visit 2), defined as **any** of the following: ALT or AST > 5 × ULN ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5) (DS and LGS studies) TBL ≥ 2 × ULN **or** INR > 1.5 (TSC study) ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)	Regulator interaction Main route of metabolism of CBD-OS	No	Hepatic impairment study performed in development programme, and advice on dosing in such patients is in the SmPC Hepatocellular injury is present as an important identified risk
Any history of suicidal behaviour or any suicidal ideation of Type 4 or 5 on the C-SSRS	Known class effect	No	Included as an important potential risk Class labelling in SmPC warnings and precautions section
Female patient is pregnant, lactating, or planning pregnancy	Risk-benefit not justified due to lack of knowledge on fertility, foetal development and postnatal development	Yes	Included as missing information

Exclusion Criterion	Reason for Exclusion	Missing Information?	Rationale (If Not Included as Missing Information)
Patients < 2 years old with DS and LGS, patients < 1 years old with TSC	Unknown safety profile and difficult to diagnose DS, LGS and TSC before these respective ages	Yes	Included under off-label use
Patients > 18 years old with DS	Misdiagnosis of DS in > 18-year-olds an issue Frequency of seizures decreases with age making investigation difficult	Yes	Included as missing information (Section Part II: Module SVIISVII.9SVII.3.2)
Patients taking felbamate for < 1 year prior to screening	Felbamate is associated with serious adverse reactions such as aplastic anaemia and hepatic failure, most commonly within the first year of use	No	This is judged to be a risk independent to CBD-OS use

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; C-SSRS = Columbia-Suicide Severity Rating Scale; INR = international normalised ratio; SmPC = summary of product characteristics; TBL = total bilirubin; ULN = upper limit of normal.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

CBD-OS has orphan drug designation in the treatment of DS, LGS and TSC.

The clinical development programme for these severe epilepsy syndromes is unlikely to detect certain types of adverse reactions such as reactions with a frequency of < 1 in 1232 (DS, LGS and TSC population from controlled studies and the EAP), adverse reactions with a longer latency than the duration of the studies, or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table Part II: Module SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	One pregnancy was reported in the CBD-OS development programme; please refer to GWEP1431 CSR Section 9.4.1.3 for further details.
Patients with relevant comorbidities:	
Patients with cardiovascular impairment or Immunocompromised patients	Not included in the clinical development programme
Patients with a disease severity different from inclusion criteria in clinical trials	Patients from the EAP included patients with DS and LGS at severities differing to the controlled studies, as well as patients with a variety of other refractory epilepsies. Further information on exposure from this pool of patients is provided in Part II: Module SIII.
Patients with renal impairment	Twenty-four patients with varying degrees of renal impairment (mild, moderate and severe) were exposed to a single oral dose of 200 mg CBD-OS (GWEP1540 CSR)
Patients with hepatic impairment	Twenty-two patients with varying degrees of hepatic impairment (mild, moderate or severe) were exposed to a single oral dose of 200 mg CBD-OS (GWEP1539 CSR)
Population with relevant different ethnic origin	Not included in the clinical development programme
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme
Other special populations: Recreational polydrug users	Study GWEP1431 had a crossover design Overall, there were 41 patients with exposure to single doses of 750, 1500 or 4500 mg CBD-OS

Abbreviations: CBD-OS = cannabidiol oral solution; DS = Dravet syndrome; EAP = expanded access programme.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

Epidiolex (cannabidiol) CBD-OS was first approved globally in June 2018 in the United States, with full launch commencing 01 Nov 2018.

Epidyolex received full European Commission marketing authorisation approval in EEA on 19 Sep 2019. In the EEA, Epidyolex is indicated as adjunctive therapy for seizures associated with LGS or DS, in combination with clobazam, for patients 2 years of age and older. Epidyolex is also indicated for use as adjunctive therapy of seizures associated with TSC for patients 2 years of age and older.

SV.1 Post-authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Exposure estimates provided are calculated based on actual pharmacy prescription information and a simple projection methodology. The projection is used for nonreporting locations where the quantity of medicine being distributed is known but prescription data are not available. The prescription data used to project the complete exposure estimate are purchased from the US specialty pharmacies and represent a significant portion of total sales.

In addition, as per Epidyolex PRAC PSUR assessment report (Procedure no.: EMEA/H/C/PSUSA/00010798/202206 Period covered by the PSUR: 25 Jun 2021 to 24 Jun 2022), the MAH was recommended to provide estimates based on the DDD for CBD of 0.7 g.

SV.1.2 Exposure

Both methodologies detailed in Section SV.1.1 Method Used to Calculate Exposure have been included in the text below. The calculation based on the treatment information provided by specialty pharmacies is provided first, while the calculation based on exposure estimates with the DDD for CBD of 0.7 g is provided in parentheses.

Cumulatively from 19 Sep 2019 (date of CBD-OS first approval in EEA) through 12 Oct 2023, there has been an estimated 98 000 (97 900 based on DDD calculation) patient-years of exposure to CBD from post-marketing use, including marketing/distribution partner territories. The vast majority of marketing exposure was from the US with only small patient numbers exposed in the EEA.

Post-authorisation use from early access programme / managed access programme / compassionate use programme:

Cumulatively through 12 Oct 2023, there has been an estimated 5800 (5800 based on DDD calculation) patient-years of exposure with CBD-OS in EAP/compassionate use programmes.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The below summaries of important aspects of the development programme for CBD-OS in DS, LGS and TSC lead the MAH to judge there to be little or no potential for abuse or misuse for illegal purposes.

An human abuse liability study (GWEP1431) was conducted with the primary objective of evaluating the abuse potential of single doses of CBD-OS compared with ALZ at a dose of 2 mg, DRO at doses of 10 mg and 30 mg, and placebo in healthy recreational polydrug users. Cannabidiol oral solution was used at the proposed therapeutic dose of 750 mg, and at high therapeutic and supratherapeutic doses of 1500 mg and 4500 mg. For the primary endpoint of drug liking maximum effect (E_{max}) no CBD-OS dose > 15 points (clinically meaningful threshold) greater than placebo, whereas the active comparators were each > 15 points greater than placebo. All doses of CBD-OS produced a drug liking visual analogue scale E_{max} that was statistically significantly lower compared with the single dose of alprazolam and compared with both doses of DRO ($p \leq 0.0033$ in each case). In summary, this human abuse liability study confirmed that CBD-OS showed no signal for abuse potential at expected therapeutic doses and that it has only a minimal signal for abuse potential at supratherapeutic doses based on results from the primary and secondary endpoints (GWEP1431 CSR).

As with all drugs, there is a risk of overdose. CBD-OS was studied in healthy subjects (GWEP1544) at single doses up to 6000 mg (about 85 mg/kg in a 70-kg adult) and was moderately well tolerated, with diarrhoea as the most common AE. This dose showed that there is a large safety margin to prevent serious overdose.

The potential for withdrawal effects of CBD-OS were studied in a Phase 1 targeted randomised withdrawal, double-blind clinical study setting (GWEP1542). The study was conducted in healthy subjects taking a therapeutic dose (1500 mg/day [750 mg twice daily]) of CBD-OS for 1 month. After 1 month of stable dosing, subjects were randomised either to stay on CBD-OS or immediately switch to placebo, in a double-blind fashion. Results showed no evidence of a withdrawal syndrome following the abrupt discontinuation of CBD-OS compared to the treatment arm that remained on CBD-OS, based on the AE profile, overall time to onset of AEs, and assessments including the cannabis withdrawal scale and physician withdrawal checklist.

In addition to the clinical studies, the MAH has also completed a thorough nonclinical evaluation of CBD-OS in accordance with the Draft Guidance for Industry issued by the FDA for the Assessment of Abuse Potential of Drugs (FDA, 2010; FDA, 2017) and specific recommendations received from the FDA.

In vitro affinity profiling and functional studies revealed that CBD, 7-OH-CBD and 7-COOH-CBD lack appreciable affinity and functional activity at known abuse potential related targets expressed in the mammalian CNS, including the CB_1 receptor. Systemic administration of CBD does not result in CB_1 receptor agonist-like effects and has no significant effect on open-field behaviour.

Furthermore, specific in vivo studies designed to examine abuse potential revealed that CBD:

- Is not a strong positive reinforcer across a wide dose range in the cocaine or heroin-maintained rat.
- Does not induce a syndrome of physical dependence or withdrawal.
- Does not produce psychoactive effects similar to those of CB_1 receptor agonists or benzodiazepines.

Consistent with data reported in the scientific literature, these data predict that CBD-OS is unlikely to be recreationally abused by humans.

In September 2018, the Drug Enforcement Agency in the USA re-scheduled CBD-OS as Schedule V. This is a drug with lower potential for abuse than Schedule IV and consists of preparations containing limited quantities of certain narcotics.

In summary, the MAH judges there to be little or no potential risk for abuse or misuse for illegal purposes. For this reason, abuse or misuse is not included in the summary of safety concerns for CBD-OS.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Risks with Minimal Clinical Impact on Patients

The below risks are judged to be risks with minimal impact on patients.

Fatigue – tiredness type events that code to the PT Fatigue have less clinical impact than events of somnolence and sedation. In Pool DS/LGS, the frequency of fatigue was less than somnolence and sedation events (combined). In the same pool, there were also less serious events of fatigue compared to somnolence and sedation events (combined).

Decreased appetite – the clinical outcome of this would be weight decreased which is described below in "Adverse Reactions and Other Risks with Clinical Consequences".

Creatinine elevations – In Pool DS/LGS, a mean treatment-emergent increase in serum creatinine of approximately 10% was observed, mostly within 2 weeks of commencing CBD-OS. The effect stabilised with no continuous increase in creatinine elevation. There was an inconsistent picture across the studies – the effect was not clear in the LGS studies and there was no clear dose relationship. As most patients who completed the studies in Pool DS/LGS enrolled straight into the OLE (GWEP1415), reversibility upon discontinuing CBD-OS was difficult to assess. In GWEP1542, a withdrawal study in healthy volunteers, similar creatinine elevations were observed on treatment with CBD-OS – and these did reverse upon the abrupt discontinuation of CBD-OS. There did not appear to be any impact on glomerular filtration rate, as blood urea nitrogen was not elevated. For these reasons, creatinine elevations do not appear to have an important impact on patients.

Haematologic abnormalities – there were small decreases in haemoglobin and haematocrit in the All CBD-OS group in Pool DS/LGS compared to the placebo group. For haemoglobin, a mean decrease from baseline to end of treatment was -0.42 g/dL in the All CBD-OS group compared to -0.03 g/dL in the placebo group. For haematocrit, the mean decrease was -1.5% in the All CBD-OS group compared to -0.4% in the placebo group. Red blood cell indices were unaffected. Thirty percent of patients in the Pool DS/LGS group on CBD-OS had a shift from normal haemoglobin at baseline to below normal at any subsequent timepoint on CBD-OS versus 13% in the placebo group, respectively. Anaemia as an AE was reported in 2 patients in Pool DS/LGS – 1 patient in the All CBD-OS group and 1 patient in the placebo group. In summary, the hematologic abnormalities described do not appear to have an important impact on patients.

Medication errors – The applicant has not found any clear and consistent risk of medication errors from the clinical studies to date, for that reason medication errors are not considered a risk in the RMP.

There have been isolated examples of the titration schedule not being followed correctly in the Phase 2/3 studies in DS and LGS patients, as well as the OLE. It is unclear whether these were due to dosing instructions for the titration schedule, or were intentional changes designed to suit individual patient circumstances. There have also been isolated examples of leaking when drawing up the IMP, resulting in the loss of IMP, as well as spitting out by the patient – making it difficult to judge accurate amounts of IMP that were swallowed by the patient. These isolated examples have neither led to harm patients nor does there appears to be a potential risk associated with the deviations from the titration schedule, or the potential under-dosing arising from leakage or from spitting out by the patient.

In the context of the intra-patient variability in exposure to CBD after the same dose, rounding up the calculated dose to the nearest tenth of each millilitre (in a syringe graduated in 0.1-mL increments) is not expected to result in important changes to the safety of CBD-OS, particularly when steady-state is achieved.

Adverse Reactions and Other Risks with Clinical Consequences

The below risks are judged to be risks with clinical consequences that are of less importance considering the severity of the disease afflicting the target population.

Diarrhoea – In Pool DS/LGS this event occurred in 18.2% of patients in the All CBD-OS group compared with 9.6% in the placebo group, with a high frequency in the 20 mg/kg/day CBD-OS group compared to the 10 mg/kg/day group (ISS Table DSLGS.35.3.1). The diarrhoea events were all non-serious and just 2 led to discontinuation (ISS Table DSLGS.35.3.1). In Pool DS/LGS, 1 patient experienced dehydration, it appears from AE reporting that dehydration did not result from the diarrhoea. The potential clinical consequences of diarrhoea such as dehydration and electrolyte imbalances are judged to be acceptable in relation to the targeted indication of DS and LGS.

Weight decreased – In Pool DS/LGS, based on measured weight, 16% of patients in the All CBD-OS group had a decrease in weight of ≥ 5% from their baseline weight, compared to 8% of patients in the placebo group. The frequency of the weight decreases ≥ 5% was similar between the 10 mg/kg/day group (9%) and the placebo group (8%). These decreases in weight were not reported as an AE as frequently. In Pool DS/LGS, weight decreased reported as an AE occurred in 3.3% of patients in the All CBD-OS group compared with 1.4% in the placebo group (ISS Table DSLGS.9.3.1). There was no impact on growth, as measured through body mass index or height. The clinical consequences are judged to be acceptable in relation to the targeted indication of DS and LGS.

Status epilepticus – In Pool DS/LGS this event occurred in 6.4% of patients in the All CBD-OS group compared with 5.5% in the placebo group. The similar incidence of SE in the All CBD-OS and placebo groups suggests that these events are most likely spontaneous fluctuations in disease severity rather than a response to CBD-OS treatment.

Irritability – In Pool DS/LGS irritability occurred in 5.5% in the All CBD-OS group compared with 1. 7% in the placebo group. Across the development programme, this event was reported as non-serious and did not lead to discontinuation. This risk is considered to be acceptable in relation to the targeted indication of DS and LGS.

