Clinical trial results:
An open label extension study to investigate the safety of cannabidiol (GWP42003-P; CBD) in children and adults with inadequately controlled Dravet or Lennox-Gastaut Syndromes

Summary

EudraCT number	2014-001834-27
Trial protocol	GB ES PL NL FR
Global end of trial date	24 September 2020

Results information

Result version number	v1 (current)
This version publication date	08 April 2021
First version publication date	08 April 2021

Trial information

Trial identification

Sponsor protocol code	GWEP1415

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02224573
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GW Research Ltd
Sponsor organisation address	Sovereign House, Vision Park, Chivers Way, Histon, Cambridge, United Kingdom, CB24 9BZ
Public contact	Medical Enquiries, GW Research Ltd, medinfo@gwpharm.com
Scientific contact	Medical Enquiries, GW Research Ltd, medinfo@gwpharm.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001964-PIP01-16
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 September 2020
Global end of trial reached?	Yes
Global end of trial date	24 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study was conducted to evaluate the long-term safety and tolerability of GWP42003-P, as adjunctive treatment, in children and adults with inadequately controlled Dravet Syndrome or Lennox-Gastaut Syndrome.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and subsequent amendments. This trial was also designed to comply with International Council for Harmonisation (ICH) E6 Guideline for good clinical practice (EMA/CHMP/ICH/135/1995) and the European Clinical Trial Directive 2001/20/EC. The ICH-adopted guidelines and other relevant international guidelines, recommendations, and requirements were taken into account as comprehensively as possible, as long as they did not violate country-specific law.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Poland: 70
Country: Number of subjects enrolled	Spain: 71
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	United States: 460
Worldwide total number of subjects	681
EEA total number of subjects	182

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	373
Adolescents (12-17 years)	179
Adults (18-64 years)	129
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who completed the double-blind, placebo-controlled, clinical studies with GWP42003-P (Core Studies: GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) were eligible for enrollment.

Period 1

Period 1 title	Treatment Phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dravet Syndrome

Arm description:

Subjects with Dravet Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], and GWEP1424 [NCT02224703]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	GWP42003-P
Other name	EPIDIOLEX, cannabidiol, CBD-OS
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

100 milligrams per milliliter (mg/mL) cannabidiol (CBD) in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring

Arm title	Lennox-Gastaut Syndrome

Arm description:

Subjects with Lennox-Gastaut Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1414 [NCT02224560] and GWEP1423 [NCT02224690]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	GWP42003-P
Other name	EPIDIOLEX, cannabidiol, CBD-OS
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

100 milligrams per milliliter (mg/mL) cannabidiol (CBD) in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring

Number of subjects in period 1	Dravet Syndrome	Lennox-Gastaut Syndrome
Started	315	366
Completed	170	243
Not completed	145	123
Continued Compassionate Use	1	-
Began Commerical Product	1	-
Subject Discontinued IMP	-	1
Withdrawal by Subject or Parent/Guardian	62	48
Refused Medication	1	1
Started on Other IMP	1	-
Placed in Group Home	-	1
Pursued Other Trials	1	-
Subject Did Not Return for Visits	-	1
Subject Began Protocol-Excluded Treatment	-	1
Lack of Efficacy per Subject/Caregiver	3	3
Caregiver Asked to Stop IMP	-	1
Met Withdrawal Criteria	5	7
Withdrawn by the Investigator	23	11
Adverse event, non-fatal	26	38
Lack of Efficiency	2	1
Lost to follow-up	2	1
Subject Moved	2	-
Lack of efficacy	15	8

Period 2

Period 2 title	Taper Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dravet Syndrome

Arm description:

Subjects with Dravet Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], and GWEP1424 [NCT02224703]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Arm type	Experimental

Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	
Other name	EPIDIOLEX, cannabidiol, CBD-OS
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

100 milligrams per milliliter (mg/mL) cannabidiol (CBD) in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring

Arm title	Lennox-Gastaut Syndrome

Arm description:

Subjects with Lennox-Gastaut Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1414 [NCT02224560] and GWEP1423 [NCT02224690]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Arm type	Experimental
Investigational medicinal product name	GWP42003-P
Investigational medicinal product code	
Other name	EPIDIOLEX, cannabidiol, CBD-OS
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

100 milligrams per milliliter (mg/mL) cannabidiol (CBD) in sesame oil with anhydrous ethanol, added sweetener (sucralose) and strawberry flavoring

Number of subjects in period 2[1]	Dravet Syndrome	Lennox-Gastaut Syndrome
Started	79	71
Completed	76	67
Not completed	3	4
Withdrawal by Subject or Parent/Guardian	-	3
Adverse event, non-fatal	1	1
Hospitalization/Dose Reduction	1	-
Completed Incorrect Number of Taper Days	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all subjects completing the Treatment Phase continued to the Taper Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Dravet Syndrome
Reporting group description:	
Subjects with Dravet Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], and GWEP1424 [NCT02224703]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.	
Reporting group title	Lennox-Gastaut Syndrome
Reporting group description:	
Subjects with Lennox-Gastaut Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1414 [NCT02224560] and GWEP1423 [NCT02224690]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.	

