26 January 2023
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Epidyolex

cannabidiol

Procedure no: EMEA/H/C/004675/P46/010.1

Note

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

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1. Introduction

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

The trial was discontinued early due to enrolment challenges during COVID-19 pandemic.

This study is part of a PIP (EMEA-001964-PIP02-19) of which the decision was received on 18th March 2020.

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

2. Scientific discussion

2.1. Information on the development program

The MAH stated that:

According to Article 46 of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, GW Pharma (International) B.V. is submitting the following paediatric trial completed on 09 Jun 2021: GWND19002, Phase 3 study

As this study falls under Article 46 paediatrics study criteria, the study results are being provided to fulfil the 6-month reporting obligation. Please be noted this trial was discontinued early due to enrolment challenges during COVID-19 pandemic. The resulting small sample size and reduced treatment duration limit the data interpretation. Therefore, a meaningful conclusion could not be made.

GWP42003-P was generally well tolerated and the limited safety data available in the trial suggests a safety profile similar to that seen in other OLE trials of GWP42003-P. No new safety concerns were identified that could result in update to the current summary of product characteristics (SmPC). Therefore, no regulatory consequence is identified by the Marketing Authorisation Holder.

2.2. Information on the pharmaceutical formulation used in the study

The Investigational Medicinal Product (GWP42003-P, Epidyolex, CBD-OS is a clear, colourless to yellow solution containing 100 mg/mL CBD dissolved in the following excipients: sesame oil and anhydrous ethanol (79 mg/mL [10% v/v]) with added sweetener (sucralose [0.5 mg/mL]) and strawberry flavoring (0.2 mg/mL).

Mode of administration is oral. Dosing via a gastrostomy (G)/nasogastric (NG) tube (as required) was planned to be discussed with the GW medical monitor.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- GWND19002, An Open-label Extension Trial to Investigate the Long-term Safety of Cannabidiol Oral Solution (GWP42003-P, CBD-OS) in Patients with Rett Syndrome.

There are no approved medications for Rett syndrome (RTT), neither disease-modifying nor for symptomatic therapy. Nonclinical and clinical data indicate that CBD-OS may benefit patients with RTT. GWND19002 was a multicenter, open-label extension (OLE) trial for patients with RTT who had participated in the randomized, double-blind, placebo-controlled trial (GWND18064). The intent of this trial was to evaluate the long-term safety of CBD-OS in patients with RTT. This trial was part of a paediatric investigational plan (EMEA-001964-PIP02-19) as approved by the European Medicines Agency's Paediatric Committee.

This trial was terminated early due to enrollment challenges for the randomized controlled trial and the Coronavirus disease 2019 (COVID-19) pandemic. Due to the early trial termination and patient withdrawal, the number of patients was small, the length of treatment was reduced, and no patients completed 104 weeks, which limited data interpretation. Therefore, no regulatory consequences were identified by the Marketing Authorisation Holder.

Assessor's comments

On December 14th 2021, the MAH submitted a synoptic clinical study report as well as a critical clinical overview describing the results for the abovementioned Study GWND19002.

The MAH informs that the present study of open label follow up for cannabidiol treatment of paediatric patients with Rett syndrome was part of a PIP and fulfils the Art. 46 paediatric study criteria and therefore, the study results are submitted. The parent study, GWND18064, a Phase 3 randomized controlled study, was also terminated early and the results were submitted on July 6th 2021 with procedure no. EMA/H/C/004675/P46-009.

Due to enrolment challenges for the randomized controlled trial and the Covid-19 pandemic, recruitment of patients into the study was difficult and resulted in a premature termination of the study following termination of parent study. Thus, an insufficient number of patients were included and no conclusions could be drawn. Therefore, the MAH highlights, that no changes to the product information including the SmPC are proposed.

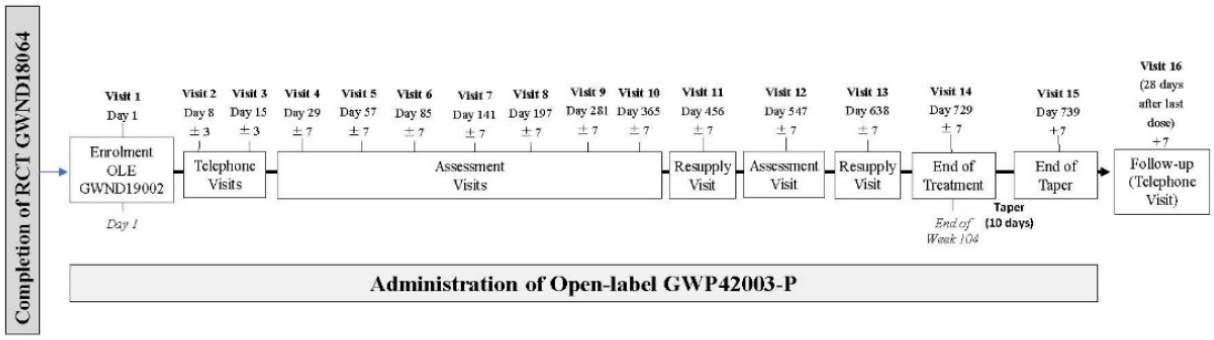
2.3.2. Clinical study

GWND19002, An Open-label Extension Trial to Investigate the Long-term Safety of Cannabidiol Oral Solution (GWP42003-P, CBD-OS) in Patients with Rett Syndrome

Description

GWND19002 was a multicenter, OLE trial for patients with RTT who had participated in the randomized, double-blind, placebo-controlled trial (GWND18064) to investigate the long-term safety of cannabidiol oral solution (GWP42003-P, CBD-OS). The trial included a 104-week maintenance period, 10-day taper period, and a 4-week follow-up period. The trial design is presented in Figure 1.

Figure 1 Trial Design and Treatment Schematic



OLE = open-label extension; RCT = randomized controlled trial.

Entry to this OLE trial was recommended to be on the same day as Visit 9 of the RCT (GWND18064); however, patients may have entered the OLE trial up to the point of the RCT follow-up visit (Visit 11). Under Protocol Annex 1, patients could enter the OLE after the RCT follow-up visit (Visit 11).

If a patient permanently discontinued treatment at any point during the trial, the patient was to attend a withdrawal visit (end of treatment) as soon as possible after the decision was made to permanently discontinue GWP42003-P. Unless inadvisable due to an AE, the patient was to taper GWP42003-P over 10 days and attend the end of Taper visit (Visit 15) and then complete the 4-week follow-up period.

Assessor's comments

Annex 1 addendum covers protocol changes which are applicable to patients who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064.

Methods

Study participants

Female or male patients, between 2 to 18 years of age, inclusive, who had completed all scheduled visits of the treatment phase of GWND18064 and had transitioned to OLE by the point of RCT follow-up (Visit 11). In addition, as covered by Protocol Annex 1, patients were also considered eligible if they had withdrawn from the RCT due to inability to adequately monitor safety and benefit risk, or transitioned after RCT Visit 11 (in both instances due to COVID-19 pandemic containment measures), or had withdrawn from RCT due to sponsor administrative decision.

Assessor's comments

The study design and enrolment criteria are endorsed.

Treatments

GWP42003-P was presented as an oral solution containing 100 mg/mL CBD dissolved in the excipients sesame oil and anhydrous ethanol (10% v/v) with added sweetener (sucralose) and strawberry flavoring.

GWP42003-P was taken orally (swallowed) b.i.d. (morning and evening) using the syringe(s) provided. GWP42003-P was to be taken at the same time each day consistently with food, i.e., within 30 minutes after the end of a meal and in line with the patients' normal feeding schedule and dietary habits. The time of GWP42003-P administration in relation to food was to be kept consistent throughout the trial. In patients with G- or NG-tubes but where oral dosing of GWP42003-P was possible, oral dosing was

preferable. Only in patients where oral dosing was not possible would GWP42003-P be administered via G- or NG-tubes made from polyurethane or silicon only. The investigator was to contact the medical monitor to review IMP administration guidelines if administration via G- or NG-tubes was planned. The volume of GWP42003-P was determined by patient's weight.

All patients entering this OLE trial began dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1. Patients were observed, and after 1 week, the dose may have been escalated further, at the investigator's discretion, up to 15 mg/kg/day GWP42003-P (7.5 mg/kg b.i.d.), in weekly increments of 5 mg/kg/day (2.5 mg/kg b.i.d.).