Insomnia – In a Phase 1 sleep study, a single evening therapeutic dose of CBD-OS had no significant effects on subjective or objective sleep quality, latency to persistent sleep, or sleep architecture in healthy subjects. In Pool DS/LGS, insomnia occurred in 3.3% in the All CBD-OS group compared with 2.1% in the placebo group. Across the development programme, this event was reported as non-serious and did not lead to discontinuation. This risk is considered to be acceptable in relation to the targeted indication of DS and LGS.

Off-label use – The main risk is the use of CBD-OS in unapproved epilepsy indications, resulting in a possible lack of effective seizure control and AEs from the treatment. Lack of effect has not been identified as a safety issue from the investigator-led EAP in the United States and Australia where there is experience of adjunctive use of CBD-OS in the treatment of a wide variety of refractory epilepsy syndromes beyond DS and LGS.

There is not enough information from the clinical development programme to date to be sure that there are no important adverse effects specific for patients aged < 2 years. Only a small number of patients < 2 years with treatment-resistant epilepsy in the EAP have been exposed to CBD-OS. The potential clinical consequences of off-label use are judged to be acceptable in relation to the targeted indication of DS and LGS.

Ethanol content – Each millilitre dose of CBD-OS, containing 100 mg of CBD, contains 10% v/v of ethanol. Each millilitre dose contains less ethanol than the same volume of wine.

Current EMA guidance states that ethanol containing medicines should not raise BACs above 0.01 g/L in patients aged < 6 years (EMA/CHMP/507988/2013).

At the lower recommended therapeutic dose of 10 mg/kg/day, a single dose of 5 mg/kg CBD-OS in a 10-kg child results in a BAC of 0.007 g/L, well within the recommended threshold of 0.01 g/L.

At the highest recommended therapeutic dose of 20 mg/kg/day, a single dose of 10 mg/kg CBD-OS in a 10-kg child theoretically results in a BAC of 0.013 g/L, slightly above the recommended threshold of 0.01 g/L.

In light of the wide safety margins observed in toxicology studies and taking the severity of the condition into account, this theoretical risk is judged to be acceptable.

The consequences of long-term ethanol intake from children aged under 6 years taking CBD-OS is not yet known. Effects of alcohol in children aged < 6 years may include sleepiness, behavioural changes and impaired ability to concentrate and participate in school activities.

A warning/precaution relating to the ethanol content in CBD-OS, particularly in patients aged under 6 years, has been added to SmPC Section 4.4.

With regards to possible overdose/accidental poisoning, in a worst-case scenario where a 10-kg child swallows a whole bottle of CBD-OS (100 mL, which is less than a small glass of wine), the theoretical BAC achieved would be 1.3 g/L. This is well below the maximum BAC permitted of 3 g/L (EMA/CHMP/507988/2013).

Furthermore, it should be noted that concurrent ethanol intake through alcoholic drinks is considered unlikely in the target population. No clear signs of ethanol intoxication (including hypoglycaemia and hypothermia) relating to CBD-OS use have been observed in the clinical development programme.

For these reasons, this potential risk is not considered important in the target population.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1 Important Identified Risk: Hepatocellular injury

Risk-benefit Impact

Hepatocellular injury is an important identified risk for CBD-OS, therefore impacting the risk-benefit assessment.

From the pivotal studies (Pool DS/LGS) in which patients were dosed for a nominal 98 days, TE ALT > 3 × ULN captured by the central laboratory occurred in:

3.1% of patients in the 10 mg/kg/day group (n = 131).

15.9% of patients in the 20 mg/kg/day group (n = 298).

0.7% of patients receiving placebo (n = 285).

TE ALT > 3 × ULN was almost twice as common as TE AST > 3 × ULN (8.8%), suggesting that the origin of the ALT elevation was the liver as opposed to other organ sources.

From the pivotal studies, TE ALT ≥ 5 × ULN (a criterion for potential DILI cases, based on the definition from an International Expert Working group [Aithal, 2011]) occurred in:

- 1.5% of patients in the 10 mg/kg/day group (n = 131).
- 6.7% of patients in the 20 mg/kg/day group (n = 298).
- 0.7% of patients receiving placebo (n = 285).

Concomitant VPA, the 20 mg/kg/day dose of CBD-OS, and elevated baseline ALT levels each increased the risk for TE elevations of ALT including elevation to ≥ 5 × ULN.

No severe liver injury has been observed. However, as elevated ALT and/or AST levels can be the first sign of DILI, this would affect how CBD-OS may be used in a patient.

Further information is contained within the Core Liver Safety Report.

SV.II.1.2.2 Important Identified Risk: Somnolence and sedation

Risk-benefit Impact

Somnolence is an important identified risk because it was the single most common AE PT across all groups in the RCTs (Pool DS/LGS) and was consistently more frequent in patients treated with CBD-OS compared with placebo. Somnolence was the third most common TEAE leading to discontinuation of CBD-OS in Pool DS/LGS, and of the 111 patients in the All CBD-OS group with somnolence, 7 patients (6.3%) had serious events and 7 patients (6.3%) had events that led to discontinuation. Sedation occurred less frequently than somnolence but is a medically

similar event. Sedation was reported in 21 patients (4.6%) in the All CBD-OS group compared with 2 patients (0.7%) in the placebo group in Pool DS/LGS. Of the 21 patients in the All CBD-OS group with sedation, 1 patient had a serious event and in none of the 21 patients did the sedation lead to discontinuation.

The applicant has included measures in the Special Warnings and Precautions for Use section of the proposed SmPC that instruct the prescriber to monitor for somnolence and sedation.

SVII.1.2.3 Important Identified Risk: Lethargy

Risk-benefit Impact

Lethargy is an important identified risk for patients with DS or LGS. Lethargy was reported in 23 patients (5.0%) in the All CBD-OS group compared with 7 patients (2.4%) in the placebo group, in Pool DS/LGS. Of the 23 patients in the All CBD-OS group with lethargy, 3 patients (13.0%) had serious events and 2 patients (8.7%) had events that led to discontinuation.

SVII.1.2.4 Important Identified Risk: Pneumonia

Risk-benefit Impact

Pneumonia is an important identified risk for patients with DS or LGS, in consideration of the significant intellectual disabilities associated with the conditions.

Patients on CBD-OS in the controlled studies have experienced a greater frequency of pneumonia than those on placebo. Overall, in Pool DS/LGS, there were 28 patients with pneumonia (PTs: pneumonia, pneumonia aspiration, pneumonia bacterial, pneumonia adenoviral, pneumonia viral, pneumonia mycoplasmal and pneumonia respiratory syncytial virus) on CBD-OS (6.1 %) compared with 4 patients on placebo (1.4%).

In terms of seriousness, in Pool DS/LGS, 20 patients in the All CBD-OS group and 1 patient in the placebo group reported SAEs. The only fatality in the All CBD-OS group was attributed to acute respiratory distress syndrome as a complication of aspiration pneumonia in a patient with a complex medical history, including previous episodes of acute respiratory distress syndrome and pneumonia (Module 2.7.4, Section 2.1.2.1).

Pneumonia has been categorised as an important identified risk based on the imbalance between the All CBD-OS group and the placebo group in Pool DS/LGS; however, further characterisation is important and the applicant will use a targeted follow-up technique for post-marketing events of pneumonia to document reports of pneumonia more completely. Further characterisation may uncover risk factors that will help to minimise the risk-benefit impact of pneumonia, or help to confirm the risk as identified.

SVII.1.2.5 Important Identified Risk: Rash Hypersensitivity Reactions

Risk-benefit Impact

Rash hypersensitivity events are an important identified risk.

In the target population, the frequency of rash events and excess over placebo is important. In Pool DS/LGS, the AESI group: rash, generalised maculopapular rash incidence was 8.6% in the All CBD-OS group compared with 2.7% in the placebo group. In the All CBD-OS group, the most common AESI PTs were rash (4.2% in the All CBD-OS group vs 1.0% in the placebo

group), rash generalised (1.3% vs 0.3%), rash maculopapular (1.1% vs 0.3%), viral rash (0.9% vs 0%), and rash erythematous (0.7% vs 0%). Three patients in the All CBD-OS group reported an event that was both serious and led to discontinuation (PTs: maculopapular rash and rash). Another patient in the All CBD-OS group reported a rash that led to discontinuation. No rashes with mucosal involvement were reported.

In Pool H-MD, an unusually higher percentage of patients in the All CBD-OS group compared with the placebo group met the criteria for AESI rash, generalised maculopapular rash (15.2% [N = 125] vs 0% [N = 6]) (ISS Table HMD.31.11.1). Specifically, this high incidence of rash was confined to two Phase 1 studies in healthy subjects at the same site (Module 2.7.4, Section 2.1.5.3.2). No rashes were judged to be SAEs; however, 12 of the 19 events in Pool H-MD did lead to discontinuation.

An independent expert consultant reviewed the data from the two Phase 1 studies, which showed an unusually high incidence of rash, as well as rash cases from the overall clinical development programme. This Rash Safety Report concluded that there could be more serious rashes with exposure in greater numbers of patients. Despite most rashes being nonserious, based on the frequency observed as well as the conclusions of the Rash Safety Report, this risk requires further evaluation as part of the pharmacovigilance programme.

SVII.1.2.6 Important Potential Risk: Suicidality

Risk-benefit Impact

Suicidality (suicidal behaviour and ideation) is a risk with all ASMs. A statistical meta-analysis of 11 ASMs performed by the FDA in 2008 (FDA statistical review: Antiepileptic drugs and suicidality) concluded that ASMs, regardless of class or mode of action, are associated with an increased risk of suicidality, relative to placebo in RCTs. Cannabidiol oral solution is an ASM and therefore is implicated in this conclusion.

Suicide-related events have also been reported more often in people with epilepsy compared with the general population (Barraclough, 1987; Bell, 2009).

From the clinical development programme, there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events.

However, taken together, and in view of the seriousness and potential clinical outcomes, suicidality has been added as an important potential risk for CBD-OS in the indications of DS and LGS.

SVII.1.2.7 Important Potential Risk: Seizure Worsening

Risk-benefit Impact

Seizure worsening is an important potential risk for CBD-OS. Seizure worsening may impact on quality of life, morbidity and mortality associated with specific seizure types, which are described and referenced further in Part II Module SI.6. Seizure worsening may constitute an increased frequency of seizures (specific types, or all), or an increase in the duration or severity of seizures. Some ASMs are known to elicit new seizure types. Worsening seizures or failure to respond to an ASM is a risk with any new treatment for seizures, and can be managed by discontinuation or dose reduction.

Based on seizure count data in the two pivotal LGS studies, some patients receiving 20 mg/kg/day CBD-OS, in the absence of clobazam, were more likely to experience a ≥ 25% increase in primary seizure frequency than those receiving placebo. This was not the case in the 10 mg/kg/day CBD-OS group. Furthermore, unlike the observations for drop seizures in patients with LGS, in the DS studies, increases in primary seizure frequency were less frequent with CBD-OS groups compared with placebo.

On a population level, it should be noted that in each LGS study, 20 mg/kg/day CBD-OS in the absence of CLB also showed greater reductions in drop seizure frequency than placebo.

SVII.1.2.8 Important Potential Risk: Aggression

Risk-benefit Impact

Aggression events would have impact on risk-benefit assessment if aggression events with serious or important outcomes occur.

To date, while aggression events have been more common in patients on CBD-OS than placebo, there is no clear association of aggression events with important outcomes.

For these reasons, aggression is an important potential risk.

SVII.1.2.9 Important Potential Risk: Euphoria

Risk-benefit Impact

Euphoria was not observed in clinical studies involving patients with DS or LGS. Therefore, there is no considered impact of euphoria on the benefit-risk assessment.

To date a low number of AEs of euphoric mood were reported only in a Phase 1 setting of polydrug abusers. The incidence of euphoria was similar across the different dose groups and did not show a dose relationship. All events were reported as mild, resolved without intervention, no action was taken with the study drug, none of the events were SAEs.

Based on the totality of the evidence, the risk of euphoria is considered to be low and is assessed as an important potential risk.

SVII.1.2.10 Important Potential Risk: Impact on Cognitive Development

Risk-benefit Impact

Negative cognition-related events would have impact on the risk-benefit assessment if they occur with serious or important outcomes.

To date, there is no clear association of negative cognition-related events, with important outcomes, in patients on CBD-OS. Improved control of seizures should result in improved cognitive functioning. DS and LGS patients are typically treated with multiple ASMs, which will confound assessment of CBD effects to cognitive development. In addition, neurocognitive status may already be impaired in some of the indicated population.

For these reasons, impact on cognitive development is an important potential risk.

SVII.1.2.11 Important Potential Risk: Urinary Retention

Risk-benefit Impact

Urinary retention is an important potential risk for patients with DS or LGS on CBD-OS. Urinary retention was reported in both males and females, with 6 patients (1.3%) in the All CBD-OS group compared with 1 patient in the placebo group in pivotal studies (Pool DS/LGS). Of the 6 patients in the All CBD-OS group with urinary retention, no patients had events that led to discontinuation.

SVII.1.2.12 Missing Information: Exposure During Pregnancy and Lactation

Risk-benefit Impact

Female patients who were pregnant, lactating, or planning pregnancy were excluded from the clinical studies in the development programme for CBD-OS. A risk-benefit assessment should be performed by the prescriber if considering use of CBD-OS in a pregnant patient, or a patient that is lactating. There is not enough information at this point to be confident that there are no important adverse effects specific to this population. This includes possible toxicity or loss of seizure control during pregnancy and possible effects on the developing foetus.

Further information on pregnancy outcomes in patients who received CBD-OS, while pregnant would help characterisation of this missing information, as would information on the mother and baby in cases where CBD-OS is administered to a nursing mother. Given the target patient population, exposure during pregnancy and lactation to CBD-OS is expected to be limited.

SVII.1.2.13 Missing Information: Long-term Safety

Risk-benefit Impact

There is no evidence that the long-term use of CBD-OS would yield a different safety profile to that seen in the clinical development programme for CBD-OS. Long-term experience with CBD-OS is as follows:

- The long-term OLE Study GWEP1415 included 391 patients (120 DS and 271 LGS) with > 12 months' exposure and showed that the safety profile of CBD-OS is consistent over time and very similar to the profile observed in the RCTs.
- The EAP provided an additional 279 patients (including 41 DS and 50 LGS) with > 12 months' continuous exposure. Of these patients, a total of 121 patients had been on CBD-OS for ≥ 2 years. Again, the safety profile of CBD-OS in the EAP was consistent with the RCTs and GWEP1415.