Reporting group values	Dravet Syndrome	Lennox-Gastaut Syndrome	Total
Number of subjects	315	366	681
Age categorical Units: Subjects			
Children (2-11 years)	216	157	373
Adolescents (12-17 years)	90	89	179
Adults (18-64 years)	9	120	129
Age continuous Units: years			
arithmetic mean	9.737	15.906	
standard deviation	± 4.4434	± 9.5392	-
Gender categorical Units: Subjects			
Female	159	168	327
Male	156	198	354
Race			
Not Applicable = Not applicable as per country-specific data protection law.			
Units: Subjects			
White/Caucasian	269	325	594
Black/African American	10	15	25
American Indian/Alaska Native	1	0	1
Asian	6	10	16
Not Applicable	15	1	16
Caucasian/Asian	1	1	2
Hispanic/Caucasian	1	2	3
White and Black Caribbean	1	0	1
Biracial	2	1	3
Caucasian and African American	3	1	4
Mulatto	1	0	1
North African	1	0	1
South American	1	0	1
Latino	1	5	6
Eurasian	1	0	1

Anglo-Indian	1	0	1
Indian	0	2	2
Unknown	0	2	2
Arab	0	1	1

End points

End points reporting groups

Reporting group title	Dravet Syndrome

Reporting group description:

Subjects with Dravet Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], and GWEP1424 [NCT02224703]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Reporting group title	Lennox-Gastaut Syndrome

Reporting group description:

Subjects with Lennox-Gastaut Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1414 [NCT02224560] and GWEP1423 [NCT02224690]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Reporting group title	Dravet Syndrome

Reporting group description:

Subjects with Dravet Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], and GWEP1424 [NCT02224703]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Reporting group title	Lennox-Gastaut Syndrome

Reporting group description:

Subjects with Lennox-Gastaut Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1414 [NCT02224560] and GWEP1423 [NCT02224690]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Primary: Number of subjects with any treatment-emergent adverse event (TEAE) occuring in ≥5% of subjects in any treatment group

End point title	Number of subjects with any treatment-emergent adverse event (TEAE) occuring in ≥5% of subjects in any treatment group[1]

End point description:

TEAEs, defined as AEs that started, worsened in severity or seriousness, following the first dose of investigational medicinal product in this study, are reported. Any AEs that continued from the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) were only classified as treatment emergent if they worsened in this study.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[2]	366[3]		
Units: subjects				
Total subjects affected by any TEAE	306	353		
Diarrhoea	135	140		
Vomiting	63	107		
Constipation	20	43		
Nausea	16	32		
Pyrexia	124	126		
Fatigue	39	38		
Upper respiratory tract infection	78	104		
Nasopharyngitis	78	58		
Sinusitis	38	49		
Pneumonia	35	51		
Ear infection	35	50		
Influenza	37	45		
Urinary tract infection	19	51		
Pharyngitis streptococcal	26	27		
Gastroenteritis viral	15	30		
Otitis media	21	22		
Bronchitis	15	23		
Viral upper respiratory tract infection	11	20		
Gastroenteritis	16	7		
Fall	22	23		
Laceration	8	35		
Contusion	15	25		
Weight decreased	21	61		
Alanine aminotransferase increased	37	30		
Aspartate aminotransferase increased	38	19		
Gamma-glutamyltransferase increased	32	20		
Decreased appetite	99	93		
Convulsion	79	141		
Somnolence	87	107		
Status epilepticus	47	42		
Lethargy	21	34		
Headache	18	26		
Sedation	16	27		
Drooling	11	21		
Abnormal behaviour	34	23		
Insomnia	16	40		
Irritability	26	29		
Aggression	20	30		
Agitation	9	19		
Cough	42	63		
Nasal congestion	13	46		
Rhinorrhoea	20	19		
Pneumonia aspiration	4	22		
Hypoxia	2	21		

Notes:

[2] - Safety Analysis Set

[3] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically significant changes in the indicated vital sign values from the pre-randomization Baseline of the Core Study at any time post-dose

End point title	Number of subjects with clinically significant changes in the indicated vital sign values from the pre-randomization Baseline of the Core Study at any time post-dose[4]

End point description:

Clinical significance was determined by the investigator. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; mmHg = millimeters of mercury. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of investigational medicinal product (IMP). Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[5]	366[6]		
Units: subjects				
Sitting SBP < -20 mmHg	59	88		
Sitting SBP > 20 mmHg	96	120		
Sitting DBP < -10 mmHg	139	176		
Sitting DBP > 10 mmHg	166	191		
Pulse Rate < -15 beats per minute	176	192		
Pulse Rate > 15 beats per minute	150	179		
Weight ≤ -7 %	47	106		
Weight ≥ 7%	213	223		

Notes:

[5] - Safety Analysis Set

[6] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in body mass index

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in body mass index[7]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243[8]	294[9]		
Units: kilograms per meters squared (kg/m^2)				
arithmetic mean (standard deviation)	0.42 (± 2.701)	0.05 (± 5.863)		

Notes:

[8] - Safety Analysis Set

[9] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with clinically significant electrocardiogram (ECG) values at the pre-randomization Baseline of the Core Study and at any time post-dose

End point title	Number of subjects with clinically significant electrocardiogram (ECG) values at the pre-randomization Baseline of the Core Study and at any time post-dose[10]

End point description:

Clinical significance was determined by the investigator. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. QTcB = corrected QT interval with Bazette correction. msec = milliseconds. The time frame represents the duration for which subjects were enrolled in GWEP1415.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[11]	366[12]		
Units: subjects				
QTcB > 450 msec, Baseline	13	21		
QTcB > 450 msec, any time post-dose	62	120		
QTcB > 480 msec, Baseline	2	4		
QTcB > 480 msec, any time post-dose	10	40		
QTcB > 500 msec, Baseline	2	2		
QTcB > 500 msec, any time post-dose	7	20		

Notes:

[11] - Safety Analysis Set

[12] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with the indicated responses to questions regarding suicidal ideation and behavior using the Children's Columbia-Suicide Severity Rating Scale (Children's C-SSRS) at Day 1 and at any time post-dose

End point title	Number of subjects with the indicated responses to questions regarding suicidal ideation and behavior using the Children's Columbia-Suicide Severity Rating Scale (Children's C-SSRS) at Day 1 and at any time post-dose[13]

End point description:

The C-SSRS questionnaire is a brief, standardized measure that uniquely assesses the essential information (behavior, ideation, lethality, and severity) and distinguishes between suicidal occurrences and non-suicidal self-injury. Analysis was conducted in members of the safety analysis set defined as all subjects who took at least 1 dose of IMP.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[14]	366[15]		
Units: subjects				
Any suicidality, Day 1	1	1		
Any suicidality, any time post-dose	1	2		
Suicidal ideation, Day 1	0	1		
Suicidal ideation, any time post-dose	1	2		
Suicidal behavior, Day 1	1	0		
Suicidal behavior, any time post-dose	1	0		
Complete suicidality, any time post-dose	1	0		

Notes:

[14] - Safety Analysis Set

[15] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean Cannabis Withdrawal Scale Score at End of Taper, the Post-Taper Safety Call, and at Safety Follow-up

End point title	Mean Cannabis Withdrawal Scale Score at End of Taper, the Post-Taper Safety Call, and at Safety Follow-up[16]

End point description:

The Cannabinoid Withdrawal Scale is a 19-item scale, with each item (withdrawal symptom) measured on a 0 to 10 numerical rating scale (0 = Not at all; 5 = Moderately; 10 = Extremely). Scores are calculated as the sum of the 19 items for each measure (each separate score has a theoretical maximum of 190). Higher scores indicate more withdrawal symptoms and an increased negative impact to quality of life. The subject/caregiver was asked to record the extent to which each withdrawal symptom was experienced in the last 24 hours and also to rate the negative impact on normal daily activities. L24S = Last 24 Hours Score. NIS = Negative Impact on Normal Daily Activity Score. The End of Treatment visit occurred after a maximum of 4 years of treatment. The End of Taper occurred up to 10 days after the End of Treatment visit. The Safety Call and Safety Follow-up occurred 2 and 4 weeks, respectively, after the End of Taper. Only subjects with available data were analyzed.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[17]	366[18]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
L24S, End of Taper, n=5, 11	9.8 (± 10.64)	4.9 (± 14.00)		
L24S, Post-Taper Safety Call, n=5, 8	3.4 (± 4.72)	0.0 (± 0.00)		
L24S, Safety Follow-Up, n=5, 11	2.4 (± 3.36)	4.9 (± 12.27)		
NIS, End of Taper, n=6, 18	9.5 (± 12.03)	5.1 (± 10.96)		
NIS, Post-Taper Safety Call, n=3, 13	16.3 (± 3.79)	1.2 (± 3.00)		
NIS, Safety Follow-Up, n=3, 10	5.3 (± 9.24)	1.8 (± 3.82)		

Notes:

[17] - Safety Analysis Set

[18] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean Pediatric Cannabinoid Withdrawal Scale (PCWS) Score at the End of

Treatment, the End of Taper, the Post-Taper Safety Call, and at Safety Follow-up

End point title	Mean Pediatric Cannabinoid Withdrawal Scale (PCWS) Score at the End of Treatment, the End of Taper, the Post-Taper Safety Call, and at Safety Follow-up[19]

End point description:

The PCWS was administered to subjects aged 4 to 17 (inclusive) that was developed from the 19-item validated CWS (adults) to assess mood, behavioral, and physical symptoms associated with cannabis. The total score was calculated as the sum of 10 items (rated on a 4-point scale: 0 = none; 1 = a little bit; 2 = quite a bit; 3 = a lot) and has a theoretical maximum of 30. Higher scores indicate more withdrawal symptoms and an increased negative impact to quality of life. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. The End of Treatment visit occurred after a maximum of 4 years (208 weeks from Visit 1) of treatment. The End of Taper occurred up to 10 days after the End of Treatment visit. The Safety Call and Safety Follow-up occurred 2 and 4 weeks, respectively, after the End of Taper. 9999 = standard deviation was not calculated for a single subject.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[20]	366[21]		
Units: scores on a scale				
arithmetic mean (standard deviation)				
End of Treatment, n=1, 1	4.0 (± 9999)	6.0 (± 9999)		
End of Taper, n=74, 46	2.9 (± 3.77)	2.1 (± 2.78)		
Post-Taper Safety Call, n=55, 25	2.4 (± 3.50)	2.0 (± 2.72)		
Safety Follow-Up, n=68, 34	1.9 (± 2.72)	1.8 (± 2.28)		

Notes:

[20] - Safety Analysis Set

[21] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in red blood cells (RBCs)

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in red blood cells (RBCs)[22]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268[23]	307[24]		
Units: 10^12 cells per Liter (L)				
arithmetic mean (standard deviation)	-0.068 (± 0.3297)	-0.059 (± 0.3424)		

Notes:

[23] - Safety Analysis Set

[24] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in hemoglobin

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in hemoglobin[25]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268[26]	307[27]		
Units: grams per Liter (g/L)				
arithmetic mean (standard deviation)	-1.6 (± 9.08)	-2.4 (± 11.14)		

Notes:

[26] - Safety Analysis Set

[27] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in hematocrit

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in hematocrit[28]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268[29]	307[30]		
Units: percentage of RBCs in whole blood (L/L)				
arithmetic mean (standard deviation)	-0.0105 (± 0.02938)	-0.0110 (± 0.02983)		

Notes:

[29] - Subject Analysis Set

[30] - Subject Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in erythrocyte mean corpuscular volume

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in erythrocyte mean corpuscular volume[31]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[31] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268[32]	307[33]		
Units: femtoliters (fL)				
arithmetic mean (standard deviation)	-1.0 (± 5.10)	-1.3 (± 5.01)		

Notes:

[32] - Safety Analysis Set

[33] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in erythrocyte mean corpuscular hemoglobin

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in erythrocyte mean corpuscular hemoglobin[34]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268[35]	307[36]		
Units: picograms (pg)				
arithmetic mean (standard deviation)	0.10 (± 1.482)	-0.15 (± 1.926)		