Patients would then remain on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day (10 mg/kg b.i.d.) based on clinical response and tolerability as deemed necessary by the investigator, until the optimal dose was found. Patients whose dose had been decreased could have had their dose increased again if tolerability improved.

At the end of treatment (end of treatment [Day 729]), the dose of GWP42003-P was to be reduced over a 10-day taper period, and patients then entered the 4-week follow-up period.

Assessor's comments

It is not quite understood if all patients who were at 15 mg/kg/day dose went back to 5 mg/kg/day dose at the beginning of OLE trial. **(OC)**

Objectives

Primary Objective:

The purpose of this study was to evaluate the long-term safety of GWP42003-P in patients with RTT.

Secondary Objective:

To evaluate the effect of GWP42003-P in measures of disease severity.

Exploratory Objectives:

To evaluate the effect of GWP42003-P on caregiver and patient quality of life (QoL).

To evaluate the effect of GWP42003-P on health utilization.

Outcomes/endpoints

Primary Endpoint: The long-term safety profile of GWP42003-P was assessed by evaluating changes in the following, relative to the pre-randomization baseline of the RCT:

- Adverse events
- Clinical laboratory parameters
- Vital signs
- Physical examination procedures
- 12-lead electrocardiogram (ECG)
- Effects on menstruation cycles
- Suicidality

- Change in growth and development by measurement of height, weight, Insulin-like growth factor-1 (IGF-1) levels, and Tanner Staging (for patients aged ≥ 7 years or earlier, if clinically indicated by the onset of menarche or other signs of precocious puberty)

Secondary Endpoint: The following were assessed by evaluating changes relative to the pre-randomization baseline of the RCT:

- RSBQ
- CGI-I
- CGI-S
- MBA-9
- CSHQ

Exploratory Endpoints: The following were assessed by evaluating changes relative to the pre-randomization baseline of the RCT:

- SF-36
- CHQ-PF50
- Hospital Services Use Questionnaire
- Caregiver assessment of Rett symptoms (symptom diary).

Assessor's comments

The primary objective and endpoints of Study GWND19002 were focused on safety. The secondary objective and endpoints were follow up of efficacy endpoints from the parent trial. RSBQ was primary endpoint and CGI-I was the key secondary endpoint for Study GWND18064.

Sample size

Approximately 252 patients were expected to be enrolled. This study was conducted at 9 sites that enrolled patients in 3 countries (USA, UK, and Spain).

Randomisation and blinding (masking)

No randomisation or blinding.

Statistical Methods

Descriptive presentations of treatment-emergent adverse events (TEAEs) were given by preferred term (PT) and system organ class (SOC) for the safety analysis set. The number of patients reporting at least 1 TEAE was provided.

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

Vital signs, physical examination, ECG, Tanner Staging, and serum IGF-1 levels were summarized at each time point during the treatment period using appropriate summary statistics. Changes in the vital signs and serum IGF-1 levels from baseline of the RCT to end of treatment were summarized.

Details of menstruation cycles (where appropriate) and suicidality assessment were summarized and listed as appropriate.

The secondary endpoints were summarized using appropriate descriptive statistics. For each secondary endpoint, the change from baseline of the RCT was derived. For visit-based endpoints, baseline was taken as the last measurement prior to the first dose of IMP (e.g., Visit 1 of the RCT).

Results

Participant flow

A total of 21 patients were enrolled into this trial (Table 1.1).

All enrolled patients received at least 1 dose of GWP42003-P and thus were included in the safety analysis set. Ten patients entered the study under the Protocol Annex 1. Of these 10 patients, 6 patients moved directly from the RCT trial (GWND18064) to the OLE trial (GWND19002) (within RCT Visit 11), while 4 patients enrolled after RCT Visit 11 (all with a study break >100 days). All patients permanently discontinued treatment and did not complete all trial visits and treatment due to the early trial termination.

All the enrolled 21 patients were exposed to at least 1 dose of GWP42003-P. The overall median total number of dosing days was 169.0. The longest duration of exposure within the OLE trial was 442 days.

Table 1.1
Summary of Patient Enrollment and Disposition
Enrolled Patients

	Double Blind Treatment: GWP42003-P		Double Blind Treatment: Placebo		
Disposition	Enrolled Under Protocol (N=9) n(%)	Enrolled Under Annex (N=5) n(%)	Enrolled Under Protocol (N=2) n(%)	Enrolled Under Annex (N=5) n(%)	Overall (N=21) n(%)
Screened for Eligibility	9 (100.0%)	5 (100.0%)	2 (100.0%)	5 (100.0%)	21 (100.0%)
Screen Failure	0	0	0	0	0
Patient Enrolled	9 (100.0%)	5 (100.0%)	2 (100.0%)	5 (100.0%)	21 (100.0%)
Safety Analysis Set [1]	9 (100.0%)	5 (100.0%)	2 (100.0%)	5 (100.0%)	21 (100.0%)
Patients Completing Study Visits and Treatment	0	0	0	0	0
Patients who Discontinued Treatment	9 (100.0%)	5 (100.0%)	2 (100.0%)	5 (100.0%)	21 (100.0%)
Reason for Permanent Treatment Discontinuation					
Withdrawal By Parent/Guardian	2 (22.2%)	0	1 (50.0%)	0	3 (14.3%)
Adverse Event	0	1 (20.0%)	0	0	1 (4.8%)
Death	2 (22.2%)	0	0	0	2 (9.5%)
Study Terminated By Sponsor	2 (22.2%)	0	0	2 (40.0%)	4 (19.0%)
Sponsor Request	3 (33.3%)	3 (60.0%)	1 (50.0%)	3 (60.0%)	10 (47.6%)
Other	0	1 (20.0%)	0	0	1 (4.8%)

Note: Percentages are calculated as 100*n/N and are based on the number of patients Enrolled according to protocol/annex and RCT treatment group.
[1] The safety set will include all patients who receive at least 1 dose of IMP.
Source: Listings 16.2.1.1, 16.2.1.2

Assessor's comments

As described above, the planned sample size was approximately 252 patients to be randomised to either cannabidiol or placebo. At time of premature closure of the parent Study GWND18064, a total of 29 patients were enrolled and randomised to treatment (cannabidiol or placebo). 21 of these patients were enrolled in Study GWND19002 for open label follow up. 10 patients entered the study under the Protocol Annex 1. Of these 10 patients, 4 patients enrolled after RCT Visit 11 with a study break >100 days. The MAH did not explain the reasons for 8 patients who did not enrol in to OLE trial after RCT. **(OC)**

The MAH did not provide discussion on the reasons for discontinuation other than study termination by MAH. **(OC)**

The MAH did not provide information on maximum dose or reasons for any dose adjustment. **(OC)**

Due to the few patients enrolled, results from the present study must be interpreted with caution and no (firm) conclusions can be based on the results.

Recruitment

This trial was terminated early due to enrolment challenges for the RCT and the COVID-19 pandemic.

The date of first informed consent/assent was 28-Feb-20.

The date of trial termination was 09-Jun-21.

The date of last observation from the last patient was 09-Jun-21.

The date of database lock was 28-Jul-21.

Baseline data

Only female patients were enrolled in this trial, with 5 (23.8%) patients being of child-bearing potential (Table 1).

The overall mean (SD) age was 10.2 (5.59) years. Of the 21 patients enrolled, the majority of patients were White or Caucasian (20 [95.2%] patients). The enrollment by region was higher in the Rest of World (Spain and United Kingdom) (13 [61.9%] patients) than in the USA (8 [38.1%] patients).