It is difficult to fully define the risks of long-term exposure. There is not enough information from the clinical development programme to date to be sure that there are no important adverse effects that may not have arisen from long-term exposure to date. Further characterisation of the long-term safety of CBD-OS is needed through post-marketing pharmacovigilance.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Post-marketing safety data collected for > 4 years since first approval in the EEA in 2019 have been evaluated in their totality. Together with any relevant findings from the clinical development programme for CBD-OS, the list of important identified and potential risks as well as missing information have been updated.

With respect to ongoing PV activities, there is an ongoing EU PASS study (GWEP21042) collecting safety data on the important identified risk of hepatocellular injury, the important potential risk of impact on cognitive development and the missing information of overall long-term safety. In addition, there is an ongoing Phase 4 long-term liver study in the USA (GWEP19022) and the MAH is participating in two external pregnancy registries (the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) and the North American Antiepileptic Drug Registry).

Since no confirmed signals have arisen from the post-marketing reports, and there are no ongoing additional PV activities or risk minimisation measures associated with selected identified risks, as well as no new consistent characteristics having been identified, it is felt that some risks can be adequately followed up via routine post marketing surveillance. The following 4 important identified risks below are removed from the list of safety concerns:

- Somnolence and sedation
- Lethargy
- Pneumonia
- Rash hypersensitivity reactions

In addition, the following 3 important potential risks below are also removed from the list of safety concerns for the same reasons mentioned above:

- Aggression
- Euphoria
- Urinary retention

Justifications for the removal of these important identified and potential risks are provided below.

Important Identified Risks

Somnolence and Sedation

Information for prescribers concerning somnolence and sedation is described in SmPC section 4.4 “Special warnings and precautions for use”, section 4.5 “Interaction with other medicinal products and other forms of interaction”, section 4.7 “Effects on ability to drive and use machines” and section 4.8 “Undesirable effects”.

From the pooled DS/LGS/TSC clinical studies, for patients treated with CBD-OS (n = 604) from 5 to 50 mg/kg/day, there were 140 (23.2%) reports of somnolence (35/368, ie, 9.5% in patients receiving placebo). In the CBD-OS treated patients, 7 (5.0%) of the somnolence events were serious (at 10 mg/kg/day [2] and 20 mg/kg/day [5]). Additionally, there were 22 (3.6%) reports

of sedation in CBD-OS treated patients (and 3, i.e., 0.8% in placebo), among which 1 (4.5%) was serious at 10 mg/kg/day (Table Part II: Module SVII.1).

Table Part II: Module SVII.1: Pooled DS/LGS/TSC Clinical Studies Event Numbers and Frequency

	CBD-OS treatment		Placebo	
Preferred term	**Total TEAEs (n = 604) N (%)**	**Proportion of Serious TEAEs (n = 604) N (%)**	**Total AEs (n = 368) N (%)**	**Proportion of Serious AEs (n = 368) N (%)**
Somnolence	140/604 (23.2)	7/140 (5.0%)	35/368(9.5)	0
Sedation	22/604 (3.6)	1/22 (4.5%)	3/368 (0.8)	0

Abbreviations: AE = adverse event; CBD-OS = cannabidiol oral solution; DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; TEAE = treatment-emergent adverse event; TSC = tuberous sclerosis complex.

From longer-term experience, data from pooled DS/LGS/TSC open-label extension studies (n = 880) showed that somnolence and sedation events were generally in line with RCT data. The median duration of exposure to CBD-OS treatment in these studies was 423 days.

Comparing this to the post-marketing experience for somnolence and sedation events, cumulatively up to the DLP of 12 Oct 2023 (data lock point for the 5-year marketing authorisation renewal for Epidyolex), out of a total of 780 somnolence and 100 sedation post-marketing cases, 60 (7.7%) and 10 (10.0%) were serious, respectively. Considering spontaneous reports are more likely to be reported if they are serious, after evaluation of these cases, this was not considered a significant increase in numbers. Therefore, considering qualitative signal evaluation of the post marketing experience to date, no change of the characteristics of the risk of somnolence and sedation has been identified. In the majority of the serious cases multiple AEs were reported concurrently, which led to the cases being reported as serious cases. It is noted from post-marketing reports that prescribers adjust doses of Epidyolex/concomitant medications such as clobazam in individual patients based on the degree of somnolence/sedation while balancing the dose against other factors such as the effectiveness of seizure control. In line with the clinical studies data on somnolence/sedation, improvement in symptoms with time were also reported in many post-marketing reports. The various existing text in sections of the EU-SmPC remain to inform prescribers regarding the risk of somnolence and sedation with CBD-OS, however the events are proposed to be removed from the RMP as an important identified risk.

Lethargy

In section 4.8 “Undesirable effects” of the SmPC, lethargy is listed as a common adverse reaction from clinical studies.

From the pooled DS/LGS/TSC clinical studies, for patients treated with CBD-OS (n = 604) from 5 to 50 mg/kg/day, there were 30 (5.0%) reports of lethargy (12/368, i.e., 3.3% in patients

receiving placebo). In the CBD-OS treated patients, 3 (10.0%) reports were serious at 20 mg/kg/day.

In addition, data from pooled DS/LGS/TSC open-label extension studies were also taken into consideration. For patients treated with CBD-OS (n = 880) from 5 to 50 mg/kg/day, there were 60 (6.8%) reports of lethargy, which were all non-serious.

Cumulatively up to the DLP of 12 Oct 2023 (data lock point for the 5-year marketing authorisation renewal for Epidyolex), out of a total of 178 post-marketing lethargy cases, 28 (15.7%) were serious, while 150 (84.3%) were non-serious.

Considering spontaneous reports are more likely to be reported if they are serious, after evaluation of these cases, this was not considered a significant increase in numbers. Therefore, considering qualitative signal evaluation of the post marketing experience to date, no change of the characteristics of the risk of lethargy has been identified. Lethargy remains an ADR in Section 4.8 of the EU-SmPC, however lethargy is proposed to be removed from the RMP as an important identified risk.

Pneumonia

In section 4.8 “Undesirable effects” of the SmPC, pneumonia is listed as a common adverse reaction from clinical studies. Grouped Terms in the SmPC included: pneumonia, pneumonia RSV, pneumonia mycoplasmal, pneumonia adenoviral, pneumonia viral, aspiration pneumonia.From the pooled DS/LGS/TSC clinical studies, for patients treated with CBD-OS (n = 604) from 5 to 50 mg/kg/day, there were 33 (5.5%) patients with pneumonia (compared to 5/368, i.e., 1.4% patients receiving placebo), the most frequent PTs were pneumonia (26) and pneumonia aspiration (5, 0.8%).

In addition, data from pooled DS/LGS/TSC open-label extension studies (n = 880) showed that there were 111 (12.6%) events relating to pneumonia reported. Three cases of pneumonia led to treatment discontinuation (Table Part II: Module SVII.2).

Table Part II: Module SVII.2: Pneumonia Events Received from Pooled DS/LGS/TSC Open-Label Extension Studies

Event	Number of patients with at least 1 Pneumonia Adverse Event (n = 880) N (%)
Pneumonia	94 (10.7)
Pneumonia aspiration	20 (2.3)
Pneumonia bacterial	3 (0.3)
Pneumonia viral	3 (0.3)
Pneumonia pseudomonal	2 (0.2)
Pneumonia staphylococcal	2 (0.2)
Atypical pneumonia	1 (0.1)
Pneumonia influenzal	1 (0.1)
Pneumonia respiratory syncytial viral	1 (0.1)
Post procedural pneumonia	1 (0.1)
Total number of patients with at least 1 Pneumonia event	**111 (12.6)**

Abbreviations: DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome; TSC = tuberous sclerosis complex.
Note: From Table 40. AESI: Pneumonia OLEDSLGSTSC.40.11.1 Crude Incidence by SOC and PT OLE-DS/LGS/TSC - Safety Analysis Set

Cumulatively up to the DLP of 12 Oct 2023 (data lock point for the 5-year marketing authorisation renewal for Epidyolex), no trends for a specific pneumonia aetiology have been observed from clinical study or post-marketing sources. Specifically, from post-marketing sources, out of a total of 385 pneumonia post-marketing cases (Table Part II: Module SVII.3), 10 types were represented, among which the most frequent one was aspiration pneumonia/pneumonitis. Among 274 the Pneumonia (NOS) events 262 were serious and 12 non-serious, while the remaining pneumonia events with a specified aetiology were all serious.

Table Part II: Module SVII.3: Pneumonia Events Received from Post-marketing Sources from 19 Sep 2019 to 12 Oct 2023

Event	Number
Pneumonia	274
Pneumonia aspiration/Pneumonitis aspiration	72
COVID-19 pneumonia	14
Pneumonia bacterial	7
Pneumonia pseudomonal	5
Pneumonia respiratory syncytial viral	5
Pneumonitis	3
Pneumonia klebsiella	2
Pneumonia viral	1
Atypical pneumonia	1
Pneumonia influenzal	1
Total	**385**

Abbreviation: COVID-19 = corona virus disease 2019.

Pneumonia was originally categorised as an important identified risk based on the imbalance between the All CBD-OS group and the placebo group in the DS and LGS pivotal clinical studies, however further attempts at characterisation through targeted follow-up for post-marketing events of pneumonia has not revealed any consistency in risk factors that will help to minimise the risk- of pneumonia. The available information from post marketing surveillance suggests a generally similar pattern in the different types of pneumonia reported with Epidyolex as seen with clinical studies, with possibly the exception of corona virus disease-2019-associated pneumonia.

Overall, no new characteristics of pneumonia associated with Epidyolex use has become evident from post-marketing surveillance with utilisation of a targeted follow up questionnaire. Pneumonia remains an ADR in Section 4.8 of the EU-SmPC; however, the event is proposed to be removed from the RMP as an important identified risk.

Rash Hypersensitivity Reactions

In section 4.8 “Undesirable effects” of the SmPC, rash is listed as a common adverse reaction from clinical studies. Section 4.3 “Contraindications” mentions hypersensitivity to the active substance or to any of the excipients listed in section 6.1, ie, refined sesame oil, anhydrous ethanol, sucralose (E955), strawberry flavour (including benzyl alcohol).

From the pooled DS/LGS/TSC clinical studies, for patients treated with CBD-OS (n = 604) from 5 to 50 mg/kg/day, the following 53 (8.8%) PTs were reported: rash (30), rash generalised (6), rash maculopapular (5), viral rash (5), rash erythematous (4), rash macular (4) and rash popular (2). In patient treated with placebo the grouped terms of rash, generalised maculopapular rash were 11/368, i.e., 3.0%.

In addition, data from pooled DS/LGS/TSC OLE studies (n = 880) showed that there were 67 subjects with at least 1 event of Rash, Generalised maculopapular rash, which were all non-serious (Table Part II: Module SVII.4).

Table Part II: Module SVII.4: Grouped Event Terms of Rash, Generalised Maculopapular Rash Received from OLE Sources from 19 Sep 2019 to 12 Oct 2023

Event	Number of patients with at least one grouped term relating to rash, generalised maculopapular rash (n = 880) N (%)
Rash	40 (4.5)
Rash generalised	10 (1.1)
Rash macular	7 (0.8)
Rash maculo-papular	6 (0.7)
Rash erythematous	4 (0.5)
Candida nappy rash	2 (0.2)
Rash papular	2 (0.2)
Rash pustular	1 (0.1)
Viral rash	1 (0.1)
Genital rash	1 (0.1)
Exfoliative rash	1 (0.1)
Perineal rash	1 (0.1)
Total number of patients with at least one grouped term relating to rash, generalised maculopapular rash	**67**

Abbreviation: OLE = open-label extension.
Note: From Table 31. AESI: Rash, Generalized maculopapular rash OLEDSLGSTSC.31.11.1 Crude Incidence by SOC and PT OLE-DS/LGS/TSC - Safety Analysis Set

Cumulatively up to the DLP of 12 Oct 2023 (data lock point for the 5-year marketing authorisation renewal for Epidyolex), out of 410 post-marketing case reports (corresponding to 452 events) within the “Hypersensitivity” SMQ narrow, 70 (15.5%) events were serious. The most frequent serious events were rash, drug hypersensitivity and hypersensitivity (often not in relation to Epidyolex but to other concomitant medication). Two cases of anaphylactic reaction (one to peas and the other case to one of the several concomitant medication), 2 angioedema and 3 shock (all poorly documented) were reported.

Out of 31 case reports (corresponding to 32 events) within the “Serious Cutaneous Adverse Reactions” SMQ broad, 6 events were serious, each of them with 1 occurrence: anal blister, mouth ulceration, stomatitis, conjunctivitis, drug eruption, erythema multiforme.

Serious cases of rash from post-marketing sources were mostly ‘medically significant’ rather than requiring hospitalisation and intensive treatment. There have been no confirmed reports of

severe skin reactions from any source, such as Stevens–Johnson syndrome /toxic epidermal necrolysis (SJS/TEN). No further consistent information on a possible characteristic morphology and/or rash presentation that may be caused by CBD-OS has emerged to date.

Overall, no change to the characterisation of rash hypersensitivity reactions has become evident from clinical study and post-marketing experience since 2019. Rash remains an ADR in Section 4.8 of the EU-SmPC, and the contraindication remains in Section 4.3 relating to hypersensitivity to CBD, or any other excipient in the formulation – however, rash hypersensitivity reactions is proposed to be removed from the RMP as an important identified risk.

Important Potential Risks

Aggression

In section 4.8 “Undesirable effects” of the SmPC, aggression is listed as a common adverse reaction from clinical studies.

From the pooled DS/LGS/TSC clinical studies, irritability was reported in 34/604 patients treated with CBD-OS (5.6%) and in 9/368 patients treated with placebo (2.4%). Aggression was reported in 22/604 patients (3.6%) receiving CBD-OS, and in 6/368 patients receiving placebo (1.6%). None of the events were serious.