Notes:

[35] - Safety Analysis Set

[36] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in platelets, white blood cells, basophils, eosinophils, lymphocytes, monocytes, and neutrophils

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in platelets, white blood cells, basophils, eosinophils, lymphocytes, monocytes, and neutrophils[37]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[37] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[38]	366[39]		
Units: 10^9 cells/L				
arithmetic mean (standard deviation)				
Platelets, n=266, 304	5.4 (± 64.84)	5.0 (± 70.47)		
White blood cells, n= 268, 307	-0.52 (± 2.531)	-0.09 (± 2.052)		
Basophils, n=268, 305	0.00 (± 0.041)	0.01 (± 0.040)		
Eosinophils, n=268, 305	-0.02 (± 0.159)	-0.02 (± 0.165)		
Lymphocytes, n=268, 305	-0.31 (± 0.988)	-0.14 (± 0.778)		
Monocytes, n=268, 305	-0.05 (± 0.276)	0.01 (± 0.245)		
Neutrophils, n=268, 305	-0.16 (± 2.041)	0.05 (± 1.878)		

Notes:

[38] - Safety Analysis Set

[39] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in the percentage of basophils, eosinophils, lymphocytes, monocytes, and neutrophils in white blood cells (WBCs)

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in the percentage of basophils,

	eosinophils, lymphocytes, monocytes, and neutrophils in white blood cells (WBCs)[40]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[40] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	268[41]	305[42]		
Units: percentage in WBCs				
arithmetic mean (standard deviation)				
Basophils/WBCs	0.08 (± 0.284)	0.12 (± 0.287)		
Eosinophils/WBCs	-0.10 (± 2.064)	-0.24 (± 2.104)		
Lymphocytes/WBCs	-1.32 (± 12.396)	-1.32 (± 11.193)		
Monocytes/WBCs	-0.05 (± 3.125)	0.18 (± 2.600)		
Neutrophils/WBCs	1.47 (± 12.982)	1.27 (± 12.245)		

Notes:

[41] - Safety Analysis Set

[42] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in sodium, potassium, blood urea nitrogen, glucsose, calcium, and high-density lipoprotein (HDL) cholesterol

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in sodium, potassium, blood urea nitrogen, glucsose, calcium, and high-density lipoprotein (HDL) cholesterol[43]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[43] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[44]	366[45]		
Units: millimoles per Liter (mmol/L)				
arithmetic mean (standard deviation)				
Sodium, n=277, 311	-0.4 (± 3.25)	-0.8 (± 2.70)		
Potassium, n=274, 307	-0.06 (± 0.372)	-0.08 (± 0.407)		
Blood urea nitrogen, n=276, 309	-0.08 (± 1.571)	0.00 (± 1.555)		
Glucose, n=275, 307	-0.06 (± 1.026)	0.06 (± 1.288)		
Calcium, n=277, 311	-0.050 (± 0.1148)	-0.054 (± 0.1218)		
HDL cholesterol, n=277, 311	0.06 (± 0.372)	0.12 (± 0.320)		

Notes:

[44] - Safety Analysis Set

[45] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in creatinine (Jaffe), creatinine (enzymatic), and bilirubin

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in creatinine (Jaffe), creatinine (enzymatic), and bilirubin[46]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[46] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[47]	366[48]		
Units: micromoles per Liter (µmol/L)				
arithmetic mean (standard deviation)				
Creatinine, Jaffe, n=268, 311	7.0 (± 9.32)	7.1 (± 10.86)		
Creatinine, enzymatic, n=148, 140	3.8 (± 8.83)	4.0 (± 9.44)		
Bilirubin, n=276, 309	0.48 (± 2.339)	0.45 (± 2.626)		

Notes:

[47] - Safety Analysis Set

[48] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in creatinine clearance (Schwartz) and creatinine clearance (Cockcroft-Gault)

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in creatinine clearance (Schwartz) and creatinine clearance (Cockcroft-Gault)[49]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. mL/min/1.73 m^2 = milliliters per minute per 1.73 meters squared. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[49] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[50]	366[51]		
Units: mL/min/1.73 m^2				
arithmetic mean (standard deviation)				
Creatinine Clearance, Schwartz, n=247, 185	0.3 (± 4.41)	0.0 (± 0.00)		
Creatinine Clearance, Cockcroft-Gault, n=7, 103	0.0 (± 0.00)	-0.6 (± 5.94)		

Notes:

[50] - Safety Analysis Set

[51] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase[52]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[52] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[53]	366[54]		
Units: Units/L				
arithmetic mean (standard deviation)				
Alkaline phosphatase, n=277, 311	-40.9 (± 88.18)	-40.1 (± 73.62)		
Aspartate aminotransferase, n=274, 308	4.0 (± 26.14)	2.8 (± 26.62)		
Alanine aminotransferase, n=275, 308	7.0 (± 39.24)	9.5 (± 43.96)		
Gamma glutamyl transferase, n=276, 309	8.7 (± 42.35)	4.9 (± 45.65)		

Notes:

[53] - Safety Analysis Set

[54] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in albumin and protein

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in albumin and protein[55]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as

Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[55] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	315[56]	366[57]		
Units: grams (g)/L				
arithmetic mean (standard deviation)				
Albumin, n=277, 311	-0.2 (± 3.43)	-0.9 (± 3.31)		
Protein, n=277, 311	-1.2 (± 5.83)	-2.0 (± 5.75)		

Notes:

[56] - Safety Analysis Set

[57] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in prolactin

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in prolactin[58]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[58] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	276[59]	309[60]		
Units: µInternational Units/milliliter (µIU/mL)				
arithmetic mean (standard deviation)	0.43 (± 132.613)	10.43 (± 230.439)		

Notes:

[59] - Safety Analysis Set

[60] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in prothrombin time

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in prothrombin time[61]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[61] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256[62]	282[63]		
Units: seconds				
arithmetic mean (standard deviation)	-0.08 (± 0.740)	-0.09 (± 0.706)		

Notes:

[62] - Safety Analysis Set

[63] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in prothrombin international normalized ratio

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in prothrombin international

	normalized ratio[64]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[64] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256[65]	282[66]		
Units: ratio				
arithmetic mean (standard deviation)	-0.012 (± 0.0784)	-0.010 (± 0.0736)		

Notes:

[65] - Safety Analysis Set

[66] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Primary: Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in insulin-like growth factor-1

End point title	Mean change from the pre-randomization Baseline of the Core Study to the end of treatment in insulin-like growth factor-1[67]

End point description:

Change from Baseline was calculated as the post-Baseline value minus the Baseline value. Pre-randomization Baseline of the Core Study (GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], GWEP1424 [NCT02224703], GWEP1414 [NCT02224560], and GWEP1423 [NCT02224690]) is defined as Baseline of the double-blind, placebo-controlled, clinical studies with GWP42003-P. Analysis was conducted in members of the Safety Analysis Set, comprised of all subjects who received at least 1 dose of IMP. Only subjects with available data were analyzed. Data for change from Baseline at pre-randomization of the Core Study are presented; however, the time frame represents the duration for which subjects were enrolled in GWEP1415. No data from the Core Studies are presented in this report.

End point type	Primary

End point timeframe:

up to a maximum of 6 years

Notes:

[67] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was conducted for this end point.

End point values	Dravet Syndrome	Lennox-Gastaut Syndrome		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[68]	142[69]		
Units: nanomoles (nmol)/L				
arithmetic mean (standard deviation)	-0.28 (± 12.701)	1.10 (± 15.970)		

Notes:

[68] - Safety Analysis Set

[69] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

up to a maximum of 6 years

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs), defined as AEs that started, worsened in severity or seriousness, following the first dose of investigational medicinal product in this study, are reported. Any AEs that continued from the Core Study were only classified as treatment emergent if they worsened in this study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Lennox-Gastaut Syndrome

Reporting group description:

Subjects with Lennox-Gastaut Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1414 [NCT02224560] and GWEP1423 [NCT02224690]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Reporting group title	Dravet Syndrome

Reporting group description:

Subjects with Dravet Syndrome who completed double-blind, placebo-controlled, clinical studies of GWP42003-P (Core Studies: GWEP1332A [NCT02091206], GWEP1332B [NCT02091375], and GWEP1424 [NCT02224703]) were titrated up to 10 to 20 milligrams per kilogram per day (mg/kg/day) GWP42003-P using a recommended titration schedule during the Titration Period. Subjects continued at this dose during the Maintenance Period. The maximum dose subjects could receive was 30 mg/kg/day.

Serious adverse events	Lennox-Gastaut Syndrome	Dravet Syndrome	
Total subjects affected by serious adverse events			
subjects affected / exposed	157 / 366 (42.90%)	133 / 315 (42.22%)	
number of deaths (all causes)	12	6	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 366 (1.09%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Foot operation			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrostomy			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Drug withdrawal syndrome			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Effusion			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	11 / 366 (3.01%)	17 / 315 (5.40%)	
occurrences causally related to treatment / all	0 / 12	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden unexplained death in epilepsy			
subjects affected / exposed	4 / 366 (1.09%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 4	
Social circumstances			
Child abuse			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Testicular torsion			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 366 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	10 / 366 (2.73%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 12	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 366 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	9 / 366 (2.46%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased bronchial secretion			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased upper airway secretion			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	16 / 366 (4.37%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	1 / 21	2 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory alkalosis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	6 / 366 (1.64%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 9	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	8 / 366 (2.19%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract inflammation			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restrictive pulmonary disease			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinorrhoea			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			

subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucinations, mixed			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritability			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	6 / 366 (1.64%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self injurious behaviour			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep disorder			

subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 366 (1.91%)	7 / 315 (2.22%)	
occurrences causally related to treatment / all	6 / 7	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ammonia increased			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticonvulsant drug level increased			
subjects affected / exposed	0 / 366 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 366 (1.64%)	10 / 315 (3.17%)	
occurrences causally related to treatment / all	4 / 6	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature fluctuation			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophil count increased			

subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 366 (0.82%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma output increased			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	6 / 366 (1.64%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	5 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Norovirus test positive			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen consumption increased			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases abnormal			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	5 / 366 (1.37%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	4 / 366 (1.09%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear injury			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye contusion			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 366 (0.82%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding tube complication			
subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			

subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Near drowning			
subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			

subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth avulsion			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal haemorrhage			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Rett's disorder			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Cardio-respiratory arrest			
subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral atrophy			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	44 / 366 (12.02%)	34 / 315 (10.79%)	
occurrences causally related to treatment / all	3 / 61	2 / 48	
deaths causally related to treatment / all	0 / 1	0 / 1	
Depressed level of consciousness			
subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia			

subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 366 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 366 (0.27%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lethargy			
subjects affected / exposed	2 / 366 (0.55%)	3 / 315 (0.95%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonic epilepsy			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyopathy			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postictal state			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sedation			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure cluster			
subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	42 / 366 (11.48%)	47 / 315 (14.92%)	
occurrences causally related to treatment / all	3 / 81	5 / 112	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophilia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 366 (0.00%)	3 / 315 (0.95%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Blindness transient			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye oedema			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 366 (0.82%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 366 (0.82%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	5 / 366 (1.37%)	5 / 315 (1.59%)	
occurrences causally related to treatment / all	0 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	4 / 366 (1.09%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 366 (0.82%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 366 (0.82%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth loss			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	13 / 366 (3.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 31	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			

subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Excessive granulation tissue			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrocalcinosis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	5 / 366 (1.37%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	3 / 366 (0.82%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site abscess			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon gangrene			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Croup infectious			

subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	0 / 366 (0.00%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 366 (0.55%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bites			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective myositis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	3 / 366 (0.82%)	7 / 315 (2.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			

subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	5 / 366 (1.37%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	2 / 366 (0.55%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pertussis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 366 (0.27%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	26 / 366 (7.10%)	20 / 315 (6.35%)	
occurrences causally related to treatment / all	0 / 42	0 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	2 / 366 (0.55%)	2 / 315 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonas infection			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 366 (0.00%)	4 / 315 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	2 / 366 (0.55%)	3 / 315 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 366 (1.64%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection bacterial			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 366 (0.55%)	3 / 315 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	9 / 366 (2.46%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	3 / 366 (0.82%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 366 (0.27%)	3 / 315 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
West Nile viral infection			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 366 (0.82%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	5 / 366 (1.37%)	6 / 315 (1.90%)	
occurrences causally related to treatment / all	0 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteral feeding intolerance			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 366 (0.27%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 366 (0.55%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	2 / 366 (0.55%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			

subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	3 / 366 (0.82%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic alkalosis			
subjects affected / exposed	1 / 366 (0.27%)	0 / 315 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	0 / 366 (0.00%)	1 / 315 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Lennox-Gastaut Syndrome	Dravet Syndrome	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	338 / 366 (92.35%)	292 / 315 (92.70%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	23 / 366 (6.28%)	31 / 315 (9.84%)	
occurrences (all)	28	35	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 366 (3.55%)	30 / 315 (9.52%)	
occurrences (all)	16	35	
Gamma-glutamyltransferase increased			
subjects affected / exposed	18 / 366 (4.92%)	29 / 315 (9.21%)	
occurrences (all)	18	34	
Weight decreased			

subjects affected / exposed	58 / 366 (15.85%)	20 / 315 (6.35%)	
occurrences (all)	63	20	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	24 / 366 (6.56%)	15 / 315 (4.76%)	
occurrences (all)	33	16	
Fall			
subjects affected / exposed	20 / 366 (5.46%)	20 / 315 (6.35%)	
occurrences (all)	33	32	
Laceration			
subjects affected / exposed	35 / 366 (9.56%)	8 / 315 (2.54%)	
occurrences (all)	66	8	
Nervous system disorders			
Convulsion			
subjects affected / exposed	120 / 366 (32.79%)	60 / 315 (19.05%)	
occurrences (all)	201	91	
Drooling			
subjects affected / exposed	21 / 366 (5.74%)	11 / 315 (3.49%)	
occurrences (all)	22	13	
Headache			
subjects affected / exposed	26 / 366 (7.10%)	18 / 315 (5.71%)	
occurrences (all)	40	23	
Lethargy			
subjects affected / exposed	32 / 366 (8.74%)	19 / 315 (6.03%)	
occurrences (all)	45	22	
Sedation			
subjects affected / exposed	27 / 366 (7.38%)	16 / 315 (5.08%)	
occurrences (all)	34	19	
Somnolence			
subjects affected / exposed	106 / 366 (28.96%)	86 / 315 (27.30%)	
occurrences (all)	130	113	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 366 (10.38%)	38 / 315 (12.06%)	
occurrences (all)	47	47	
Pyrexia			

subjects affected / exposed	123 / 366 (33.61%)	117 / 315 (37.14%)	
occurrences (all)	280	298	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	41 / 366 (11.20%)	20 / 315 (6.35%)	
occurrences (all)	59	25	
Diarrhoea			
subjects affected / exposed	138 / 366 (37.70%)	133 / 315 (42.22%)	
occurrences (all)	230	286	
Nausea			
subjects affected / exposed	30 / 366 (8.20%)	16 / 315 (5.08%)	
occurrences (all)	35	20	
Vomiting			
subjects affected / exposed	99 / 366 (27.05%)	63 / 315 (20.00%)	
occurrences (all)	192	96	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	63 / 366 (17.21%)	42 / 315 (13.33%)	
occurrences (all)	89	57	
Nasal congestion			
subjects affected / exposed	46 / 366 (12.57%)	13 / 315 (4.13%)	
occurrences (all)	70	21	
Rhinorrhoea			
subjects affected / exposed	19 / 366 (5.19%)	19 / 315 (6.03%)	
occurrences (all)	33	29	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	22 / 366 (6.01%)	32 / 315 (10.16%)	
occurrences (all)	30	39	
Aggression			
subjects affected / exposed	29 / 366 (7.92%)	19 / 315 (6.03%)	
occurrences (all)	35	28	
Insomnia			
subjects affected / exposed	40 / 366 (10.93%)	16 / 315 (5.08%)	
occurrences (all)	48	23	
Irritability			