Table 1	Demographics and Baseline Characteristics (Safety Set)				
Demographic Characteristic	Double-Blind Treatment[a]: GWP42003-P		Double-Blind Treatment[a]: Placebo		
	Enrolled Under Protocol (N = 9)	Enrolled Under Annex (N = 5)	Enrolled Under Protocol (N = 2)	Enrolled Under Annex (N = 5)	Overall (N = 21)
	Age (Years)[b]				
n	9	5	2	5	21
Mean (SD)	10.7 (5.59)	10.6 (5.32)	10.5 (10.61)	9.0 (5.92)	10.2 (5.59)
Median	10.0	9.0	10.5	6.0	9.0
Min, Max	3, 18	5, 19	3, 18	4, 18	3, 19
	Age Group n (%)				
2-5 years	2 (22.2%)	1 (20.0%)	1 (50.0%)	2 (40.0%)	6 (28.6%)
6-12 years	4 (44.4%)	3 (60.0%)	0	2 (40.0%)	9 (42.9%)
13-19 years	3 (33.3%)	1 (20.0%)	1 (50.0%)	1 (20.0%)	6 (28.6%)
	Sex n (%)				
Female	9 (100.0%)	5 (100.0%)	2 (100.0%)	5 (100.0%)	21 (100.0%)
Child-bearing potential	2 (22.2%)	2 (40.0%)	1 (50.0%)	0	5 (23.8%)
	Race n (%)				
White/Caucasian	9 (100.0%)	4 (80.0%)	2 (100.0%)	5 (100.0%)	20 (95.2%)
American Indian/Alaska Native	0	1 (20.0%)	0	0	1 (4.8%)
	Ethnicity n (%)				
Hispanic or Latino	0	1 (20.0%)	0	0	1 (4.8%)
Not Hispanic or Latino	9 (100.0%)	4 (80.0%)	2 (100.0%)	5 (100.0%)	20 (95.2%)
	Country n (%)				
Spain	2 (22.2%)	3 (60.0%)	0	3 (60.0%)	8 (38.1%)
Great Britain	4 (44.4%)	0	0	1 (20.0%)	5 (23.8%)
United States	3 (33.3%)	2 (40.0%)	2 (100.0%)	1 (20.0%)	8 (38.1%)
	Region n (%)				
Rest of the world	6 (66.7%)	3 (60.0%)	0	4 (80.0%)	13 (61.9%)
USA	3 (33.3%)	2 (40.0%)	2 (100.0%)	1 (20.0%)	8 (38.1%)

Max = maximum; Min = minimum; N = total number of patients enrolled; SD = standard deviation; USA = United States of America.
Note: Percentages are calculated as 100 × n/N.
a Randomized treatment in GWND18064.
b Age = (Date of screening – date of birth) ÷ 365.25
Source: Table 3.1, Listing 16.2.4.1.

Assessor's comments

Few patients were enrolled (n=21) to receive cannabidiol (5 mg/kg/day) treatment.

Median age at baseline was 9 years; range 3-19 years. 6 patients were 2-5 years, 9 patients were 6-12 years and 6 patients were 13-19 years.

Number analysed

Approximately 252 patients were expected to be enrolled. A total of 21 patients were actually enrolled.

Safety data are presented for the Safety Analysis Set, defined as all patients who received at least 1 dose of GWP42003-P in the trial. Only patients for whom it was confirmed that they did not take any GWP42003-P were to be excluded from the Safety Analysis Set.

Efficacy results

All efficacy statistical analyses were purely descriptive.

- Rett Syndrome Behavior Questionnaire

The overall mean (SD) RSBQ Total Score at Visit 14 was 39.3 (15.75). The overall mean (SD) change from RCT baseline to Visit 14 was -7.4 (14.93).

- Clinical Global Impressions Questionnaire

The overall mean (SD) change from RCT baseline in CGI-I Score at Visit 14 was 3.3 (1.15). A total of 4 (19%) patients had a much or very much improvement in the CGI-I Score at Visit 14.

- Rett Syndrome Motor-Behavioral Assessment Scale

The overall mean (SD) change from RCT baseline in MBA-9 Total Score at Visit 14 was 0.7 (5.19).

- Children's Sleep Habits Questionnaire

The overall mean (SD) change from RCT baseline in CSHQ Total Score at Visit 14 was -0.3 (6.87).

- SF-36 and CHQ-PF50

The overall mean (SD) change from RCT baseline in the Physical Component Score at Visit 14 was -6.19 (15.369). The overall mean (SD) change from RCT baseline in the Mental Component Score at Visit 14 was 1.55 (7.994).

The overall mean (SD) change from RCT baseline in the Standardized Physical Summary Score at Visit 14 was 2.09 (11.412) and the overall mean (SD) change from RCT baseline Standardized Psychosocial Summary Score at Visit 14 was 0.87 (5.484).

- Caregiver Assessment of Rett Symptoms (symptom diary)

The overall mean (SD) change from RCT baseline in Total Score at Visit 14 was -3.90 (15.811).

Assessor's comments

For RSBQ (total score), the improvement from RCT baseline to Visit 14 was -7.4 (14.93) which is more at the level of placebo improvement observed in the parent trial (-6.1, SD:7.22) and much lower than response observed with the 15 mg/kg/day GWP42003-P dose level at the end of 24 weeks treatment (-12.1, SD:13.63). This was the primary endpoint for the parent trial (study GWND18064) and no clinically relevant effect was observed for this endpoint in open label follow up trial (study GWND19002).

Safety results

Table 2	Overall Summary of Treatment-emergent Adverse Events (Safety Set)				
	Double-Blind Treatment[a]: GWP42003-P		Double-Blind Treatment[a]: Placebo		
Patients with at Least One:	Enrolled Under Protocol (N = 9) n (%)	Enrolled Under Annex (N = 5) n (%)	Enrolled Under Protocol (N = 2) n (%)	Enrolled Under Annex (N = 5) n (%)	Overall (N = 21) n (%)
TEAE	8 (88.9%)	4 (80.0%)	2 (100.0%)	5 (100.0%)	19 (90.5%)
Treatment-related TEAE	1 (11.1%)	3 (60.0%)	0	3 (60.0%)	7 (33.3%)
TEAEs leading to IMP discontinuation	2 (22.2%)	1 (20.0%)	0	0	3 (14.3%)
Treatment-related TEAEs leading to IMP discontinuation	0	1 (20.0%)	0	0	1 (4.8%)
Serious TEAEs	2 (22.2%)	2 (40.0%)	1 (50.0%)	0	5 (23.8%)
Fatal TEAEs	2 (22.2%)	0	0	0	2 (9.5%)
Treatment-related serious TEAEs	0	0	0	0	0

IMP = investigational medicinal product; TEAE = Treatment-emergent adverse event
Note: Percentages are calculated as 100 × n/N. Patients who reported more than 1 TEAE within each category were only counted once.
a Randomized treatment in GWND18064.
Source: Table 11.1, Table 12.3, Listing 16.2.7.1.

- Treatment Emergent Adverse Events

There were limited safety data available due to the limited sample size and reduced treatment duration of this trial. Overall, the most common TEAEs by SOC were gastrointestinal disorders (12 [57.1%] patients), infections and infestations (12 [57.1%] patients), and psychiatric disorders (11 [52.4%] patients). Overall, the most common TEAEs by PT were vomiting (7 [33.3%] patients), pyrexia (4 [19.0%] patients), and diarrhoea (4 [19.0%] patients). All patients reporting TEAEs experienced more than 1 TEAE. No TEAEs of special interest were reported during this trial.

Overall, the most common treatment-related TEAEs by SOC were gastrointestinal disorders (4 [19.0%] patients), psychiatric disorders (4 [19.0%] patients), and nervous systems disorders (3 [14.3%] patients) (Table 11.2).

Overall, 2 (9.5%) patients experienced at least 1 severe TEAE, including the PTs of RTT (1 [4.8%] patient), respiratory failure (2 [9.5%] patients), and respiratory arrest (1 [4.8%] patient).

One (4.8%) patient experienced a treatment-related TEAE that lead to the permanent discontinuation of IMP (PT: hyperventilation).