In addition, data from pooled DS/LGS/TSC open-label extension studies (n = 880) showed that there were 61 (6.9%) events of irritability and 60 (6.8%) of aggression (among which 1 [0.1%] and 3 [0.3%] were serious, respectively), for a total of 109 (12.4%) subjects with at least 1 Aggression, Irritability AESI.

From the post-marketing sources to date, there were 255 cases with the PT aggression, of 22 (9%) were serious and of the 146 cases with the PT irritability, 9 (6%) were serious. It appears to remain the case that the events of this nature remain generally non-serious, as was seen in the clinical studies.

To date, whilst aggression events have been more common in patients on CBD-OS compared with placebo in the clinical studies, aggression events are not clearly associated with important outcomes, in both clinical and post-marketing settings. No signal has emerged from any source for more severe psychiatric events to be associated with CBD-OS, for which the signal of aggression/irritability type events may have been a precursor for.

Considering spontaneous reports are more likely to be reported if they are serious, after evaluation of these cases, this was not considered a significant increase in numbers. Therefore, considering qualitative signal evaluation of the post marketing experience to date, no change of the characteristics of the risk of aggression has been identified. Aggression remains an ADR in Section 4.8 of the EU-SmPC, however the event is proposed to be removed from the RMP as an important potential risk.

Euphoria

In SmPC Section 5.3 “Preclinical safety data”, it is reported that animal abuse-related studies show that cannabidiol does not produce cannabinoid-like behavioural responses, including generalisation to delta-9-tetrahydrocannabinol (THC) in a drug discrimination study. Cannabidiol also does not produce animal self-administration, suggesting it does not produce rewarding effects.

From the pooled DS/LGS/TSC clinical studies, from a total of 604 patients treated with CBD-OS from 5 to 50 mg/kg/day, there was 1 non-serious report of euphoric mood (none in placebo from a total of 368 patients).

To date a small number of adverse events of euphoric mood were reported only in a Phase 1 setting of polydrug abusers in a dedicated human abuse liability study (GWEP1431). The incidence of euphoria was similar across the different CBD-OS dose groups and did not show a dose relationship. All events were reported as mild, resolved without intervention, no action was taken with the study drug, none of the events were serious AEs.

In addition, data from pooled DS/LGS/TSC open-label extension studies were also taken into consideration. From a total of 880 patients treated with CBD-OS from 5 to 50 mg/kg/day, there were 3 (0.3%) cases of euphoric mood, which were all non-serious.

Generally, AEs relating to euphoria, or euphoria-like responses are important with respect to the possible abuse potential of a drug. A total of 8 case reports were received during the interval for the PT “Euphoric mood”, among which 1 was serious and confounded by a positive result for marijuana in the bloodstream. Evaluation of the post marketing case reports of euphoria-like events, as well as actual case reports of abuse and misuse has shown that either other products appeared to be referred to with respect to abuse (eg, cocaine, cannabis joints, alcohol) or there was not enough information to evaluate whether actual abuse/misuse of CBD-OS occurred. Overall, these cases were not considered to be instances of true abuse/misuse.

Overall, no change to the characterisation of potential risk of euphoria has become evident from clinical study and post-marketing experience. The event is proposed to be removed from the RMP as an important potential risk.

Urinary Retention

Urinary retention is not a listed event in the Epidyolex SmPC.

From the pooled DS/LGS/TSC clinical studies, from a total of 604 patients treated with CBD-OS from 5 to 50 mg/kg/day, there were 8 patients (1.3%) of urinary retention (vs 1 patient receiving placebo from a total of 368 patients) which were all non-serious. In addition, data from pooled DS/LGS/TSC open-label extension studies were also taken into consideration. For a total of 880 patients treated with CBD-OS from 5 to 50 mg/kg/day, there were 21 cases of urinary retention (2.4%).

Out of the 32 post-marketing case reports of urinary retention that were received, the majority of cases were reported along with other confounding events, which by themselves are risk factors for urinary retention. These included previous history of urinary retention, scoliosis surgery, multiple sclerosis or constipation. Some of the urinary retention events were reported as occurring when the patient had other ongoing comorbidities such as pneumothorax, ileus and non-obstructive renal failure. In some cases, urinary retention was reported along with neurogenic bladder, concurrent UTI, dysuria, haematuria, chromaturia and even bowel or bladder incontinence. In a number of cases a single episode urinary retention was reported with a latency period was more than a year and in many cases the patients have continued dosing with Epidyolex. After individual review of these cases, it is clear that in majority of the reported events of urinary retention, other concurrent events are more likely to have contributed to the

urinary retention. Overall, the individual review of the post-marketing cases did not suggest a causal association to CBD-OS.

The important potential risk at the time of initial approval does not appear to have been borne out in post-marketing experience. Therefore, urinary retention is proposed to be removed from the RMP as an important potential risk.

SVII.3 Details of Important Identified Risks, Important Potential Risks and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Identified Risk: Hepatocellular injury

Potential Mechanisms

There are in vitro data suggesting that 7-COOH-CBD could cause serum ALT elevations via direct action on hepatic mitochondria at concentrations achieved in vivo.

HepG2 cells were incubated for 1 hour or 24 hours with CBD and its major plasma metabolite, 7-COOH-CBD and analysed for effects on mitochondrial function via the mitochondria stress test measured in the Seahorse XF Analyzer. Three independent experimental runs were completed.

CBD showed the potential for mitochondrial ETC inhibition with an oxygen consumption rate reduction at 1 hour and 24 hours (mean minimum effective concentration of 4.9 and 4.1 µM for 1 and 24 hours, respectively). 7-COOH-CBD also showed the potential for mitochondrial ETC inhibition with oxygen consumption rate reduction at 1 and 24 hours (mean minimum effective concentration of 35 and 34.9 µM for 1 and 24 hours, respectively).

The commonly used ASM, VPA and its metabolite 4-ene-VPA, have been implicated as ETC inhibitors (Komulainen, 2015). Therefore, a potential interaction effect between CBD and VPA at the level of the mitochondrion could underlie observations in the clinical data. This hypothesis is currently being investigated further via additional data collection and simulations in collaboration with CCI [redacted]. Further information is described in the Core Liver Safety Report.

From the clinical data, rapid reversal of the ALT elevations with or without continued treatment with CBD-OS, together with the general absence of clinical hypersensitivity signs, make involvement of an innate or/and adaptive immune response unlikely. This is somewhat reassuring as it makes occurrence of a sudden and severe idiosyncratic liver injury less likely (Core Liver Safety Report).

Evidence Source(s) and Strength of Evidence

Clinical study results have shown that CBD-OS is associated with dose-related ALT elevations in a subset of patients. AST elevations have also been observed, but to a lesser extent than ALT. No severe liver injury has been observed. However, as elevated ALT and AST can be the first sign of a DILI, this would affect how CBD-OS may be used in a patient.

Characterisation of the Risk

Summary

- Results from the RCTs showed that CBD-OS was associated with dose-related ALT elevations in a subset of patients and a lesser number with AST elevations.
- Evaluation of the liver test results and AE reports from the 961 patients with DS, LGS or TSC (Pool LT-DS/LGS/TSC) who were administered long-term CBD-OS did not identify any patient as meeting published consensus criteria for severe DILI. None of the clinical study patients were identified as meeting Hy's law.
- This was also true for patients from all other studies, including an EAP in the USA and Australia involving 1067 patients that represents more "real-world" use of CBD-OS.
- Among the 961 patients on CBD-OS in Pool LT-DS/LGS/TSC, there were 80 patients (8.3%) who met the DILI criterion of TE ALT ≥ 5 × ULN.
- The elevations tended to occur early in treatment. In the pivotal studies (Pool DS/LGS/TSC), the period of risk for an ALT elevation to ≥ 5 × ULN was generally confined to the first 60 days of treatment.
- Concomitant VPA, higher doses of CBD-OS, and elevated baseline ALT levels increased the risk for TE elevations of ALT, including elevation to ≥ 5 × ULN.

Detailed characterisation

The intention of this section is to characterise the important potential risk of hepatocellular injury to an appropriate level of detail for a RMP. Greater detail on most of the observations below can be obtained from the Core Liver Safety Report and Ancillary Liver Safety Report, including detailed narratives and graphical displays for individual patients with TE ALT or AST > 3 × ULN, liver-related SAEs, or liver-related TEAEs leading to discontinuation.

Frequency and dose

From the pivotal studies (Pool DS/LGS/TSC), TE ALT > 3 × ULN captured by the central laboratory occurred in:

- 3.1% of patients in the 10 mg/kg/day group (n = 131)
- 15.9% of patients in the 20 mg/kg/day group (n = 298)
- 12.0% of patients in the 25 mg/kg/day group (n = 75)
- 24.7% of patients in the 50 mg/kg/day group (n = 73) – (dose not being applied for)
- 0.6% of patients receiving placebo (n = 361).

TE ALT > 3 × ULN was more common than TE AST > 3 × ULN, suggesting that the origin of the ALT elevation was the liver as opposed to other organ sources. Hence, the subsequent characterisation of this risk will focus on ALT; however, analysis results for AST and AT (ALT and/or AST) are provided in the Core Liver Safety Report and Ancillary Liver Safety Report.

From the pivotal studies, TE ALT ≥ 5 × ULN (a criterion for potential DILI cases, based on the definition from an International Expert Working group) occurred in:

- 1.5% of patients in the 10 mg/kg/day group (n = 131)
- 6.7% of patients in the 20 mg/kg/day group (n = 298)
- 6.7% of patients in the 25 mg/kg/day group (n = 75)
- 11.0% of patients in the 50 mg/kg/day group (n = 73) – (dose not being applied for)
- 0.6% of patients receiving placebo (n = 361).

At both thresholds, there is a clear correlation to CBD-OS dose. This is supported by a population pharmacokinetic analysis in LGS patients where consistent, statistically significant correlations ($p<0.01$) were observed for ALT > 2 × ULN and AST > 2 × ULN, suggesting that increasing exposure to CBD and its 7-OH-CBD metabolite was associated with an increased frequency of TE ALT and AST elevations > 2 × ULN (GWPP17004 CSR). In TSC patients, increasing exposure to the 7-OH-CBD was significantly correlated with an increased frequency of TE AST elevations > 2 × ULN; however, the magnitude of exposure effect appears to be limited (GWPP19217 CSR).

Among the 961 patients on CBD-OS in Pool LT-DS/LGS/TSC, there were 80 patients (8.3%) who met the DILI criterion of TE ALT ≥ 5 × ULN.

In the EAP, TE ALT elevations occurred less frequently than in the RCTs, with 3.4% of patients experiencing TE ALT ≥ 5 × ULN.

TE ALT elevations also occurred in Phase 2 studies in patients with epilepsy, with similar characteristics to that observed in the studies in the target population.

Results from the Phase 1 studies in healthy volunteers and patients with other diseases are as follows:

- In Pool H-SD, there were a total of 224 unique exposures to 1 or more single doses of CBD-OS ranging from 200 mg to 6000 mg. In this pool 2 subjects had TE ALT or AST > 3 × ULN.
- In Pool H-MD, there were a total of 189 unique exposures to CBD-OS. In this pool, there were 10 subjects with TE ALT or AST > 3 × ULN. One of these patients experienced concurrent eosinophilia. Eosinophil count peaked at 15.1×10^{-9}/L.
- In Pool PPI-SD, there were a total of 87 unique exposures to 1 or more single doses of CBD-OS ranging from 200 mg to 4500 mg. In this pool, 2 patients had TE ALT or AST > 3 × ULN.

Severity

No patients have met published consensus criteria for severe DILI. None of the clinical study patients, from any source, were identified as meeting the criteria for Hy's Law. Importantly, this includes 1067 patients receiving CBD-OS in the EAP, which represents a more "real-world" use of CBD-OS than the controlled studies. This EAP population includes patients with DS, LGS or TSC, as well as patients with other severe refractory epilepsies.

The maximum transaminase elevation observed and evaluated in the Core LSR was ALT at 50.9 × ULN in a PP year-old PP on valproate on Day 17 of Study GWEP1415 (after receiving placebo in the pivotal Study GWEP1424). The patient's ALT recovered to < 3× ULN 18 days

after this peak, after tapering CBD-OS. The patient was reported to be asymptomatic. The patient's bilirubin level did not exceed the ULN throughout the transaminase elevation.

In the RCTs, the maximum transaminase elevation was ALT at 32.6 × ULN in a P -year-old PP taking VPA and felbamate amongst other ASMs. Treatment with 20 mg/kg/day CBD-OS was discontinued due to the elevation, as was VPA, and the patient's ALT recovered to < 3 × ULN 11 days after the maximum elevation.

Although primarily a laboratory result-based risk, the AESI analyses for abnormal liver TEAEs provide characteristics in terms of seriousness. From Pool DS/LGS/TSC, 19.2% of patients in the All CBD-OS group had at least 1 AESI from Abnormal Liver TEAEs, compared with 2.4% in the placebo group. A total of 3.5% of patients in the all CBD-OS group experienced an SAE in this AESI compared to 0 in the placebo group (ISS Table DSLGSTSC.29.5.3).

Time to onset

TE ALT elevations tended to occur early in treatment.

From the pivotal studies (Pool DS/LGS/TSC), the risk window in the absence of VPA was generally confined to the first 30 days of treatment.

The risk window was wider for patients taking concomitant VPA, although the majority of events occurred within the first 60 days.

Isolated elevations have occurred beyond these times, generally in patients taking concomitant VPA.

Reversibility

Data on both an individual patient and pooled level show that the characteristic profile of transaminase elevations observed was one of a short, sharp peak, with a correspondingly swift resolution. Due to study protocols and guideline recommendations containing liver test-based withdrawal criteria, it is difficult to fully characterise reversibility whilst continuing on CBD-OS. However, it should be noted that among the 80 patients on CBD-OS meeting ALT criteria for DILI in Pool LT-DS/LGS/TSC, 43 patients, including 1 with an elevation to 15.9 × ULN, recovered while continuing to receive treatment with CBD-OS at the same or lower dose. This is consistent with liver "adaptation" or "tolerance".