subjects affected / exposed	28 / 366 (7.65%)	26 / 315 (8.25%)	
occurrences (all)	33	34	
Infections and infestations			
Bronchitis			
subjects affected / exposed	23 / 366 (6.28%)	14 / 315 (4.44%)	
occurrences (all)	30	18	
Ear infection			
subjects affected / exposed	50 / 366 (13.66%)	35 / 315 (11.11%)	
occurrences (all)	101	61	
Gastroenteritis			
subjects affected / exposed	6 / 366 (1.64%)	16 / 315 (5.08%)	
occurrences (all)	6	24	
Gastroenteritis viral			
subjects affected / exposed	29 / 366 (7.92%)	11 / 315 (3.49%)	
occurrences (all)	37	15	
Influenza			
subjects affected / exposed	42 / 366 (11.48%)	31 / 315 (9.84%)	
occurrences (all)	51	41	
Nasopharyngitis			
subjects affected / exposed	58 / 366 (15.85%)	78 / 315 (24.76%)	
occurrences (all)	91	136	
Otitis media			
subjects affected / exposed	21 / 366 (5.74%)	21 / 315 (6.67%)	
occurrences (all)	37	30	
Pharyngitis streptococcal			
subjects affected / exposed	26 / 366 (7.10%)	24 / 315 (7.62%)	
occurrences (all)	49	37	
Sinusitis			
subjects affected / exposed	48 / 366 (13.11%)	38 / 315 (12.06%)	
occurrences (all)	62	71	
Pneumonia			
subjects affected / exposed	31 / 366 (8.47%)	22 / 315 (6.98%)	
occurrences (all)	42	24	
Upper respiratory tract infection			
subjects affected / exposed	102 / 366 (27.87%)	77 / 315 (24.44%)	
occurrences (all)	176	134	

Urinary tract infection subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	 47 / 366 (12.84%) 91 19 / 366 (5.19%) 30	 18 / 315 (5.71%) 30 9 / 315 (2.86%) 10	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 92 / 366 (25.14%) 113	 99 / 315 (31.43%) 134	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 January 2015	• Added secondary objective/endpoint to evaluate change in duration of subtypes of seizures as assessed by the Subject/Caregiver Global Impression of Change in Seizure Duration (S/CGICSD) • Included the Pediatric Cannabinoid Withdrawal Scale (PCWS) for children 4–17 years of age • Clarified the exclusion criteria addressing previous and current use of cannabinoids and concerning subjects of child bearing potential • Clarified that the safety follow-up period must have been a minimum of 28 days after end of treatment in order to capture sufficient safety data • Clarified the definition of drop seizure of subtypes of seizures and added "countable partial seizures" and "partial seizures" to the definition of terms; in order to aid identification of seizure types • Clarified that the pre-randomization pregnancy test was to be performed using urine rather than serum in order to provide an immediate result for assessment of inclusion/exclusion criteria • Changed maximum dose from 50 milligrams per kilograms per day (mg/kg/day) to 30 mg/kg/day. • Limited maximum treatment to 1 year. The sponsor could look to extend the duration of this study. • Clarified withdrawal criteria to state that subjects with drug-induced liver injury (DILI) were to be withdrawn from the study
23 March 2015	Amendment in France only: • Documented effects on growth and development in subjecs less than 18 years of age by measurement of height, weight, serum insulin-like growth factor-1 and Tanner Staging (for subjects aged 12–17 [inclusive]) • Included measurement of serum triglycerides in clinical laboratory samples • Limited the maximum duration of prescription of IMP to 28 days • Specified that the IMP was to be stored in a locked cabinet or room designated solely for the storage of narcotics (i.e., containing nothing other) • Specified that any missing/unaccountable or theft or diversion of IMP should be promptly reported to the police authorities, the regional inspectorate of pharmacy and the ANSM. • Clarified that the first dose of IMP was to be taken in the clinic under medical supervision, followed by a two-hour safety observation period • Amended the number of subjects expected to enroll in line with increased sample sizes in each of the Core Studies • Amended the eligibility criterion regarding contraception requirements • Allowed subjects who have had study medication suspended due to an adverse event (AE) to resume dosing prior to complete recovery, provided that the AE was well tolerated
16 April 2015	Not implemented

11 August 2015	• Updated dosing following recommendations from the Data Safety Monitoring Committee of Study GWEP1332 Part A • Allowed for additional clinic visits to be scheduled by the Investigator in order to facilitate necessary dose adjustments • Allowed for an interim analysis to be conducted approximately 6 months after the first subject first dose in order to satisfy the Food and Drug Administration (FDA) requirement for an interim analysis to be performed within 6 months of the New Drug Application (NDA) submission • Required additional weekly safety telephone calls when increasing doses above 20 mg/kg/day until stable dosing was achieved • During follow-up of subjects with potential cases of DILI, added further details to state that alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), alkaline phosphatase and gamma-glutamyl transferase levels should all be monitored until levels normalized (in the Investigator's opinion) or returned to Baseline state. • Amended the eligibility criterion regarding impaired hepatic function to bring into line with the criteria for DILI • Allowed Investigators to monitor anti-epileptic drug (AED) plasma concentrations and discuss possible changes in drug dosage with the medical advisor(s) at GW Research Ltd. (GW)
26 August 2015	Amendment in France only: • Added recommendation of the DSMC of Study GWEP1332 Part A of a target dose of 20 mg/kg/day and titration schedule • Allowed for additional clinic visits to be scheduled by the Investigator in order to facilitate necessary dose adjustments • Allowed for an interim analysis to be conducted approximately 6 months after the first subject first dose in order to satisfy the FDA requirement for an interim analysis to be performed within 6 months of the NDA submission • Required additional weekly safety telephone calls when increasing doses above 20 mg/kg/day until stable dosing was achieved • During follow-up of subjects with potential cases of DILI, added further details to state that ALT, AST, TBL, alkaline phosphatase and gamma-glutamyl transferase levels should all be monitored until levels normalized (in the Investigator's opinion) or returned to Baseline state • Amended the eligibility criterion regarding impaired hepatic function to bring into line with the criteria for DILI • Allowed Investigators to monitor AED plasma concentrations and discuss possible changes in drug dosage with the medical advisor(s) at GW
22 April 2016	Amendment in the United States only: • Extended trial duration from 12 months to 24 months • Added IMP dispensing appointments between assessment visits in Year 2 • Simplified the adjustment of concomitant AEDs and deleted the requirement for 6 months of seizure freedom to allow flexibility in reducing or discontinuing AEDs following consultation with the medical monitor • Added information that Investigators should consider when monitoring liver function enzymes during the titration period in subjects taking concomitant medications known to affect liver function • Added that, where permitted by blood volume sampling guidelines, blood samples should have been taken for AED plasma level monitoring • Increased predicted number of subjects to be recruited to the study • Added additional details regarding C-SSRS questionnaire administration • Clarified details regarding liver transaminase monitoring prior to withdrawal • Clarified that subjected needed to have "completed" the treatment period of the Core study to be eligible for the open-label extension study