Table 11.2
Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Set

System Organ Class [1] Preferred Term	Double Blind Treatment: GWP42003-P Enrolled Under Protocol (N=9) n (%)	Double Blind Treatment: GWP42003-P Enrolled Under Annex (N=5) n (%)	Double Blind Treatment: Placebo Enrolled Under Protocol (N=2) n (%)	Double Blind Treatment: Placebo Enrolled Under Annex (N=5) n (%)	Overall (N=21) n (%)
Number of Patients with at Least One TEAE	8 (88.9%)	4 (80.0%)	2 (100.0%)	5 (100.0%)	19 (90.5%)
Blood and lymphatic system disorders	1 (11.1%)	1 (20.0%)	0	1 (20.0%)	3 (14.3%)
Eosinophilia	0	0	0	1 (20.0%)	1 (4.8%)
Hypochromic anaemia	1 (11.1%)	0	0	0	1 (4.8%)
Lymphocytosis	0	0	0	1 (20.0%)	1 (4.8%)
Neutropenia	0	1 (20.0%)	0	1 (20.0%)	2 (9.5%)
Congenital, familial and genetic disorders	3 (33.3%)	0	0	0	3 (14.3%)
Developmental hip dysplasia	1 (11.1%)	0	0	0	1 (4.8%)
Rett syndrome	2 (22.2%)	0	0	0	2 (9.5%)
Gastrointestinal disorders	4 (44.4%)	3 (60.0%)	1 (50.0%)	4 (80.0%)	12 (57.1%)
Abnormal faeces	0	1 (20.0%)	0	0	1 (4.8%)
Constipation	1 (11.1%)	0	0	0	1 (4.8%)
Diarrhoea	1 (11.1%)	1 (20.0%)	0	2 (40.0%)	4 (19.0%)
Dysphagia	1 (11.1%)	0	0	0	1 (4.8%)
Flatulence	1 (11.1%)	0	0	0	1 (4.8%)
Gingival bleeding	1 (11.1%)	0	0	0	1 (4.8%)
Tooth discolouration	0	1 (20.0%)	0	0	1 (4.8%)
Vomiting	2 (22.2%)	2 (40.0%)	1 (50.0%)	2 (40.0%)	7 (33.3%)
General disorders and administration site conditions	3 (33.3%)	2 (40.0%)	0	2 (40.0%)	7 (33.3%)
Asthenia	1 (11.1%)	0	0	0	1 (4.8%)
Crying	1 (11.1%)	0	0	0	1 (4.8%)
Fatigue	1 (11.1%)	0	0	0	1 (4.8%)
Gait disturbance	0	0	0	1 (20.0%)	1 (4.8%)
Pyrexia	1 (11.1%)	2 (40.0%)	0	1 (20.0%)	4 (19.0%)
Screaming	0	0	0	1 (20.0%)	1 (4.8%)
Infections and infestations	7 (77.8%)	2 (40.0%)	2 (100.0%)	1 (20.0%)	12 (57.1%)
COVID-19	0	0	1 (50.0%)	0	1 (4.8%)
Cellulitis	1 (11.1%)	0	0	0	1 (4.8%)
Gastroenteritis viral	1 (11.1%)	0	0	0	1 (4.8%)
Lower respiratory tract infection	1 (11.1%)	0	0	0	1 (4.8%)
Nasopharyngitis	1 (11.1%)	0	0	0	1 (4.8%)
Otitis media	1 (11.1%)	0	1 (50.0%)	0	2 (9.5%)
Pneumonia	1 (11.1%)	0	0	0	1 (4.8%)
Postoperative wound infection	0	1 (20.0%)	0	0	1 (4.8%)
Sinusitis	1 (11.1%)	0	0	0	1 (4.8%)
Stoma site infection	1 (11.1%)	0	0	0	1 (4.8%)
Tinea infection	0	0	1 (50.0%)	0	1 (4.8%)
Upper respiratory tract infection	1 (11.1%)	1 (20.0%)	0	1 (20.0%)	3 (14.3%)
Urinary tract infection	0	1 (20.0%)	0	0	1 (4.8%)
Vulvovaginal candidiasis	1 (11.1%)	0	0	0	1 (4.8%)
Injury, poisoning and procedural complications	2 (22.2%)	0	1 (50.0%)	0	3 (14.3%)
Arthropod bite	0	0	1 (50.0%)	0	1 (4.8%)
Burns second degree	1 (11.1%)	0	0	0	1 (4.8%)
Fall	1 (11.1%)	0	1 (50.0%)	0	2 (9.5%)
Investigations	3 (33.3%)	1 (20.0%)	1 (50.0%)	1 (20.0%)	6 (28.6%)
Basophil count decreased	0	1 (20.0%)	0	0	1 (4.8%)
Breath sounds abnormal	1 (11.1%)	0	0	0	1 (4.8%)
Cardiac murmur	1 (11.1%)	0	0	0	1 (4.8%)
Mean cell volume increased	0	1 (20.0%)	0	1 (20.0%)	2 (9.5%)
Monocyte count decreased	1 (11.1%)	1 (20.0%)	0	1 (20.0%)	3 (14.3%)
Neutrophil count increased	0	1 (20.0%)	0	0	1 (4.8%)
Swallow study abnormal	0	0	1 (50.0%)	0	1 (4.8%)
Weight decreased	0	0	0	1 (20.0%)	1 (4.8%)
Metabolism and nutrition disorders	0	0	0	4 (80.0%)	4 (19.0%)
Decreased appetite	0	0	0	3 (60.0%)	3 (14.3%)
Hyponatraemia	0	0	0	1 (20.0%)	1 (4.8%)
Musculoskeletal and connective tissue disorders	2 (22.2%)	0	1 (50.0%)	1 (20.0%)	4 (19.0%)
Limb discomfort	0	0	1 (50.0%)	0	1 (4.8%)
Muscle rigidity	1 (11.1%)	0	0	0	1 (4.8%)
Pain in extremity	1 (11.1%)	0	0	0	1 (4.8%)
Scoliosis	0	0	0	1 (20.0%)	1 (4.8%)
Nervous system disorders	3 (33.3%)	2 (40.0%)	1 (50.0%)	3 (60.0%)	9 (42.9%)
Clonus	1 (11.1%)	0	0	0	1 (4.8%)
Dystonia	1 (11.1%)	0	0	0	1 (4.8%)
Epilepsy	1 (11.1%)	0	0	1 (20.0%)	2 (9.5%)
Generalised tonic-clonic seizure	0	1 (20.0%)	0	0	1 (4.8%)
Lethargy	0	0	0	1 (20.0%)	1 (4.8%)
Muscle spasticity	0	1 (20.0%)	0	0	1 (4.8%)
Seizure	1 (11.1%)	1 (20.0%)	0	1 (20.0%)	3 (14.3%)
Seizure like phenomena	1 (11.1%)	0	0	0	1 (4.8%)
Somnolence	0	1 (20.0%)	0	0	1 (4.8%)
Status epilepticus	1 (11.1%)	0	0	0	1 (4.8%)
Tremor	1 (11.1%)	0	1 (50.0%)	0	2 (9.5%)

Psychiatric disorders	3 (33.3%)	4 (80.0%)	0	4 (80.0%)	11 (52.4%)
Aggression	0	1 (20.0%)	0	0	1 (4.8%)
Anxiety	0	2 (40.0%)	0	0	2 (9.5%)
Apathy	1 (11.1%)	0	0	0	1 (4.8%)
Bruxism	0	2 (40.0%)	0	0	2 (9.5%)
Depressed mood	0	0	0	1 (20.0%)	1 (4.8%)
Inappropriate affect	0	0	0	1 (20.0%)	1 (4.8%)
Insomnia	0	1 (20.0%)	0	0	1 (4.8%)
Irritability	1 (11.1%)	1 (20.0%)	0	1 (20.0%)	3 (14.3%)
Mood altered	1 (11.1%)	0	0	0	1 (4.8%)
Nervousness	0	0	0	1 (20.0%)	1 (4.8%)
Poor quality sleep	0	0	0	1 (20.0%)	1 (4.8%)
Staring	1 (11.1%)	0	0	0	1 (4.8%)
Stereotypy	1 (11.1%)	0	0	0	1 (4.8%)
Respiratory, thoracic and mediastinal disorders	4 (44.4%)	2 (40.0%)	1 (50.0%)	0	7 (33.3%)
Aspiration	0	0	1 (50.0%)	0	1 (4.8%)
Atelectasis	0	1 (20.0%)	0	0	1 (4.8%)
Cough	1 (11.1%)	0	1 (50.0%)	0	2 (9.5%)
Dyspnoea	1 (11.1%)	0	0	0	1 (4.8%)
Hyperventilation	0	1 (20.0%)	0	0	1 (4.8%)
Oropharyngeal pain	0	0	1 (50.0%)	0	1 (4.8%)
Respiratory arrest	1 (11.1%)	0	0	0	1 (4.8%)
Respiratory disorder	1 (11.1%)	0	0	0	1 (4.8%)
Respiratory failure	2 (22.2%)	0	0	0	2 (9.5%)
Rhinorrhoea	0	1 (20.0%)	0	0	1 (4.8%)
Skin and subcutaneous tissue disorders	2 (22.2%)	1 (20.0%)	0	0	3 (14.3%)
Acne	1 (11.1%)	0	0	0	1 (4.8%)
Alopecia	1 (11.1%)	0	0	0	1 (4.8%)
Dermatitis atopic	0	1 (20.0%)	0	0	1 (4.8%)

Note: Percentages are calculated as 100*n/N. At each level of summarization (System Organ Class and Preferred Term), subjects who reported more than one adverse event (AE) were only counted once. System Organ Class and Preferred Term are sorted alphabetically.
[1] All AEs are coded by using MedDRA v24.0.
Source: Listing 16.2.7.1

- Serious Adverse Events (SAE)

Overall, 5 (23.8%) patients experienced a range of 1 to 3 serious TEAEs. COVID-19 was reported for 1 (4.8%) patient. Although COVID-19 cases were reported as SAEs due to sponsor requirements, it did not mean that the event met an SAE criterion. There were no treatment-related serious TEAEs reported during this trial.

Overall, a total of 2 (9.5%) patients had at least 1 fatal TEAE: 1 patient experienced fatal TEAEs of RTT and respiratory failure, and 1 patient experienced a fatal TEAE of respiratory failure.

Assessor's comments

The majority of all patients (19 out of 21) treated with cannabidiol experienced at least one TEAE during the study period.

Treatment related TEAE were experienced by 1 patient each except for decreased appetite experienced by 2 patients: diarrhoea, flatulence, tooth discoloration, vomiting, gait disturbance, lethargy, seizure, somnolence, anxiety, bruxism, depressed mood, poor quality sleep, hyperventilation.

2 patients experienced severe and fatal TEAE: 1 patient experienced fatal TEAEs of RTT and respiratory failure, and 1 patient experienced a fatal TEAE of respiratory failure. One patient experienced a treatment-related TEAE that lead to the permanent discontinuation of IMP (PT: hyperventilation). The MAH is requested to discuss respiratory failure as a new signal and possible identified risk in the light of 3 cases in study GWND19002 and include all safety database (clinical trials and postmarketing data) in the analysis. The discussion should also include other events such as dyspnoea or respiratory disorder which could be related. **(OC)**

On Day 139, the participant experienced SAEs of respiratory arrest, lower respiratory tract infection, and a non-serious AE of seizure. The participant had a moderate chest infection and was admitted to the hospital. Treatment included oxygen therapy and intravenous antibiotics. Action taken with study intervention in response to the event of respiratory arrest was dose interrupted. No action was taken with study intervention in response to the event of lower respiratory tract infection. On Day 141, the SAE of respiratory arrest was considered resolved with sequelae; however, the participant continued to experience respiratory issues. On Day 171, the SAE of lower respiratory tract infection was considered

resolved and the participant was discharged from the hospital. On Day 190, the participant experienced an SAE of respiratory failure and was readmitted to ICU following a severe respiratory arrest during a seizure. Action taken with study intervention in response to the event of respiratory failure was considered not applicable as the study intervention was stopped previously due to the SAE of respiratory arrest. On Day 299, the SAE of respiratory failure resulted in a fatal outcome. The investigator assessed the events of respiratory arrest and respiratory failure as serious, severe, and not related to study intervention. The investigator assessed the event of lower respiratory tract infection as serious, moderate, and not related to study intervention.

On Day 139, the participant experienced a medically significant SAE of status epilepticus and NSAEs of cardiac murmur and pneumonia and was hospitalized in the intensive care unit. The participant had experienced 3 generalized myoclonic seizures and 1 TCGS in 3 hours. During the TCGS, the participant presented with vomiting leading to bronchoaspiration. Treatment included a single dose of iv levetiracetam, 1500 mg, for the event of status epilepticus, iv levetiracetam, 2000 mg qd to treat the status epilepticus, iv lacosamide, 200 mg bid, iv valproate, 600 mg once iv valproate, 1500 mg continuous for the event of status epilepticus, iv amoxicillin, dose unknown, and iv potassium clavulanate, dose unknown for the NSAE of pneumonia. The participant's dose of topiramate was increased to 50 mg BID. Treatment with iv valproate, 1500 mg was discontinued, and the participant was started on iv valproate, 500 mg tid. Study intervention was interrupted due to the participant incapacity to take it. On Day 143, the participant experienced an NSAE of hypochromic anaemia. Treatment included ferrous sulphate, 3 ml daily, topiramate, 50 mg, levetiracetam, 1000 mg bid, lacosamide, 350 mg qd, and valproate, 500 mg tid via nasogastric route for the event of status epilepticus. Study intervention was restarted. The participant recovered from the NSAE of pneumonia and completed treatment with amoxicillin, levetiracetam, lacosamide, and valproate. On Day 151, the outcome of the SAE status epilepticus was considered resolved and the participant was discharged from the hospital. On Day 169, the participant experienced an NSAE of dysphagia. On an unknown day in February 2021, the participant experienced an NSAE of epilepsy. On Day 203, the participant experienced medically significant SAEs of Rett syndrome (progressive global worsening of baseline condition) and respiratory failure and was hospitalized. The participant showed progressive functional deterioration in the last two months, exacerbated in the last weeks with generalized weakness, lethargy, refusal to eat, and weight loss of 6 kg in two months. Due to weakness and lethargy, the participant presented with cough with increased secretions but had not presented epileptic decompensating. Laboratory tests were performed and showed hypernatremic dehydration secondary to the lack of fluid or food intake and hyperammonemia secondary to the various high dose antiepileptic drugs. Treatment included morphine sulphate of 0.5 mL as needed. The participant was discharged from the hospital and was accompanied by a palliative medical team. It was decided by the palliative medical team to leave the participant on an absolute diet due to worsening lethargy. Antiepileptic drugs with oral administration were changed to iv administration. Action taken with study intervention in response to the events Rett syndrome and respiratory failure was drug withdrawn. On Day 211, the participate died at home due to the Rett syndrome worsening. The SAEs Rett syndrome and respiratory failure resulted in a fatal outcome. Per the death certificate, the cause of death was reported as due to respiratory failure. The investigator assessed the event of status epilepticus as serious, moderate, and not related to study intervention. The investigator assessed the fatal events of Rett syndrome and respiratory failure as serious, severe, and not related to study intervention.

On Day 3, the participant experienced an NSAE of hyperventilation. Treatment included topiramate (dose not provided), which was started on Day 49. Action taken with study intervention in response to the event of hyperventilation was drug withdrawn with the last dose commenced on Day 48. At the time of this report, the NSAE of hyperventilation was considered not recovered/not resolved. The

investigator assessed the event of hyperventilation as nonserious, moderate, and related to study intervention.

The other identified issues are mostly covered in SmPC in section 4.8 by seizures, pyrexia, gastrointestinal disorders, nervous system and psychiatric disorders.

- Summary of Clinical Laboratory Findings, Vital Signs, and Physical Examinations

Overall, there were no new adverse trends observed in clinical laboratory values and vital signs. One (4.8%) patient reported a treatment-emergent AST or ALT > 3 × ULN at Visit 4, with a peak ALT of 4.5 × ULN at Visit 6, and ALT was 4.1 × ULN at Visit 14. The patient continued in the OLE until trial termination. No patient met Hy's law laboratory criteria.

Due to the limited sample size and reduced treatment duration of this trial, there were limited safety data available.

There were several post-baseline flagged ECG results reported during this trial: QTcB > 450 msec at Visit 4 (4 [20.0%] patients), Visit 6 (4 [21.1%] patients), and Visit 14 (4 (22.2%] patients); QTcB > 480 msec at Visit 6 (1 [5.3%] patient) and Visit 14 (1 [5.6%] patient); and QTcF > 450 msec at Visit 6 (1 [5.3%] patient). These flagged ECG results were not considered clinically significant, and overall, no new safety concern was evident.

The overall mean (SD) change from RCT baseline in weight was 1.68 (3.248) kg and in height was 3.70 (4.770) cm.

- Other Observations Related to Safety

No changes to typical menstrual cycle were reported at Visit 8 and Visit 10. At Visit 14, 3 patients reported a change to typical menstrual cycles.

The responses to the suicidality assessment questionnaire did not indicate any treatment-emergent risk relating to suicidality.

Assessor's comments

The hepatic signal is covered by the identified risk of hepatocellular injury.

2.3.3. Discussion on clinical aspects

This trial was terminated early due to enrolment challenges and the COVID-19 pandemic. The resulting small sample size and reduced treatment duration, limit data interpretation. Therefore, meaningful conclusions could not be made. GWP42003-P was generally well tolerated and the limited safety data available in the trial suggests a safety profile similar to that seen in other OLE trials of GWP42003-P. No new safety concerns were identified that could result in update to the current summary of product characteristics (SmPC). Therefore, no regulatory consequence is identified.

Assessor's comments

It is agreed with the MAH, that due to the few patients included in parent trial and open label follow up, no conclusions can be made. Due to synoptic clinical study report all details necessary for full evaluation were not available. The dosing upon entry, maximum dose during the trial, dose adjustments observed during the open label trial were not clear and all queried.

The efficacy endpoints were not supporting presence of a clinically relevant effect.

The safety data is mostly similar to safety profile observed in approved indications in terms of identified risks or potential risks. However, there are concerns around possible safety signals such as respiratory failure, which necessitate further discussion. The MAH is requested to discuss respiratory failure as a new signal and possible identified risk in the light of 3 cases in study GWND19002 and include all safety database (clinical trials and postmarketing data) in the analysis. The discussion should also include other events such as dyspnoea or respiratory disorder which could be related.

It is not agreed with the MAH that there is no need for amendments of the product information. Based on the parent and open label follow up trials being prematurely terminated due to recruitment problem and thus, with only 29 and 21 patients included respectively, no efficacy or safety conclusions could be made for Epidyolex use in Rett Syndrome. However, due to paediatric population involved, a brief summary of these trials should be provided in SmPC. **(OC)** A communication with PDCO for termination of a P46 PIP study could not be located and the MAH is requested to provide this information. **(OC)**

The MAH is requested to respond to the list of questions presented in section 4 below.

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

3. Rapporteur's overall conclusion and recommendation

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

It is agreed with the MAH, that due to the few patients included in parent trial and open label follow up, no conclusions can be made for treatment of patients with Rett syndrome with Epidyolex. The limited data regarding efficacy endpoints were not supporting presence of a clinically relevant effect.

Due to synoptic clinical study report all details necessary for full evaluation were not available. The dosing upon entry, maximum dose during the trial, dose adjustments observed during the open label trial were not clear and all queried.

The safety data is mostly similar to safety profile observed in approved indications in terms of identified risks or potential risks. However, there are concerns around possible safety signals such as respiratory failure, which necessitate further discussion.

It is not agreed with the MAH that there is no need for amendments of the product information. Due to paediatric population involved, a brief summary of these trials should be provided in the SmPC.

The MAH is requested to respond to the list of questions presented in section 4 below.

☒ Fulfilled:

No regulatory action required.

The MAH will provide further evaluation on respiratory failure as an important risk in the future PSURs.

☐ Not fulfilled:

Based on the data submitted, the MAH should address the following questions as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

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

1. It is not quite understood if all patients who were at 15 mg/kg/day dose went back to 5 mg/kg/day dose at the beginning of OLE trial.
2. At time of premature closure of the parent Study GWND18064, a total of 29 patients were enrolled and randomised to treatment (cannabidiol or placebo). 21 of these patients were enrolled in Study GWND19002 for open label follow up. The MAH did not explain the reasons for 8 patients who did not enrol in to OLE trial after RCT.
3. The MAH did not provide discussion on the reasons for discontinuation other than study termination by MAH.
4. The MAH did not provide information on maximum dose or reasons for any dose adjustment.
5. 2 patients experienced severe and fatal TEAE: 1 patient experienced fatal TEAEs of RTT and respiratory failure, and 1 patient experienced a fatal TEAE of respiratory failure. One patient experienced a treatment-related TEAE that lead to the permanent discontinuation of IMP (PT: hyperventilation). The MAH is requested to discuss respiratory failure as a new signal and possible identified risk in the light of 3 cases in study GWND19002 and include all safety database (clinical trials and postmarketing data) in the analysis. The discussion should also include other events such as dyspnoea or respiratory disorder which could be related.
6. Due to a paediatric population involved, a brief summary of Study GWND18064 and Study GWND19002 should be provided in the SmPC.
7. A communication with PDCO for termination of a P46 PIP study could not be located and the MAH is requested to provide this information.

The timetable is a 30-day response timetable without clock stop.

5. Assessment of MAH responses to Request for supplementary information

Question 1

It is not quite understood if all patients who were at 15 mg/kg/day dose went back to 5 mg/kg/day dose at the beginning of OLE trial.

Summary of the MAH Response

Per protocol, 'All patients entering this OLE trial will begin dosing with 5 mg/kg/day GWP42003-P (2.5 mg/kg b.i.d.) on Day 1'. IMP allocation was blinded at the time of entry into the OLE so all patients were required to initiate dosing at 5 mg/kg/day to account for those patients who may have been on placebo in the parent study and required titration at the start of the OLE treatment.

Assessment of the MAH Response

The MAH confirmed that all patients had to go down to 5 mg/kg/day dose regardless of being on a higher dose already.

Conclusion

Issue resolved

Question 2

At time of premature closure of the parent Study GWND18064, a total of 29 patients were enrolled and randomised to treatment (cannabidiol or placebo). 21 of these patients were enrolled in Study GWND19002 for open label follow up. The MAH did not explain the reasons for 8 patients who did not enrol in to OLE trial after RCT.

Summary of the MAH Response

The reasons for patients not entering the OLE are provided in Table 1 below:

Table 1 Reasons for Not Entering the Open-label Extension Study - All Randomised Patients

Unique Patient Identifier	Reason for Not Entering OLE
1316001	CAREGIVER DOES NOT WANT TO ENROLL IN OPEN LABEL EXTENSION.
1316002	
1316004	COVID.
1316005	UNSURE, DUE TO COVID-19 SUBJECT HAD TO WITHDRAW. UNABLE TO HAVE PROTOCOL LABS DONE. SUBJECT STILL HAS TOO MANY VISITS LEFT IN THE STUDY.
1316006	UNSURE, DUE TO COVID-19 SUBJECT HAD TO WITHDRAW. UNABLE TO HAVE PROTOCOL LABS DONE. SUBJECT STILL HAS TOO MANY VISITS LEFT IN THE STUDY.

1316007	UNSURE, DUE TO COVID-19 SUBJECT HAD TO WITHDRAW. UNABLE TO HAVE PROTOCOL LABS DONE. SUBJECT STILL HAS TOO MANY VISITS LEFT IN THE STUDY.
1332001	PATIENT STOPPED DRUG AS IT IS UNSAFE FOR THEM TO TRAVEL TO CAMPUS DUE TO COVID. DISCUSSION WITH SPONSOR UNDERWAY TO POTENTIALLY HAVE THIS PATIENT ENROLL IN OLE ONCE RESTRICTIONS ARE LIFTED.
1338002	WITHDREW OF PARENT CONSENT.

Abbreviations: COVID-19/COVID = coronavirus disease 2019; OLE = open-label extension.
Source: Appendix 1 -GWND18064 Ad Hoc Listings 2022-05-05.

The majority of patients not transitioning into the OLE completed or withdrew from the RCT during COVID-19 restrictions and were unable to be safely enrolled into the OLE (this includes patient 1316002, who completed the RCT on 28 May 2020 [GWND18064 CSR Listing 16.2.1.1]and for whom the reason for not entering the OLE was not recorded). The guidance provided to sites on enrolment into the OLE during COVID-19 restrictions was that patients who completed the blinded phase of the study were to be allowed to enrol onto the OLE study GWND19002, provided the investigator documented the basis for expecting patients to be able to comply with all study requirements under the current public health environment and discussed this plan with a Premier Research Medical Monitor (letter to investigators dated 18 March 2020).

Assessment of the MAH Response

Reasons for not enrolling in OLE are provided: 5 patients did not enter OLE due to covid related issues, 1 patient did not have a documented reason, 2 patients withdrew due to caregiver not allowing.

Conclusion

Issue resolved.

Question 3

The MAH did not provide discussion on the reasons for discontinuation other than study termination by MAH.

Summary of the MAH Response

Reasons for discontinuation are provided in Table 2 below.

Of the 21 patients enrolled, 15 patients withdrew due to the study discontinuation (reason for discontinuation recorded as 'study terminated by the sponsor', 'sponsor request', and 'other'). Of the remaining 6 patients: 3 patients discontinued due to withdrawal of consent to participate, 2 patients discontinued due to death, and 1 patient discontinued due to an AE of 'hyperventilation increase' which was moderate in severity and considered related to the IMP. The 2 cases of 'death' are discussed and evaluated further in the response to Question 5.

Table 2 Summary of Patient Enrolment and Disposition - Enrolled Patients

Disposition	Double-blind Treatment: GWP42003-P		Double-blind Treatment: Placebo		Overall (N=21) n (%)
	Enrolled Under Protocol (N=9) n (%)	Enrolled Under Annex (N=5) n (%)	Enrolled Under Protocol (N=2) n (%)	Enrolled Under Annex (N=5) n (%)	
Screened for eligibility	9 (100.0)	5 (100.0)	2 (100.0)	5 (100.0)	21 (100.0)
Screen failure	0	0	0	0	0
Patient enrolled	9 (100.0)	5 (100.0)	2 (100.0)	5 (100.0)	21 (100.0)
Safety analysis set[1]	9 (100.0)	5 (100.0)	2 (100.0)	5 (100.0)	21 (100.0)
Patients completing study visits and treatment	0	0	0	0	0
Patients who discontinued treatment	9 (100.0)	5 (100.0)	2 (100.0)	5 (100.0)	21 (100.0)
Reason for permanent treatment discontinuation					
Withdrawal by parent/ guardian	2 (22.2)	0	1 (50.0)	0	3 (14.3)
Adverse event	0	1 (20.0)	0	0	1 (4.8)
Death	2 (22.2)	0	0	0	2 (9.5)
Study terminated by sponsor	2 (22.2)	0	0	2 (40.0)	4 (19.0)
Sponsor request	3 (33.3)	3 (60.0)	1 (50.0)	3 (60.0)	10 (47.6)
Other	0	1 (20.0)	0	0	1 (4.8)

Abbreviations: IMP = investigational medicinal product; RCT = randomised controlled trial.
[1] The safety set included all patients who received at least 1 dose of IMP.
Note: Percentages are calculated as 100 × n/N and are based on the number of patients enrolled according to the protocol/annex and RCT treatment group.
Source: GWND19002 CSR Table 1.1.

Assessment of the MAH Response

MAH provided reasons for discontinuations. Of the 21 patients enrolled, 15 patients withdrew due to the study discontinuation, 3 patients discontinued due to withdrawal of consent to participate, 2 patients discontinued due to death, and 1 patient discontinued due to an AE of 'hyperventilation increase'. Deaths and AE case are assessed in question 5.

Conclusion

Issue resolved.

Question 4

The MAH did not provide information on maximum dose or reasons for any dose adjustment.

Summary of the MAH Response

Per protocol, the GWP42003-P dose could be escalated to a maximum of 20 mg/kg/day at the discretion of the investigator. There was no electronic dosing diary for this study; caregivers were to confirm IMP administration in the dosing schedule, sites were to review dosing information at each visit and record dosing information in the CRF drug dispensation form, dose adjustment form and missed or

interrupted doses form. Based on the drug dispensation form the maximum dose ranged from 5 to 20 mg/kg/day with a median of 15 mg/kg/day (refer to Appendix 2- GWND19002 Ad Hoc Tables 2022-05-05), which is in accordance with the protocol. As per the dose adjustment form, dose reductions were recorded for 3 patients due to an AE (GWND19002 CSR Listing 16.2.5.2).

Assessment of the MAH Response

MAH informed that maximum dose was 20 mg/kg/day at the discretion of the investigator. There were no predefined criteria for dose adjustments. 3 patients had dose reductions due to an AE.

Conclusion

Issue resolved.

Question 5

2 patients experienced severe and fatal TEAE: 1 patient experienced fatal TEAEs of RTT and respiratory failure, and 1 patient experienced a fatal TEAE of respiratory failure. One patient experienced a treatment-related TEAE that lead to the permanent discontinuation of IMP (PT: hyperventilation). The MAH is requested to discuss respiratory failure as a new signal and possible identified risk in the light of 3 cases in study GWND19002 and include all safety database (clinical trials and postmarketing data) in the analysis. The discussion should also include other events such as dyspnoea or respiratory disorder which could be related.

Summary of the MAH Response

As part of the PRAC Assessment of PBRER#2 - Reporting Period: 25 December 2019 to 24 June 2020 (procedure number: EMEA/H/C/PSUSA/00010798/202006), it was requested to address the below issue in the subsequent PBRER:

- "*A more detailed description of acute respiratory failure cases is expected, including a discrimination between those due to pneumonia or other thoracic disorder or due to CNS depression or dysfunction such as seizures.*"

This was completed, and the MAH concluded that there was no signal for acute respiratory failure with any aetiology. This was endorsed by the PRAC as part of their review of PBRER#3 - Reporting Period: 25 June 2020 to 24 December 2020 (procedure number: EMEA/H/C/PSUSA/00010798/202012).

The MAH has performed an update to the previous signal evaluation, including the findings from the study GWND19002, and this is included in Appendix 3. Overall, whilst the signal is considered validated, after comprehensive review it is not a confirmed signal and is refuted.

Assessment of the MAH Response

The MAH informs that respiratory failure signal was evaluated 2 years ago and while it is a valid signal they refuted the signal, and PRAC agreed (procedure number EMEA/H/C/PSUSA/00010798/202006).

From the Rett OLE trial, 2 cases relating to respiratory failure were identified; 1 patient experienced fatal TEAEs of Rett Syndrome worsening and respiratory failure, and 1 patient experienced a fatal TEAE of end stage respiratory failure. One other patient experienced a non-serious treatment-related TEAE of hyperventilation increase that led to the permanent discontinuation.

There is 1 case documented with temporal relationship to commencing therapy with Epidyolex and many cases with different background problems.

Patient ID: 1339001 was a 9-year-old female patient who experienced a non-serious event of hyperventilation (verbatim: hyperventilation increase) after 3 days on open-label CBD-OS in the OLE GWND19002. On day 17 the patient also experienced self-aggressiveness, anxiety increased, and irritability, which did not resolve prior to the end of the study. CBD-OS was withdrawn after 48 days. The patient has a history of hyperventilation and anxiety. It is noted that the patient was receiving CBD-OS 15 mg/kg/day in the parent RCT (GWND18064, under annex). The investigator assessed the event of (worsening) hyperventilation as nonserious, moderate, and related to CBD-OS. The MAH assesses and acknowledges the temporal correlation with commencing treatment with CBD-OS in the OLE, however notes that the patient has a history of hyperventilation. The fact that autonomic dysfunction which may manifest as hyperventilation (or as breath holding, or peripheral vasomotor disturbances) is a well-recognised feature of Rett syndrome leads the MAH to assess this event as unlikely related to CBD-OS. This is not fully agreed although nature of disease is acknowledged.

In other MAH clinical trials, EAP/compassionate use programs and post-marketing experience, there was a low frequency of respiratory failure events in the controlled trials in patients with LGS, DS, or TSC. Although the absolute number of events was low (Table 4), there was an imbalance between the frequency of respiratory failure events in the CBD treatment groups compared to placebo. The characteristics of the respiratory failure cases were complex, with important confounding factors present. However, any possible suppressive effect on respiratory function can occur in presence of baseline respiratory issues including lung disease, infections, or epileptic attacks. Also, these can make the patient more susceptible. Short duration of RCTs is also a limiting factor for determining the absence of a risk due to small numbers (Table 4). It should be also weighed in that CBD-OS is a centrally acting drug which may cause sedation and may increase risk of pneumonia to add on more complexity.

Table 4: Frequency of Respiratory Failure events in placebo-controlled trials of CBD-OS in DS, LGS and TSC patients

	CBD-OS					
	10 mg/kg/ day (N = 139)	20 mg/kg/ day (N = 307)	25 mg/kg/ day (N = 75)	50 mg/kg/ day (N = 73)	All CBD-OS (N = 604)	Placebo (N =368)
Patient with event						
Acute respiratory failure	0	3 (1.0%)	1 (1.3%)	0	4 (0.7%)	0
Respiratory failure	1 (0.7%)	2 (0.7%)	0	0	3 (0.5%)	1 (0.3%)

Source: ISS Table DSLGSTSC.9.5.1

There were no respiratory failure type events in the 5 mg/kg/day dose group from 3-week pilot trial GWEP1332A.

As it is a valid signal, with at least one documented case which is evaluated as related to CBD-OS and with temporal correlation with commencing treatment, and an imbalance which is not in favour of CBD-OS combination in clinical trials, (due to the serious or potentially fatal nature of the event) the MAH is requested to follow up on respiratory failure as an important possible risk in future PSURs **(OC)**.

Conclusion

Issue not resolved. (OC)

Question 6

Due to a paediatric population involved, a brief summary of Study GWND18064 and Study GWND19002 should be provided in the SmPC.

Summary of the MAH Response

Study GWND18064 (randomised phase) was submitted to the EMA via an Article 46 procedure which concluded on 11 November 2021 (procedure number: EMA/H/C/004675/P46-009).

The EMA conclusion was as follows:

"It is agreed with the MAH, that due to the few patients included in each treatment group and in total, no conclusions can be made. Compared to placebo, a numeric improvement in RSBQ Total Score (primary endpoint) was observed for the cannabidiol 15 mg/kg/day group but no effect was observed in the lower 5 mg/kg/day dosing group. Data for the (key) secondary endpoint in general supported the primary endpoint.

No new safety data emerged.

Overall, it is agreed with the MAH, that based on the present study prematurely terminated due to recruitment problem and thus, with only 29 patients included, there is no need for amendments of the product information (including the SmPC)."

Further to the response to questions above regarding the OLE study GWND19002, the MAH maintains that GWP42003-P was generally well tolerated and the limited safety data available in the study suggests the safety profile is similar to that seen in other OLE studies of GWP42003-P.

No new safety concerns were identified that could result in an update to the current SmPC.

Therefore, these results from an efficacy and safety perspective are not viewed as being useful to the healthcare professionals, caregivers, and patients in the SmPC.

Assessment of the MAH Response

The MAH has argued that there is no need to update section 5.1 of the SmPC. This is not agreed. In general, all relevant information from paediatric studies, also in non-authorised indications, should be presented in the SmPC section 5.1; this is also in line with the paediatric regulation (1901/2006).

While it is acknowledged that only few patients were included in Trials GWND18064 and GWND1902 (29 patients and 21 patients, respectively), it is considered that the studies do represent relevant data with regards to efficacy and safety of Epidyolex-treatment of patients with Rett syndrome.

Taken together, the MAH should update section 5.1 of the SmPC with the results from the primary efficacy endpoints as well as the most important safety findings.

A brief extract of the EMA text 'Frequently asked questions on paediatric information in the SmPC'[1)], is as follows:

"In line with the SmPC guideline, results of all pharmacodynamic (clinically relevant) or efficacy studies conducted in children should be presented in section 5.1, even if there is no authorised indication in any subset of the population (adult and paediatric populations) and/or no paediatric investigation plan for the condition covering this non-authorised indication, if the information is considered relevant to prescribers.
In keeping with the aim of the Paediatric Regulation (1901/2006) to improve the availability of information on the use of medicines for children, it would be desirable for all efficacy and safety data from paediatric studies, even in non-authorised indications, to be assessed and communicated

appropriately. A scientific judgement brought on a case-by-case basis may be needed to ascertain whether the results may be of use to healthcare professionals and patients and therefore included in the summary of product characteristics and, if appropriate, in the package leaflet.

The information provided has to be balanced and has to state uncertainties or conclude on lack of efficacy or safety as appropriate. A cross-reference should be included to section 4.2 which summarises available information and recommendations in the paediatric population through the use of the standard statements (see above sections 2.3 and 2.5).”

1) https://www.ema.europa.eu/en/documents/other/frequently-asked-questions-smpc-paediatric-information_en.pdf

Conclusion: Issue not resolved.

The MAH should commit to submit an update as a Type 2 variation including an update of section 5.1 of the SmPC with the results from the primary efficacy endpoints as well as the most important safety findings. (OC)

Question 7

A communication with PDCO for termination of a P46 PIP study could not be located and the MAH is requested to provide this information.

Summary of the MAH Response

A notification of discontinuation for PIP EMEA-001964-PIP02-19 was submitted to the PDCO on 21 April 2022 to confirm development of Epidyolex for the treatment of Rett syndrome has been put on long-term hold. Please find enclosed the notification as Appendix 4 for information.

Assessment of the MAH Response

The document is provided.

Conclusion

Issue solved.

6. 2nd Request for supplementary information

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

1. the MAH is requested to follow up on respiratory failure as an important possible risk in future PSURs.
2. The MAH should commit to submit an update as a Type 2 variation including an update of section 5.1 of the SmPC with the results from the primary efficacy endpoints as well as the most important safety findings.

The timetable is a 30-day response timetable without clock stop.

7. Assessment of MAH responses to 2nd Request for supplementary information

Question 1

The MAH is requested to follow up on respiratory failure as an important possible risk in future PSURs.

Summary of the MAH Response

The Applicant acknowledges the CHMP recommendation and will provide further evaluation on respiratory failure as an important risk in the future PSURs.

Assessment of the MAH Response

Will be followed up as important risk.

Conclusion

Issue solved.

Question 2

The MAH should commit to submit an update as a Type 2 variation including an update of section 5.1 of the SmPC with the results from the primary efficacy endpoints as well as the most important safety findings.

Summary of the MAH Response

The Applicant acknowledges the agency's comment and the need to provide relevant data on efficacy and safety findings in completed trials in paediatric patients. However, the Applicant would like to re-clarify that GWND19002 was terminated early due to enrolment challenges and the COVID-19 pandemic. The resulting small sample size and reduced treatment duration severely limits the data interpretation, thus meaningful efficacy and safety conclusions for the population of patients with Rett Syndrome cannot be drawn from the study results.

GWND19002 was an open-label study and the primary objective was collection of long-term safety data. Considering the lack of a placebo control group, efficacy conclusions should not be drawn from GWND19002. The reductions observed in the Rett Syndrome Behaviour Questionnaire (RSBQ; efficacy endpoint), were not consistent between the active treatment groups in GWND18064 (RCT, also terminated early due to pandemic) and GWND19002 overall, and were not significantly different from the differences observed in the placebo arm of GWND18064. In GWND18064 a mean point difference of -12.1 (SD 13.63) was observed in the higher dose group while 0.4 (SD12.51) was observed in the low dose group; the placebo group showed a mean point difference of -6.1 (SD 7.22). In GWND19002 the mean point difference was -7.4 (SD 14.93) which is comparable with the difference observed in placebo group of GWND18064. Higher standard deviation values were observed, due to reduced sample size, further limiting the interpretation of data. Based on this data set, no clinically relevant conclusions can be drawn regarding efficacy of GWP42003-P in this indication.

With regard to safety, CBD was generally well tolerated in GWND19002 study population, with a safety profile similar to that observed in other pivotal studies in other patient populations. No additional important safety findings were identified. However, the safety data set is limited and not sufficient to characterize long-term safety in this patient population. Inclusion of inconclusive efficacy and limited safety data in the SmPC could potentially mislead or confuse the prescribers.

This position is in line with the CHMP guidance (EMA/551202/2010 Rev 1- Revision 1 - Frequently asked questions on SmPC paediatric information- 4 SmPC Section 5.1), which clearly outlines "Scientific judgement brought on a case-by-case basis may be needed to ascertain whether the results may be of use to healthcare professionals and patients and therefore included in the summary of product characteristics and, if appropriate, in the package leaflet". The Applicant would like to reiterate that the results from GWND19002 provide no clinically relevant information for prescribers, caregivers, or patients. The current SmPC accurately reflects the results from all the completed CBD pivotal and open-label studies from an efficacy and safety perspective and addition of information from this early-terminated study, with very limited data, would not benefit the prescribers.

Assessment of the MAH Response

The MAH argues that no meaningful efficacy or long-term safety conclusions could be drawn from studies hence they should not be summarized in the SmPC. This is not agreed, available data can be summarized transparently. Even if much lower than planned numbers, the number of enrolled patients is larger than some PIP studies in rare indications. However, the argument that inclusion of inconclusive efficacy data in the SmPC will not be useful in the clinic is acknowledged.

Conclusion

Issue solved.