For the 80 patients from Pool LT-DS/LGS/TSC with ALT ≥ 5 × ULN, where possible, an estimated ALT recovery time was calculated for the period from a peak ALT elevation ≥ 5 × ULN to a value of 2.9 × ULN (just below the threshold of 3.0 × ULN commonly considered to define clinical significance). The ALT recovery times estimated in this way were typically < 2 weeks and were similar for patients who:

- Abruptly discontinued or tapered over ≤ 3 days then discontinued (n = 14).
- Tapered over 4 to 16 days, then discontinued (n = 20).
- Continued through the elevations (n = 31).

The latter group of 31 patients included 2 patients who had peak TE ALT values of 15.9 × ULN and 10.3 × ULN.

The similarity of these estimated recovery times could signal the presence of an adaptation to CBD-OS and might indicate that some of the patients who were discontinued due to an increased ALT value would also have recovered had CBD-OS administration been continued. However, with the available data, it is not possible to predict whether an individual patient with an ALT elevation to > 8 × ULN would have recovered with continued CBD-OS treatment or sustained further liver injury if CBD-OS had not been discontinued.

Risk factors of concurrent VPA use

Pooled data from the pivotal RCTs clearly showed the importance of concomitant VPA as a risk factor for potential DILI, in terms of both frequency and severity. Overall in Pool DS/LGS/TSC, approximately half of the patients were receiving concomitant valproate (LSR Table DSLGSTSC.3.3.2).

Patients who were not receiving concomitant valproate exhibited TE ALT > 5 × ULN frequencies of 0% in the 10 mg/kg/day, 2.1% in the 20 mg/kg/day, 2.2% in the 25 mg/kg/day and 2.7% in the 50 mg/kg/day CBD-OS groups versus 0.6% in the placebo group. Patients receiving concomitant valproate treatment exhibited TE ALT > 5 × ULN frequencies of 3% in the 10 mg/kg/day, 11% in the 20 mg/kg/day, 13.8% in the 25 mg/kg/day and 19.4% in the 50 mg/kg/day CBD-OS groups versus 0.6% in the placebo group. Results from OLE studies and the EAP supported the observations from the RCTs.

As described above, the risk window for developing ALT elevations appears to be greater in patients on concomitant VPA.

Since CBD and a major metabolite have both been demonstrated to cause impairment of mitochondrial respiration in 1 test system, and as VPA is also known to cause mitochondrial dysfunction, the apparent synergy between these 2 drugs may reflect their combined mitochondrial effects; CCI modelling is underway to test this hypothesis.

Risk factor of elevated baseline ALT

Across all dose groups in Pool DS/LGS/TSC, frequencies of TE ALT > 5 × ULN were numerically greater in patients with an ALT > ULN at baseline compared to patients with ALT ≤ ULN at baseline in all CBD-OS dose groups. A similar pattern was observed for TE ALT > 3 × ULN (LSR Table DSLGSTSC.5.3.13).

An alternative analysis of TE ALT elevations expressed as multiples of baseline ALT (LSR Table DSLGSTSC.11.3.9) showed the opposite pattern. Reasons for this are unclear, although some subgroup sample sizes are small.

It is unclear whether baseline ALT > ULN is an inherent risk factor for CBD-OS DILI or whether a given level of liver injury will result in higher ALT values if the patient starts treatment with a higher baseline ALT value. Having an elevated ALT at baseline (> ULN) is a risk factor to TE ALT elevations identified as fold ULN, but it remains unclear whether elevated baseline ALT is a risk factor for DILI due to CBD-OS.

Risk Factors and Risk Groups

Elevations in liver enzymes called transaminases (such as ALT and AST) appear to be more frequent in patients on higher doses of CBD-OS.

Patients who were also using VPA, a commonly used drug in epilepsy, were at an increased risk of developing elevated transaminases during treatment.

Patients with higher levels of ALT at the beginning of treatment were at an increased risk developing elevated transaminases.

The majority of elevations in transaminases occurred within the first 60 days of commencing CBD-OS. Some patients had elevations after this time and therefore periodic monitoring is recommended.

Preventability

As described in the characteristics section for this risk, there are several identified risk factors for developing hepatocellular injury. These identified risk factors demonstrate the possibility of reducing the risk in an individual patient:

- **Concomitant VPA** – the SmPC highlights to prescribers the association of hepatocellular injury with concomitant VPA. A prescriber can also consider reducing the VPA dose or discontinuing VPA, dependent on the risk-benefit assessment in an individual patient.
- **Time to onset** – the transaminase elevations observed to date have generally occurred early, within the first 2 months of starting CBD-OS, meaning enhanced predictability for a prescriber.
- **Baseline ALT > ULN** – a prescriber can minimise the potential for hepatocellular injury if they have awareness of ALT > ULN in a patient, prior to commencing CBD-OS.
- **Doses > 10 mg/kg/day** – the initial target dose is 10 mg/kg/day in the SmPC. Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) to 10 mg/kg twice daily (20 mg/kg/day) in patients with DS and LGS, and up to 25 mg/kg/day in patients with TSC.

Reversibility of transaminase elevations has been observed in both controlled studies and the EAP. If transaminase elevations are observed, these should be able to be managed by dose reduction or discontinuation of either CBD-OS or a concomitant medication. Continued monitoring of transaminases before trying dose reduction may also be an option.

As the characteristics of the transaminase elevations are generally predictable but asymptomatic, periodic monitoring by the prescriber is a worthwhile precaution. This is supplemented by using monitoring to reduce the chance of further progression to a potential severe liver injury. Severe liver injury has not been observed with CBD-OS to date.

Impact on the Risk-Benefit Balance of the Product

Hepatocellular injury is an important identified risk; however, the risk is manageable within routine risk minimisation measures. In particular, periodic liver test monitoring is an important precaution a prescriber can take to improve the risk-benefit balance, particularly as there will be much greater exposure post-marketing.

As it is recommended that the target patient populations should be followed closely by specialist physicians familiar with the liver safety liabilities of the other anti-seizure drugs they prescribe, the physician should be able to weigh the benefit of CBD-OS with the potential risk.

Public Health Impact

Since the intended population for treatment with CBD-OS (patients with DS, LGS or TSC) is the same as the population evaluated in the Phase 3 studies, the expected frequency of TE transaminase elevations post-marketing is expected to be similar to the frequencies observed in the CBD-OS RCTs. There were no reports of severe DILI and no reports of Hy's Law cases among the 961 patients with DS, LGS or TSC receiving CBD-OS treatment. Among these patients, 924 were exposed to CBD-OS for > 28 days. Based on the rule of 3, the absence of serious liver injury in the 924 patients excludes an incidence of Hy's law cases > 1 in 308 treated patients and excludes an incidence of liver failure > 1 in 3080 treated patients (Core Liver Safety Report and Ancillary Liver Safety Report).

From Pool LT-DS/LGS/TSC, there were 80 patients (8.3%) who met the DILI criterion of TE ALT ≥ 5 × ULN, which best informs on the frequency of patients who may meet DILI criteria post-marketing.

Based on the estimated prevalence of DS, LGS and TSC in the EU (Part II Module SI.3), if 100% usage of CBD-OS was assumed, 12 889 patients (8.3 %) in the EU would be predicted to experience ALT ≥ 5 × ULN.

A caveat to this estimate is how marketed use of CBD-OS may increase or decrease the number of patients meeting DILI criteria compared to the controlled clinical studies. As transaminase elevations were more frequent in patients receiving doses higher than 10 mg/kg/day in the clinical studies, the dose that patients achieve post-marketing will influence the numbers of patients meeting DILI criteria.

SVII.3.1.2 Important Potential Risk: Suicidality

Potential Mechanisms

The MAH is not aware of any plausible biological mechanism specifically linking CBD-OS to suicidality.

The FDA statistical review and evaluation into ASMs and suicidality conclude that ASMs, regardless of mode of action, are associated with an increased risk of suicidality relative to placebo in RCTs. As an ASM, CBD-OS is implicated in this potential risk (FDA statistical review and evaluation: Antiepileptic drug and suicidality, 2008).

Evidence Source(s) and Strength of Evidence

Suicidality-related events have been reported more often in people with epilepsy, than in the general population.

Suicidality-related events have also been reported more often in people taking any epilepsy medication.

From the clinical development programme, there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events.

However, taken together, suicidality has been added as an important potential risk for CBD-OS in the indications of DS/LGS and TSC.

Characterisation of the Risk

A statistical meta-analysis of 11 ASMs performed by the FDA in 2008 concluded that ASMs, regardless of class or mode of action, are associated with an increased risk of suicidality relative to placebo in randomised placebo-controlled studies (FDA statistical review: Antiepileptic drugs and suicidality). CBD-OS is an ASM and therefore is implicated in this conclusion.

Pooled analyses of 199 placebo-controlled clinical studies (mono- and adjunctive therapy) of 11 different ASMs showed that patients randomised to 1 of the ASMs had approximately twice the risk (adjusted relative risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behaviour compared with patients randomised to placebo. In these studies, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 ASM-treated patients was 0.43%, compared with 0.24% among 16029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behaviour for every 530 patients treated. There were 4 suicides in drug-treated patients in the studies and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide (FDA statistical review and evaluation: Antiepileptic drug and suicidality, 2008).

The increased risk of suicidal thoughts or behaviour with ASMs was observed as early as 1 week after starting drug treatment with ASMs and persisted for the duration of treatment assessed. Because most studies included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed (FDA statistical review and evaluation: Antiepileptic drug and suicidality, 2008).

No TEAEs related to suicidality (ideation or actual attempts) were reported in the 604 patients exposed to CBD-OS in the controlled DS/LGS or TSC studies. Similarly, of the 681 patients exposed to CBD-OS in the OLE Study GWEP1415 and in the 199 patients exposed to CBD-OS in the OLE Study GWEP1521 no TEAEs related to suicidality (ideation or actual attempts) were reported. In addition, no event met the AESI suicidality search criteria in healthy subjects in the Phase 1 single-dose studies (Pool H-SD) or multiple dose studies (Pool H-MD) or patients with hepatic or renal impairment, or recreational polydrug users included in the supportive safety pool (Pool PP1-SD; ISS Table HSD.32.15.1, ISS Table PP1SD.32.16.1, ISS Table HMD.32.17.1).

Results of the C-SSRS questionnaire in the target population also support the low risk of suicidality. In the pivotal studies, results of the C-SSRS identified no TE suicidal ideation or behaviour in patients on CBD-OS during the studies.

In the OLE study, 1 patient with LGS had an emergence and worsening of suicidal ideation and is further described in 2.7.4 Section 3.3.5. No emergence of suicidal behaviour was noted in the OLE study.

Risk Factors and Risk Groups

Having epilepsy and using ASMs means that the target population already have risk factors for developing suicidality-related events.

From the clinical studies, there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events.

Preventability

There is no specific data from the clinical development for CBD-OS to aid preventability of suicidality developing.

Individual patient circumstances known by the prescriber will be important in being vigilant for initial signs of suicidal thoughts, behaviour or changes in mood. This is augmented by the inclusion of suicidality as a warning/precaution to the prescriber in the SmPC.

Patients should be advised to seek medical advice immediately if they experience suicidal thoughts, behaviour or changes in mood.

Impact on the Risk-Benefit Balance of the Product

The DS/LGS and TSC patient populations have several risk factors for suicidality, including epilepsy and concomitant ASM usage. Despite this combination of risk factors, the absence of positive responses on the C-SSRS across studies and the absence of suicidality-related TEAEs in the controlled DS/LGS and TSC studies, means the risk of suicidality specific to CBD-OS use is considered to be low in the patient populations. The Special Warnings and Precautions for Use section of the SmPC for CBD-OS will include ASM class label language.

Public Health Impact

From the FDA statistical review, the risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed (FDA statistical review and evaluation: Antiepileptic drug and suicidality, 2008). The finding of increased risk with ASMs of varying mechanisms of action and across a range of indications suggests that the risk applies to all ASMs used for any indication. The risk did not vary substantially by age (5–100 years) in the clinical studies analysed. Table Part II: Module SVII.5 shows absolute and relative risk by indication for all evaluated ASMs.

Table Part II: Module SVII.5: Risk of Suicidal Thoughts or Behaviours by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

Source: FDA statistical review: Antiepileptic drugs and suicidality.

From the controlled studies in patients with DS/LGS and TSC, there were no patients with TEAEs relating to suicidality. Using the incidence of 2 patients with TEAEs relating to suicidality from Pool EAP gives a frequency of 0.29%.

Based on the estimated prevalence of DS, LGS and TSC in the EU (Part II Module SI.3), if 100% usage of CBD-OS was assumed, 450 patients (0.29%) in the EU may potentially experience suicidality-related events.

SVII.3.1.3 Important Potential Risk: Seizure Worsening

Potential Mechanisms

A plausible biological mechanism linking CBD-OS with seizure worsening is unclear at this time.

Evidence Source(s) and Strength of Evidence

Based on seizure count data in the LGS studies, some patients receiving 20 mg/kg/day CBD-OS, in the absence of clobazam were more likely to experience a ≥ 25% increase in primary seizure frequency, than those receiving placebo; however, this was not the case in the 10 mg/kg/day CBD-OS groups and did not occur in the DS or TSC studies.

Based on AE reporting, there was no difference in the frequency of seizure worsening type events between patients receiving CBD-OS and placebo.

Seizure worsening can occur when patients do not respond to an ASM, particularly in severe, difficult-to-treat epilepsies such as DS/LGS and TSC. It is also possible that an ASM may worsen certain seizure types.

Taken together, seizure worsening has been considered as an important potential risk.

Characterisation of the Risk

Seizure Count Data

In the 2 pivotal LGS studies, in the absence of CLB, there was a trend for a greater degree of seizure worsening (≥ 25% increase in seizure frequency from baseline) for patients taking 20 mg/kg/day CBD-OS compared with placebo, whereas in the presence of CLB, patients taking CBD-OS were less likely to experience this degree of seizure worsening than patients taking placebo. Comparatively, the difference between 10 mg/kg/day CBD-OS and placebo was small, especially in the absence of CLB (Module 2.7.3, Section 3.4.2.2). Caution is advised in these comparisons as the subgroups are small. This did not occur in the 2 pivotal DS studies.

It is important to note that this phenomenon did not occur in the pivotal TSC study, where clobazam use was lower in the DS/LGS studies, making subgroup analysis difficult. For these reasons, the focus of the following characterisation is on the DS/LGS population.

Detailed examination of the DS and LGS patients with ≥ 25% increase from baseline in drop seizure frequency showed that CBD and 7-OH-CBD exposure (based on area under the concentration-time curve at end of treatment) tended to be higher than in patients who did not have this degree of seizure worsening. Of note, these subgroups contained a few patients, so caution is advised with any interpretation of the data (Module 2.7.3, Section 3.4.2.2).

Across the 4 pivotal studies in DS and LGS, a total of 92 patients with a ≥ 25% increase in the primary seizure endpoint were identified, with 42 patients receiving CLB and 50 not receiving CLB (**Error! Reference source not found.**). A > 25% increase in drop seizure or convulsive seizure frequency was not associated with increased seizure-related AEs or untoward combinations of events (sedation, somnolence or pneumonia) or CBD-OS discontinuation Off-CLB. A case-by-case review of patients experiencing > 25% increase in seizures did not reveal evidence of harm or increase in untoward clinical or safety related issues Off-CLB. The total number of discontinuations from the studies due to either seizures or lack of efficacy or both was

increased for the 20 mg/kg/day group (16%), with none in the 10 mg/kg/day patients and 1 individual discontinuation in placebo.

Table Part II: Module SVII.6: Summary of Serious TE AEs, AEs Leading to Discontinuation and AEs of Special Interest of Seizure Worsening and Status Epilepticus by Clobazam Use in Patients with Increased Seizure Frequency of > 25% in Controlled DS and LGS Studies (Pool DS/LGS)

Adverse Event of Special Interest/Disposition	ON-CLB Patients with LGS or DS			OFF-CLB Patients with LGS or DS		
	Placebo (N = 23)	CBD-OS 10 mg/kg/d (N = 8)	CBD-OS 20 mg/kg/d (N = 11)	Placebo (N = 13)	CBD-OS 10 mg/kg/d (N = 10)	CBD-OS 20 mg/kg/d (N = 27)
Seizure Worsening AESI[a]	8.7%	25.0%	36.4%	23.1%	30.0%	25.9%
Status Epilepticus AESI	0	25.0%	18.2%	15.4%	10.0%	3.7%
AEs potentially related to increased seizure activity[b]	13.0%	75.0%	45.5%	23.1%	0	25.9%
Discontinuation due to Seizure-Related AE[c]	0	0	9.1%	0	0	14.8%
Discontinuation due to Lack of Efficacy[d]	4.3%	0	0	0	0	3.7%
Serious AE	0	50.0%	36.4%	15.4%	20.0%	18.5%

Abbreviations: AE = adverse event; AESI = adverse events of special interest; CBD-OS = cannabidiol oral solution; CLB = clobazam; d = day; DS = Dravet syndrome; LGS = Lennox-Gastaut syndrome.

[a] Seizure worsening, or change in the pattern of seizures AESI: defined in Appendix F of ISS and Core and Ancillary Liver Safety Report SAP for CBD-OS.

[b] Somnolence, fatigue, lethargy, sedation AESI (somnolence, fatigue, lethargy, sedation, asthenia or malaise) aggression, irritability or pneumonia AESI (defined as any PT containing the word pneumonia).

[c] Discontinuation from study and any occurrence of seizure worsening AESI (defined above) with action taken as study medication stopped.

[d] Discontinuation with withdrawal reason related to lack of efficacy.

Source: Annex 7 GW Summary of Safety Tables.

Adverse Event Data

In keeping with the interactive voice recognition system data, Pool DS/LGS AEs for seizure worsening were similar between those on CBD-OS (15.1%) versus those on placebo (14.4%) in the pivotal studies (ISS Table DSLGS 26.4.1). This was based on an AESI category of seizure worsening, or change in the pattern or severity of seizures. However, in Pool DS/LGS overall seizure worsening AEs with CLB were 14.3% with CBD-OS compared to 12.8% with CLB on placebo and 16.2% with CBD-OS without CLB versus 16.4 on placebo. The difference was mainly a change in the placebo group, where CLB seemed to reduce the incidence of seizures with placebo while CBD-OS stayed about the same. Most of the events were considered unrelated to treatment and a few patients were discontinued. This suggests the investigators treated seizure worsening as part of the fluctuations of the underlying severe, refractory epilepsy. Further, no difference in incidence was noted in ON- versus OFF-CLB in the GWEP1415-DS/LGS OLE study (45.4% vs 40.8%).

Comparison of all CBD-OS-treated patients in Pool DS/LGS (N = 456) with all CBD-OS-treated patients in GWEP1415-DS/LGS (N = 644) showed that the overall incidence of TEAEs meeting the criteria of AESI seizure worsening, or change in the pattern or severity of seizures was notably higher in GWEP1415-DS/LGS (43.6 % vs. 15.1% in Pool DS/LGS) (ISS Table CNCDSLGSP.26.7.1). Although the incidence of seizure worsening or change in the pattern or severity of seizures in the OLE study increased over time, the incidence of these events leading to discontinuation remained the same over time. The most common AESI PTs in GWEP1415-DS/LGS were seizure (31.7%) and status epilepticus (12.8%). Whereas the incidence of seizure was higher in GWEP1415-DS/LGS compared with Pool DS/LGS (31.7% vs. 7.0%, respectively), the incidence of status epilepticus was similar between the cohorts (ISS Table CNCDSLGSP.27.7.1).

Risk Factors and Risk Groups

In the LGS studies, in the absence of CLB, patients taking 20 mg/kg/day CBD-OS were more likely to experience seizure worsening (≥ 25% increase from the number of seizures experienced prior to starting CBD-OS) than those taking placebo. In such patients taking concomitant CLB, the opposite trend was seen. Seizure worsening ≥ 25% was not seen in patients on 10 mg/kg/day CBD-OS compared to placebo.

Patients with a greater number of seizures prior to starting CBD-OS tended to be more likely to experience ≥ 25% increase in the number of seizures on treatment with CBD-OS and may be at a greater risk.

Patients with DS and TSC appear to have less risk as in these studies, the frequency of patients with ≥ 25% seizure increases was no greater with CBD-OS treatment groups, compared with placebo.

Preventability

Fluctuations and transient increases in seizure frequency are common in drug-resistant epilepsy, including DS/LGS and TSC. This clinical phenomenon can also occur in temporal relation to introduction of a new ASM. Improvement or worsening of seizure frequency is a readily observable clinical phenomenon, and can be mitigated by appropriate clinical management, including adjustment or discontinuation of therapy, particularly by the neurology specialists who treat treatment resistant epilepsies such as LGS, DS and TSC.

Patients with a greater number of seizures prior to starting CBD-OS are also likely to be under closer observation; therefore, this risk-factor for treatment emergent seizure worsening is also manageable.

Impact on the Risk-Benefit Balance of the Product

Seizure worsening is an important potential risk for CBD-OS. Seizure worsening may impact on quality of life, morbidity and mortality associated with specific seizure types, which are described and referenced further in Section Part II: Module SI. Worsening or failure to respond to an ASM is a risk with any new treatment for seizures, which is managed by discontinuation or dose reduction.

However, in each LGS study, 20 mg/kg/day CBD-OS in the absence of CLB also showed greater reductions in drop seizure frequency than placebo.

Routine PV activities are considered to be sufficient to enable further post-marketing characterisation.

Public Health Impact

It is difficult to estimate the public health impact due to the risk of seizure worsening appearing to be confined to a subset of LGS patients on 20 mg/kg/day in the absence of clobazam, and being based on the evaluation of interactive voice recognition system data. This risk is not replicated based on AE reporting. The picture is also clouded by the observation that overall, 20 mg/kg/day CBD-OS in the absence of CLB also shows greater reduction in drop seizure frequency compared with placebo. In DS and TSC patients, the frequency of patients with ≥ 25% seizure increases was no greater with CBD-OS treatment groups than placebo.

On a high-level, seizure worsening would mean an increased impact on quality of life, morbidity and mortality associated with specific seizure types in patients. However, in the target population it is likely that prescribers and caregivers will be vigilant to seizure worsening in patients – and as with all ASMs – patients would likely be discontinued from CBD-OS, minimising impact on both an individual and population level.

SVII.3.1.4 Important Potential Risk: Impact on Cognitive Development

Potential Mechanisms

A plausible biological mechanism linking CBD-OS with negative effects on cognitive development has not been established at this time.

Evidence Source(s) and Strength of Evidence

In the clinical studies, the available data makes the assessment of a possible decrease in cognitive function impossible. Some AE reports have been received that may potentially indicate a change in some aspects of cognitive function, although patients with DS/LGS and TSC often have impaired cognitive function. It should also be noted that CBD-OS is an anti-epileptic drug, and reduction of seizure may help improve cognitive function.

However, taken together, a possible decrease in cognitive function has been added as an important potential risk for CBD-OS.

Characterisation of the Risk

From the available data, it is known that LGS is commonly associated with severe cognitive delays that persist into adulthood, meaning many patients require lifelong care (Arzimanoglou, 2009). In LGS, causes of cognitive regression are multifactorial: high seizure rate, numerous head trauma related to epileptic drop attacks, continuous slow wave discharges during all sleep stages, polytherapy, etc. However, global prognosis is better if seizures can be controlled and EEG improved early by the treatment (van Rijckevorsel, 2008).

Wolff et al., found a correlation between cognitive impairment and seizure frequency in their sample of DS children aged 11 months to 12.5 years (Wolff, 2006). Children that showed > 5 seizures per month showed the worse cognitive and behavioural outcome (Acha, 2014).

Cognitive impairment is observed in around 60% of all TSC patients with a history of seizures and in approximately three-quarters of all TSC patients with a history of refractory epilepsy (Chu-Shore, 2010).

The prescriber must weigh the benefits of improved seizure control against the short- and long-term risks of side effects according to the College Report CR206 October 2017 by the Royal College of Psychiatrists. Specific to CBD-OS, it is known that somnolence or sedation could have an effect on cognitive function (and assessment of cognitive function) in patients with epilepsy. In Pool DS/LGS/TSC, 26.5% of all patients on CBD-OS versus 10.3% of patients on placebo had a TEAE of somnolence and/or sedation and the incidence was higher in the higher dose groups than lower dose groups in each indication (ISS Table DSLGSTSC 39.5.1). Most events of somnolence or sedation were non-serious, were mild or moderate, generally occurred in the first 2 weeks of treatment, did not lead to discontinuation, and resolved with continued treatment with CBD-OS.

Given the disparity between GWEP1414 and GWEP1423 as outlined below, this prevents the ability to conclude that CBD-OS may decrease cognitive function. In GWEP1414, executive functioning (assessed using the Behaviour Rating Inventory of Executive Function) 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; however, in GWEP1423, executive functioning improved in the 20 mg/kg/day CBD-OS group and worsened in the placebo group. 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 in GWEP1414: however, in GWEP1423 the 20 mg/kg/day CBD-OS group showed an improvement and the placebo group showed a worsening in behavioural symptoms. Further, the index of adaptive skills showed worsening in both CBD-OS groups and improvement in the placebo group in GWEP1414, whereas both CBD-OS and placebo groups showed an improvement in GWEP1423. One assessment that did show worsening with CBD-OS across both LGS studies was the index of internalizing behaviours (GWEP1414: worsening in the 20 mg/kg/day CBD-OS group versus an improvement in both the 10 mg/kg/day CBD-OS and placebo groups; GWEP1423: worsening in the 20 mg/kg/day CBD-OS group and improvement in the placebo group).

Over the duration of the GWEP1424 study, there were no clinically meaningful differences between the CBD-OS dose groups and the placebo group for assessments of sleep disruption, daytime sleepiness, quality of life, adaptive behaviours, or cognitive function. The limited number of patients completing the behavioural and cognitive measures limits the ability to interpret these data (GWEP1424 CSR, Section 10.1).

The results of the CAB in Pool DS/LGS were reviewed and independently interpreted by an external consultant psychometrician and provided as separate reports (GWEP1423 CSR, Appendix 1.13.4 and GWEP1414 CSR, Appendix 1.13.4 for independent CAB reports). The reports revealed no significant adverse effects of CBD-OS on cognitive function in either study, an assessment supported by the MAH; however, as explained above, the cognitive tests were completed by a small number of patients, which limited the interpretation of the data.

In Pool, TSC the assessment of cognition was conducted through the Wechsler Test. The assessments were conducted by an experienced psychometrician. The results of the assessment were limited due to the age specificity of the test and the administration being restricted to sub-group sites that had expertise to conduct the assessment. Bearing this information in mind, the reports revealed no significant adverse effects of CBD-OS on cognitive function, an assessment that is supported by the MAH; however, as explained above, the cognitive tests were completed

by a small number of patients, which limited the interpretation of the data and ability to conclude.

In addition to the CAB, assessment of quality of life via the Quality of Life in Childhood Epilepsy questionnaire in patients up to 18 years of age included cognitive subscales. In GWEP1423, LGS patients showed statistically significant improvements in the memory, language and 'other cognition' subscales, in favour of 20 mg/kg/day CBD-OS and numerical differences in favour of CBD-OS in the overall quality of life and attention/concentration subscale scores (GWEP1423 CSR, Section 8.4.1.2.2.14); the adjusted mean difference between treatments in the GWEP1424 was in favour of CBD-OS over placebo for both CBD-OS groups (20 mg/kg/day and 10 mg/kg/day), although none of the differences were nominally statistically significant (GWEP1424 CSR, Section 8.4.1.2.2.13); no significant differences in favour of CBD-OS were noted in GWEP1414 (GWEP1414 CSR, Section 8.4.1.2.2.14) or GWEP1332 (GWEP1332 CSR, Section 8.4.1.2.13). In GWEP1414, statistically significant differences in favour of placebo were noted for the attention/concentration subscale score and numerical differences in favour of placebo were noted for overall quality of life and the following subscale scores: memory, language, 'other cognition'. In GWEP1424, there was no statistically significant differences between CBD-OS and placebo for the subscale scores and overall quality of life. Numerical differences in favour of CBD-OS were noted for overall quality of life and the following subscale scores in GWEP1332: attention/concentration, and language. For LGS patients aged 19 years of age and older, similar assessments were conducted via QOLIE-31-P questionnaire which also includes a cognitive subscale. In GWEP1414, nonsignificant treatment differences in favour of CBD-OS were observed in the QOLIE-31-P cognition subscale (GWEP1414 CSR, Section 8.4.1.2.2.14). In GWEP1423 no statistical analysis was performed for the QOLIE-31-P in patients 19 years of age and above due to the low number of patients completing the questionnaire (GWEP1423 CSR, Section 8.4.1.2.2.14). Overall, given the disparity in the cognitive scores obtained from the Quality of Life in Childhood Epilepsy in GWEP1414 and GWEP1424 vs. GWEP1423 and GWEP1332, this precludes the ability to conclude that CBD-OS may decrease cognitive function.

In addition to the cognitive assessments described above, 'disturbance in cognition' was a triggering AE of interest on the supplemental AE form used in DS/LGS studies. One patient in the 20 mg/kg/day treatment group of the GWEP1424 had a triggering AE of cognitive impairment after the end of treatment (GWEP1424 CSR, Section 9.5.5.6.3). No LGS patients in either study had a triggering AE of disturbance in cognition and there was no evidence that CBD-OS impaired cognition (GWEP1414 CSR, Section 9.5.5.6.3; GWEP1423 CSR, Section 9.5.5.6.3). The AE profile overall does not show a clear risk for cognitive impairment caused by CBD-OS. In Pool DS/LGS, the following TEAEs related to cognition were observed:

- One 20 mg/kg/day patient on CBD-OS had a moderate intensity non-serious TEAE of speech disorder that was considered treatment-related by the investigator (ISS Table DSLGS.12.4.1; ISS Table DSLGS.16.4.1). The event was ongoing at the end of the study and no action was taken regarding IMP (ISS Table DSLGS.22.4.1; ISS Table DSLGS.23.4.1). Two patients on placebo had non-serious TEAEs of speech disorder that were not considered treatment-related by the investigators (ISS Table DSLGS.9.4.1; ISS Table DSLGS.10.4.1). One event was mild in intensity and

the other moderate. Both resolved during the study and no action was taken regarding IMP (ISS Table DSLGS.11.4.1; ISS Table DSLGS.22.4.1; ISS Table.23.4.1).

- One 20 mg/kg/day CBD-OS patient had a mild intensity non-serious TEAE of attention deficit/hyperactivity disorder that was not considered treatment-related by the investigator (ISS Table DSLGS.9.4.1; ISS Table DSLGS.10.4.1; ISS Table DSLGS.11.4.1). The event resolved during the study and no action was taken regarding IMP (ISS Table DSLGS.22.4.1; ISS Table.23.4.1).
- One 20 mg/kg/day CBD-OS patient had a moderate intensity non-serious TEAE of cognitive disorder that was considered treatment-related (ISS Table DSLGS.9.4.1; ISS Table DSLGS.10.4.1; ISS Table DSLGS.11.4.1). The event was ongoing at the end of the study and no action was taken regarding IMP (ISS Table DSLGS.22.4.1; ISS Table.23.4.1).
- One placebo patient had a mild intensity non-serious TEAE of mental disorder that was not considered treatment-related by the investigator (ISS Table DSLGS.10.4.1; ISS Table DSLGS.11.4.1). The event resolved with no action taken regarding IMP (ISS Table DSLGS.22.4.1; ISS Table DSLGS.23.4.1).

In the OLE Study GWEP1415, 681 patients with DS or LGS had at least 1 year of continuous exposure. There were 11 patients who reported TEAEs related to cognition (15/681, 2.2%). The majority of cases were mild or moderate and none of them lead to discontinuation of CBD-OS.

The data from the OLE study and the EAP also showed isolated patient examples of TEAEs that may potentially indicate a change in cognitive function across a broad spectrum of cognitive aspects (PTs: cognitive disorder, attention deficit/hyperactivity disorder, learning disorder, speech disorder, disturbance in attention, abnormal behaviour, memory impairment). However, given the existing comorbidities in DS/LGS patients and the lack of a control group in the OLE and EAP studies, no clear signal for a decrease in cognition with CBD-OS has been observed.

Risk Factors and Risk Groups

No clear risk factors or risk groups for a negative impact on cognitive development have been identified. Patients with a higher number of seizures, and those experiencing somnolence and/or sedation, may be at a higher risk.

Preventability

It is known that adverse cognitive events of ASMs can be avoided to some extent by slow titration to the lowest effective dosage (Park, 2008). A low starting dose and careful slow up titration of CBD-OS in weekly increments will allow the prescriber to evaluate efficacy and tolerability before increasing dose if required. This allows clinicians to balance the clinical benefit against the risk of higher doses that could pose potential risk of untoward effects.

Impact on the Risk-Benefit Balance of the Product

The important potential risk for impact on cognitive development is for negative cognition events leading to serious outcomes. To date, there is no clear signal of negative cognitive function with serious outcomes, however based on the characterisation of the risk, it cannot be excluded in the post-marketing setting. Based on the available data, the potential risk is manageable within routine risk minimisation measures.

Public Health Impact

In Pool DS/LGS/TSC, 3 patients in the All CBD-OS group had TEAEs of cognitive disorder, attention deficit/hyperactivity disorder and speech disorder and 4 patients in the placebo group had TEAEs speech disorder and mental disorder. The incidence of abnormal behaviour was 2.3% in the All CBD-OS group vs. 1.4% in the placebo group. Data from the OLE study (GWEP1415/GWEP1521) and the EAP also showed isolated patient examples of TEAEs that may potentially indicate a change in cognitive function across a broad spectrum of cognitive aspects. However, given the existing comorbidities in DS/LGS and TSC patients and the lack of a control group in the OLE and EAP studies, no clear signal for a decrease in cognition with CBD-OS has been observed – and it is difficult to meaningfully extrapolate the clinical study findings to the post-marketing setting.

SVII.3.2 Presentation of the Missing Information

SVII.3.2.1 Missing Information: Exposure During Pregnancy and Lactation

Evidence Source

Since many lipophilic drugs are excreted in human milk, it is plausible that CBD-OS may be present in the human breast milk as literature studies have shown that lactating rabbits have CBD present in their breast milk (Yoo, 1994).

There has been 1 PPD in the clinical development programme for CBD-OS, from the Phase 1 GWEP1431 study investigating the abuse potential of CBD-OS in recreational polydrug users. The P -year-old patient received a single dose of 750 mg CBD-OS on PPD 2016. The patient then received a single dose of 1500 mg CBD-OS on PPD 2016 and a single dose of 4500 mg CBD-OS on PPD 2016. On PPD 2016, the patient reported PPD . The patient's last PPD was PPD 2016. The patient PPD on PPD 2016 without any complications.

There is no evidence that the safety profile of CBD-OS in pregnancy is expected to be different from that in the target population; however, due to the exclusion criteria in the clinical studies for CBD-OS to date, there is little clinical experience of exposure to CBD-OS in patients who are pregnant or lactating. Therefore, the risk to such patients and their offspring is difficult to define and as such, CBD-OS should only be used in these patients if the potential benefit justifies the potential risks to the foetus or breastfed child.

Participation in pregnancy registries in North America and Europe should further help characterise this missing information.

Population in Need of Further Characterisation

- Female patients who are pregnant or attempting conception.
- Babies who are breastfed by female patients exposed to CBD-OS.

SVII.3.2.2 Missing Information: Long-term Safety

Evidence Source

There is no evidence that the long-term use of CBD-OS would yield a different safety profile to that seen in the clinical development programme for CBD-OS.

The long-term extension study in DS and LGS (GWEP1415) and TSC (GWEP1521 OLE) has shown that the safety profile of CBD-OS is consistent over time and very similar to the profile observed in the RCTs. GWEP1415 has 471 patients with greater than 12 months exposure. The TSC OLE has 55 patients having been exposed to CBD-OS for longer than 12 months. Another source of longer-term safety data comes from the EAP, which provides an additional 706 patients with at least 1 year of exposure, 466 of whom had been on CBD-OS for ≥ 2 years. Again, the safety profile of CBD-OS in the EAP was consistent with the RCTs and GWEP1415.

Since it is difficult to define the risks of long-term exposure, further characterisation is needed.

Population in Need of Further Characterisation

As this is an orphan application, post-marketing safety data will be important for confirming the extensive long-term safety data collected for CBD-OS in the clinical studies and supporting EAP data.

PART II: MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Important identified risks	• Hepatocellular injury
Important potential risks	• Suicidality (class effect) • Seizure worsening • Impact on cognitive development
Missing information	• Exposure during pregnancy and lactation • Long-term safety

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

III.1.A Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Specific Adverse Reaction Follow-up for Hepatocellular injury

The MAH has implemented detailed, specific, adverse reaction follow-up for significant liver abnormality reports (Annex 4). This will enable individual case safety reports to be further characterised and will facilitate robust routine pharmacovigilance activities such as ADR reporting and signal detection and evaluation.

III.2 Additional Pharmacovigilance Activities

III.2.A European and North American Antiepileptic Pregnancy Registries

Although the expected pregnancy rate is expected to be very low in these 3 rare epileptic disorders, the MAH will participate in ASM pregnancy registries including the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) and the North American Antiepileptic Drug Pregnancy Registry.

Rationale and Study Objectives

These registries will be used to collect data on the use of the product in pregnancy and lactation.

The primary objective of EURAP is to evaluate and determine the comparative degree of safety of ASMs in the human foetus, with reference to new and old ASMs, individual drugs and drugs in combinations. The secondary objectives are to establish the pattern of major malformations, if there is any, associated with ASMs, individually and in combinations.

A major goal of the North American Antiepileptic Drug Pregnancy Registry is to document how many infants exposed to each drug during pregnancy have a major malformation. These findings are used to determine whether or not the mother’s use of this drug in pregnancy is associated with an increased risk of malformations. The Registry also evaluates whether there is an increase in the occurrence of any specific abnormalities, such as spina bifida, heart defects or cleft lip and palate.

Study Design

European and International Registry of Antiepileptic Drugs in Pregnancy is an observational study and does not interfere with the treatment prescribed by the patient’s physician. The data collected are part of the information that should be generally available during good medical care. The study does not entail any special evaluation procedure or extra visits.

For the American Antiepileptic Drug Pregnancy Registry, the medical records of the anticonvulsant drug-exposed infants are obtained to confirm that the infant does or does not have a major malformation. A major malformation is defined as a structural abnormality with surgical, medical or cosmetic importance. Features excluded as not being major malformations are minor anomalies, deformities, physiologic features (such as patent ductus arteriosus heart defect in a

premature infant), biochemical disorders (phenylketonuria, cystic fibrosis) and neurologic findings (hearing loss).

Study Population

All women taking ASMs at conception are eligible for inclusion in EURAP whether the indication for treatment is epilepsy or other disorders. To avoid selection bias, only pregnancies enrolled before foetal outcome is known and within Week 16 of gestation contribute to the prospective study.

Any woman who is pregnant and taking anticonvulsant drugs for any reason is eligible to participant in the North American Antiepileptic Drug Pregnancy Registry. Women who have completed their pregnancy, or women who are planning to become pregnant, are not eligible to enroll.

Milestones

The MAH has enrolled in the North American Antiepileptic Drug Pregnancy Registry and also the EURAP. Any updates from these registries will be discussed in the PSURs.

III.2.B Prospective, Observational Cohort Study to Assess Long-term Safety in Patients Prescribed Epidyolex with a Focus on Drug-induced Liver Injury – PASS – GWEP21042

Rationale and Study Objectives

Evaluate the long-term safety profile of Epidyolex when used under conditions of routine clinical care. To assess DILI and adverse effects on cognitive development/behaviour.

Study Design

Multicentre, prospective non-interventional observational cohort study of patients who are planned to receive or already receiving Epidyolex under real-world conditions of clinical care.

Study Population

Patients prescribed Epidyolex in the EU and UK, including after completion of a GW sponsored OLE study or a compassionate access scheme and CBD-naïve patients.

Table Part III.1: Milestones

Milestone	Planned date
Start of data collection	Started 05/2023
End of data collection	10/2026
Study progress report 1	12 months post FPI
Study progress report 2	24 months post FPI
Study progress report 3	36 months post FPI
Registration in the EU PAS register	Registered 06/2022
Final report of study results	04/2027

Abbreviations: EU PAS = European Union Post-Authorisation Studies; FPI = first patient in.

III.2.C A Long-term Safety Study to Assess the Potential for Chronic Liver Injury in Participants Treated with Epidiolex (Cannabidiol Oral Solution) – GWEP19022

Rationale and Study Objectives

To assess the potential for chronic liver injury and liver fibrosis, in participants undergoing long-term treatment with Epidiolex. The study will also monitor the overall long-term safety of Epidiolex.

Study Design

Phase IV long-term safety study

Study Population

Participant is either on existing Epidiolex therapy for treatment of a seizure disorder or is to be started on Epidiolex for treatment of an FDA-approved indication.

The study is taking place at multiple sites in the USA.

Milestones

Final CSR – 01/2030

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.2: On-Going and Planned Additional Pharmacovigilance Activities

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities				
Post-marketing Cohort Study PASS GWEP21042 Ongoing	Evaluate the long-term safety profile of Epidyolex when used under conditions of routine clinical care. To assess DILI and adverse effects on cognitive development/behaviour.	-Long term safety -Hepatocellular injury -Impact on cognitive development	Study Progress Report Final CSR	Annually 04/2027
Participation in ASM Pregnancy Registries including: European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) and North American Antiepileptic Drug Pregnancy Registry Ongoing	Collect data on pregnancy and lactation	Pregnancy and lactation	Not applicable	Ongoing - will be discussed in Periodic Safety Update Reports

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022 Ongoing	Primary Objective - Monitor for potential chronic liver injury and liver fibrosis in participants prescribed Epidiolex in the USA	-Hepatocellular injury -Long-term safety	Final CSR	01/2030

Abbreviations: CSR = clinical study report; DILI = drug-induced liver injury; USA = Unites States of America.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None at this time.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The product labelling and the patient information leaflet are the routine communication tools for risk and are described in relation to the safety specification below. No additional risk minimisation measures are proposed.

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Hepatocellular injury	SmPC Section 4.3: Contraindications SmPC Section 4.4: Special warnings and precautions for use SmPC Section 4.8: Undesirable effects Package Leaflet Section 2 Available by prescription only
Suicidality	SmPC Section 4.4: Special warnings and precautions for use Package Leaflet Section 2 Available by prescription only
Seizure worsening	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
Impact on cognitive development	Available by prescription only
Exposure during Pregnancy and Lactation	SmPC Section 4.6: Fertility, Pregnancy and Lactation Available by prescription only
Long-term safety	Available by prescription only

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Table Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table Part V.2: 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 4.3: Contraindications SmPC Section 4.4: Special warnings and precautions for use SmPC Section 4.8: Undesirable effects Package Leaflet Section 2 Available by prescription only	Routine activities including: Specific Pharmacovigilance adverse reaction follow-up form Additional pharmacovigilance activities: Post-marketing cohort Study PASS GWEP21042 – final CSR - 04/2027 Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022 – final CSR - 01/2030
Suicidality	Routine Risk Minimization: SmPC Section 4.4: Special warnings and precautions for use Package Leaflet Section 2 Available by prescription only	Routine activities
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
Impact on cognitive development	Routine Risk Minimisation: Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing cohort Study PASS GWEP21042 – final CSR - 04/2027
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 ASM Pregnancy Registries including: European and International Registry of Antiepileptic Drugs and Pregnancy and North American Antiepileptic Drug Pregnancy Registry

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety	Routine Risk Minimization: Available by prescription only	Routine activities Additional pharmacovigilance activities: Post-marketing cohort Study PASS GWEP21042 – final CSR - 04/2027 Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022 – final CSR - 01/2030

Abbreviation: CSR = clinical study report.

PART VI SUMMARY OF RISK MANAGEMENT PLAN FOR EPIDYOLEX

This is a summary of the RMP for Epidyolex. The RMP details the important risks of Epidyolex, how these risks can be minimised, and how more information will be obtained about Epidyolex's risks and uncertainties (missing information).

Epidyolex's SmPC and its package leaflet give essential information to healthcare professionals, patients and their carers on how Epidyolex should be used.

This summary of the RMP for Epidyolex should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which are part of the European Public Assessment Report.

Important new concerns or changes to the current concerns will be included in updates of Epidyolex's RMP.

VI.1 The Medicine and What It is Used for

Epidyolex is authorised for use as adjunctive therapy of seizures associated with LGS or DS in conjunction with clobazam, for patients 2 years of age and older.

Epidyolex is authorised for use as adjunctive therapy of seizures associated with TSC for patients 2 years of age and older.

It contains CBD as the active substance, and it is given as an oral solution (CBD-OS).

Further information about the evaluation of the benefits of Epidyolex can be found in Epidyolex's European Public Assessment Report, including its plain-language summary, available on the European Medicines Agency website, under the medicine's European Public Assessment Report 2019.

VI.2 Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Epidyolex, together with measures to minimise such risks and the proposed studies for learning more about Epidyolex's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

If important information that may affect the safe use of Epidyolex is not yet available, it is listed under "missing information" below.

VI.2.A List of Important Risks and Missing Information

Important risks of Epidyolex are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Epidyolex. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine) (Table Part V.1Table Part VI.1).

Table Part VI.1: Lists of Important Risks and Missing Information

Important identified risks	• Hepatocellular injury
Important potential risks	• Suicidality (class effect) • Seizure worsening • Impact on cognitive development
Missing information	• Exposure during pregnancy and lactation • Long-term safety

VI.2.B Summary of Important Risks

Table Part VI.2: Important Identified Risk 1: Hepatocellular Injury

Evidence for linking the risk to the medicine	Clinical study results have shown that CBD-OS is associated with dose-related ALT elevations in a subset of patients. AST elevations have also been observed, but to a lesser extent than ALT. No severe liver injury has been observed. However as elevated ALT and AST can be the first sign of a DILI, this would affect how CBD-OS may be used in a patient.
Risk factors and risk groups	Elevations in liver enzymes called transaminases (such as ALT and AST) appear to be more frequent in patients taking higher doses of CBD-OS. Patients who were also using valproate, a commonly used drug in epilepsy, were at an increased risk of developing elevated transaminases during treatment. Patients with higher levels of ALT at the beginning of treatment were at an increased risk developing elevated transaminases. The majority of elevations in transaminases occurred within the first 60 days of commencing CBD-OS. Some patients had elevations after this time and therefore periodic monitoring is recommended.
Risk minimisation measures	Routine Risk Minimisation: SmPC Section 4.3: Contraindications SmPC Section 4.4: Special warnings and precautions for use SmPC Section 4.8: Undesirable effects Package Leaflet Section 2 Available by prescription only
Additional pharmacovigilance activities	Specific detailed adverse reaction follow-up form for significant liver abnormality reports. Post-marketing cohort Study PASS GWEP21042 Long-term safety study to assess the potential for chronic liver injury GWEP19022

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBD-OS = Cannabidiol oral solution; DILI = drug-induced liver injury.

Table Part VI.3: Important Potential Risk 1: Suicidality (Class Effect)

Evidence for linking the risk to the medicine	Suicidality-related events have been reported more often in people with epilepsy, than in the general population. Suicidality-related events have also been reported more often in people taking any epilepsy medication. From the clinical development programme, there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events. However, taken together, suicidality has been added as an important potential risk for CBD-OS in the indications of DS, LGS and TSC.
Risk factors and risk groups	Having epilepsy and using ASMs means that the target population already have risk factors for developing suicidality-related events. From the clinical studies, there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events.
Risk minimisation measures	Routine risk minimisation: SmPC Section 4.4: Special warnings and precautions for use Package Leaflet Section 2 Available by prescription only

Abbreviations: ASM = antiseizure medication; CBD-OS = cannabidiol oral solution; DS = Darvet syndrome; TSC = tuberculosis sclerosis complex.

Table Part VI.4: Important Potential Risk 2: Seizure Worsening

Evidence for linking the risk to the medicine	Based on seizure count data in the LGS studies, some patients receiving 20 mg/kg/day CBD-OS, in the absence of CLB, were more likely to experience a ≥ 25% increase in primary seizure frequency, compared to those receiving placebo. This was not the case in the 10 mg/kg/day CBD-OS groups. This did not occur in the DS or TSC studies. Based on AE reporting, there was no difference in the frequency of seizure worsening type events between patients receiving CBD-OS and placebo. Seizure worsening can occur when patients do not respond to an ASM, particularly in severe, difficult-to-treat epilepsies such as DS, LGS or TSC. It is also possible that an ASM may worsen certain seizure types. Taken together, seizure worsening has been considered as an important potential risk.
Risk factors and risk groups	In the LGS studies, in the absence of CLB, patients taking 20 mg/kg/day CBD-OS were more likely to experience seizure worsening (≥ 25% increase from the number of seizures experienced prior to starting CBD-OS) than those taking placebo. In such patients taking concomitant CLB, the opposite trend was seen. Seizure worsening ≥ 25% was not seen in patients on 10 mg/kg/day CBD-OS as compared to placebo. Patients with a greater number of seizures prior to starting CBD-OS tended to be more likely to experience a ≥ 25% increase in the number of seizures on treatment with CBD-OS and may be at greater risk. Patients with DS and TSC appear to have less risk as in the DS and TSC studies, the frequency of patients with ≥ 25% seizure increases was no greater with CBD-OS treatment groups, compared with placebo.
Risk minimisation measures	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

Abbreviations: ASM = antiseizure medication; CBD-OS = cannabidiol oral solution; LGS = Lennox-Gastaut syndrome; CLB = clobazam; TSC = tuberculosis sclerosis complex.

Table Part VI.5: Important Potential Risk 3: Impact on Cognitive Development

Evidence for linking the risk to the medicine	In the clinical studies, the available data make the assessment of a possible decrease in cognitive function impossible. Some adverse event reports have been received that may potentially indicate a change in some aspects of cognitive function, although patients with DS, LGS or TSC often have impaired cognitive function. It should also be noted that CBD-OS is an anti-epileptic drug, and reduction of seizure may help improve cognitive function. However, taken together, a possible decrease in cognitive function has been added as an important potential risk for CBD-OS.
Risk factors and risk groups	No clear risk factors or risk groups for a negative impact on cognitive development have been identified. Patients with a higher numbers of seizures and those experiencing somnolence and/or sedation may be at a higher risk.
Risk minimisation measures	Routine Risk Minimisation: Available by prescription only
Additional pharmacovigilance activities	Post-marketing cohort Study PASS GWEP21042

Abbreviations: CBD-OS = cannabidiol oral solution; DS = Darvet syndrome; TSC = tuberculosis sclerosis complex.

Table Part VI.6: Missing Information 1: Exposure during Pregnancy and Lactation

Risk minimisation measures	Routine Risk Minimisation: SmPC Section 4.6: Fertility, Pregnancy and Lactation Available by prescription only
Additional pharmacovigilance activities	Participation in Antiepileptic Drug Pregnancy Registries including: European and International Registry of Antiepileptic Drugs and Pregnancy and North American Antiepileptic Drug Pregnancy Registry

Table Part VI.7: Missing Information 2: Long-term Safety

Risk minimisation measures	Routine Risk Minimisation: Available by prescription only
Additional pharmacovigilance activities	Post-marketing cohort Study PASS GWEP21042 Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022

VI.2.C Post-Authorisation Development Plan

VI.2.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Epidyolex.

VI.2.C.2 Other Studies in Post-authorisation Development Plan

European and North American Antiepileptic Pregnancy Registries

Purpose of the studies:

These registries will be used to collect data on the use of the product in pregnancy and lactation.

Prospective, Observational Cohort Study to Assess Long-term Safety in Patients Prescribed Epidyolex with a Focus on Drug-induced Liver Injury (DILI) – PASS – GWEP21042

Purpose of the study:

Evaluate the long-term safety profile of Epidyolex when used under conditions of routine clinical care. To assess DILI and adverse effects on cognitive development/behaviour.

Long-term Safety Study to Assess the Potential for Chronic Liver Injury in Participants Treated with Epidiolex (Cannabidiol) Oral Solution – GWEP19022

Purpose of the study:

To assess the potential for chronic liver injury and liver fibrosis, in participants undergoing long-term treatment with Epidiolex. The study will also monitor the overall long-term safety of Epidiolex.

PART VII ANNEXES

LIST OF ANNEXES

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ANNEX 1 EUDRAVIGILANCE INTERFACE

Not applicable.

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table Part VII.1: Planned and On-Going Studies

Table Part VII.2: Completed Studies

Table 1 Annex 2: Planned and Ongoing Studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
Participation in antiepileptic drug Pregnancy Registries including: European and International Registry of Antiepileptic Drugs and Pregnancy (EURAP) and North American Antiepileptic Drug Pregnancy Registry Category 3	Collect data on pregnancy	Pregnancy and lactation	Protocol link for NamAED Registry *(available upon request)* EURAP protocol Milestones not applicable, but results will be ongoing and will be discussed in periodic safety update reports.
Post-marketing cohort Study PASS GWEP21042	Evaluate the long-term safety profile of Epidyolex when used under conditions of routine clinical care. To assess DILI and adverse effects on cognitive development/behaviour	-Long term safety -Hepatocellular injury -Impact on cognitive development	Protocol version 2 for Post-marketing cohort Study GWEP21042 PASS Protocol (5.3.5.2) Study Progress Report - Annually Final CSR -04/2027
Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022	Primary Objective - Monitor for potential chronic liver injury and liver fibrosis in participants prescribed Epidiolex in the USA	-Hepatocellular injury -Long-term safety	Protocol for Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022 8.1 Protocol (5.3.5.2) Final CSR - 01/2030

Table 2 Annex 2: Completed Studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
Not applicable			

Abbreviations: CSR = clinical study report; DILI = drug-induced liver injury.

ANNEX 3 PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Part A (not applicable)

Part B (not applicable)

Part C:

1. European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP). An International Registry of Antiepileptic Drugs and Pregnancy (Protocol). Revised 2004.
   Agreed as part of initial MAA: EMEA/H/C/004675/0000 – 25 July 2019
2. Protocol for North American Antiepileptic Drug Registry
   Agreed as part of initial MAA: EMEA/H/C/004675/0000 – 25 July 2019
3. Protocol for Post-marketing cohort study to Assess Long Term Safety with a focus on Drug-induced Liver Injury – PASS - GWEP21042
   Agreed as part of PASS protocol assessment procedure EMEA/H/C/004675/MEA/007.2
4. Protocol for Long-term Safety Study to Assess the Potential for Chronic Liver Injury - GWEP19022

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Follow-up forms

Hepatocellular Injury

ANNEX 5 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Table Part VII.3: Summary of Change to the Risk Management Plan Over Time

Version	Approval date Procedure	Change
2.0	25 February 2021 EMEA/H/C/004675/II/0005	Part I: New proposed indication Part II, SI: Information for TSC added Part II, SV: New updated information Part II, SVII.2: Updated for ethanol content and new excipient guideline Part II, SVII.3: Important identified risks, important potential risks and missing information updated with respect to proposed indication extension. Part III.2: Updated milestones for PASS Part III.3: Updated milestones for PASS
3.0	April 2023 EMEA/H/C/004675/II/020	Part III – Update of the following additional PV activities: 1. PASS details (GWEP21042) to reflect the agreed PASS protocol from separate procedure EMEA/H/C/004675/MEA/007.2 2. Addition of details to reflect final protocol for long-term liver safety Study GWEP19022 Annex 2: Incorporation of above additional PV activity details Annex 3: Inclusion of final protocols for the EU PASS (GWEP21042) and the US based long-term liver safety Study GWEP19022

Version	Approval date Procedure	Change
4.0	Date Renewal	Part II SI – New information added on epidemiology based on updated literature searches and new data SII – New information added on toxicology SV – Updated Post-authorisation Experience SVII – Removal of the important identified risks of somnolence and sedation, lethargy, pneumonia, rash hypersensitivity reactions and the important potential risks of aggression, euphoria, urinary retention from the list of safety concerns Part III III.1 – Routine Pharmacovigilance Activities III.I.A – Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection: removal of follow-up forms for pneumonia and rash hypersensitivity III.I.B – Removal of the section Other Forms of Routine Pharmacovigilance Activities for Safety Concerns