19 May 2016	Amendment in France only: • Extended trial duration from 12 months to 24 months • Simplified the adjustment of concomitant AEDs and deleted the requirement for 6 months of seizure freedom to allow flexibility in reducing or discontinuing AEDs following consultation with the medical monitor • Added information that Investigators should consider when monitoring liver function enzymes during the titration period in subjects taking concomitant medications known to affect liver function • Added that, where permitted by blood volume sampling guidelines, blood samples should have been taken for AED plasma level monitoring • Increased predicted number of subjects to be recruited to the study • Added additional details regarding C-SSRS questionnaire administration • Clarified details regarding liver transaminase monitoring prior to withdrawal • Clarified that subjected needed to have "completed" the treatment period of the Core study to be eligible for the open-label extension study
28 June 2016	Amendment in the United States only: Allowed for collection of additional blood samples from patients with Dravet syndrome (DS) taking GWP42003-P to understand more fully the pharmacokinetics (PK) of cannabidiol (CBD) and its metabolites in this subject population
28 July 2016	Amendment in Poland only: • Extended trial duration from 12 months to 24 months • Added IMP dispensing appointments between assessment visits in Year 2 • Clarified wording around the titration period to enable adjustments if intolerability or increased seizures were observed • Simplified the adjustment of concomitant AEDs and deleted the requirement for 6 months of seizure freedom to allow flexibility in reducing or discontinuing AEDs following consultation with the medical monitor • Added information that Investigators should consider when monitoring liver function enzymes during the titration period in subjects taking concomitant medications known to affect liver function • Added that, where permitted by blood volume sampling guidelines, blood samples should have been taken for AED plasma level monitoring • Increased predicted number of subjects to be recruited to the study • Clarified details regarding liver transaminase monitoring prior to withdrawal • Clarified that subjected needed to have "completed" the treatment period of the Core study to be eligible for the open-label extension study
29 March 2017	Amendment in France only: • Extended trial duration from 24 months to 36 months • Extended the recommended dose from 20 mg/kg/day to 10-20 mg/kg/day based on the results of trial GWEP1414 for Lennox-Gastaut syndrome • Added the option of administration of CBD through a gastrostomy (G)/nasogastric (NG) feeding tube after consultation with the medical monitor • Allowed for the frequency of dosing to change after consultation with the medical monitor • Added information to the dose titration regimen advising the investigator to consider monitoring hepatic function
28 April 2017	• Updated secondary objective to include assessment of the total seizures, for all subjects, as well as seizure subtypes • Updated the study design and treatment schema to reflect the correct treatment duration between Visits 10 and the End of Treatment/Withdrawal visit

03 May 2017	• Extended the recommended dose from 20 mg/kg/day to 10-20 mg/kg/day • Simplified the adjustment of concomitant AEDs and deleted the requirement for 6 months of seizure freedom to allow flexibility in reducing or discontinuing AEDs following consultation with the medical monitor • Permitted new AEDs in long-term trials, but stated that the investigator should consider whether CBD therapy resulted in an adequate clinical response and if continued participation in the trial was appropriate or if higher CBD doses should have been considered • Added the option of administration of CBD through a G/NG feeding tube after consultation with the medical monitor • Allowed for the frequency of dosing to change after consultation with the medical monitor • Added information that Investigators should consider when monitoring liver function enzymes during the titration period in subjects taking concomitant medications known to affect liver function • Added that, where permitted by blood volume sampling guidelines, blood samples should have been taken for AED plasma level monitoring • Increased predicted number of subjects to be recruited to the study • Clarified details regarding liver transaminase monitoring prior to withdrawal
29 August 2017	Amendment in Israel only: Extended study duration in Israel to include a second year of treatment
25 April 2018	Amendment in the United States only: • Extended the trial duration from 3 years to a maximum of 4 years • Updated description of the term "study completion," to include clarification of when subjects should transition to commercial supply
26 April 2018	Amendment in France only: Extended the trial duration from 3 years to a maximum of 4 years
01 May 2018	Amendment in Poland only: Extended the trial duration from 3 years to a maximum of 4 years
06 June 2018	Amendment in Israel only: Extended the trial duration from 2 years to a maximum of 3 years
30 April 2019	Amendment in Israel only: • Extended the trial duration has been extended from 3 years to a maximum of 4 years • Updated Introduction to clarify that GWP42003-P contains not more than 0.1% (weight to weight [w/w]) THC and not 0.15% (w/w) THC
07 May 2019	Amendment in Poland only: • Extended the trial duration has been extended from 4 years to a maximum of 5 years • Updated Introduction to clarify that GWP42003-P contains not more than 0.1% (w/w) THC and not 0.1% (w/w) THC
07 May 2019	Amendment in France only: • Extended the trial duration has been extended from 4 years to a maximum of 5 years • Updated Introduction to clarify that GWP42003-P contains not more than 0.1% (w/w) THC and not 0.1% (w/w) THC
11 June 2020	Amendment in Poland only: • Added withdrawal criterion to allow for withdrawal of subjects with significant disease or disorder which, in the opinion of the Investigator, may have either put the subject, other subjects, or site staff at risk, may have influenced the result of the study, or may have affected the subject's ability to participate in the study • Removed the Study Medication Use and Behavior Survey requirement, as no potential for abuse was expected in the remaining subjects in the study • Specified that evaluations and data collection could be made directly or remotely

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported