



Clinical trial results:

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

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2019-001605-24 |
| Trial protocol | GB ES IT |
| Global end of trial date | 09 June 2021 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 24 December 2021 |
| First version publication date | 24 December 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | GWND19002 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04252586 |
| 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) | EMA-001964-PIP02-19 |
| 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 | 08 November 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 June 2021 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the long-term safety of cannabidiol oral solution (GWP42003-P) in participants with Rett syndrome.

Protection of trial subjects:

This study was conducted in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 28 February 2020 |
| 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 | Spain: 8 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | United States: 8 |
| Worldwide total number of subjects | 21 |
| EEA total number of subjects | 8 |

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) | 13 |
| Adolescents (12-17 years) | 3 |
| Adults (18-64 years) | 5 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who had participated in the randomized, double-blind, placebo-controlled parent study GWND18064 (NCT03848832/ 2018-003370-27) entered in this open label extension study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|-----------|------------|
| Arm title | GWP42003-P |
|-----------|------------|

Arm description:

Participants were administered with 5 mg/kg/day GWP42003-P orally for 1 week. Depending on clinical response and tolerability, the participants' dose was increased in weekly increments of 5 mg/kg/day up to 15 mg/kg/day GWP42003-P. Participants then remained on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with an option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day, as deemed necessary by the investigator.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | GWP42003-P |
| Investigational medicinal product code | |
| Other name | Cannabidiol |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

GWP42003-P oral solution (100 mg/mL) was administered twice daily as morning and evening doses based on participant's body weight.

| Number of subjects in period 1 | GWP42003-P |
|-----------------------------------|------------|
| Started | 21 |
| Completed | 0 |
| Not completed | 21 |
| Adverse event, serious fatal | 2 |
| Did Not Complete Treatment Period | 1 |
| Adverse event, non-fatal | 1 |
| Study Terminated By Sponsor | 4 |
| Withdrawal By Parent/Guardian | 3 |
| Sponsor Request | 10 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | GWP42003-P |
|-----------------------|------------|

Reporting group description:

Participants were administered with 5 mg/kg/day GWP42003-P orally for 1 week. Depending on clinical response and tolerability, the participants' dose was increased in weekly increments of 5 mg/kg/day up to 15 mg/kg/day GWP42003-P. Participants then remained on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with an option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day, as deemed necessary by the investigator.

| Reporting group values | GWP42003-P | Total | |
|---|----------------|-------|--|
| Number of subjects | 21 | 21 | |
| Age categorical Units: | | | |
| Age continuous Units: years arithmetic mean standard deviation | 10.2 ± 5.59 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 21 | 21 | |
| Male | 0 | 0 | |
| Age, Customized Units: Subjects | | | |
| 2-5 years | 6 | 6 | |
| 6-12 years | 9 | 9 | |
| 13-19 years | 6 | 6 | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 1 | |
| Asian | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 0 | |
| White | 20 | 20 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 1 | 1 | |
| Not Hispanic or Latino | 20 | 20 | |
| Unknown or Not Reported | 0 | 0 | |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | GWP42003-P |
| Reporting group description: | |
| Participants were administered with 5 mg/kg/day GWP42003-P orally for 1 week. Depending on clinical response and tolerability, the participants' dose was increased in weekly increments of 5 mg/kg/day up to 15 mg/kg/day GWP42003-P. Participants then remained on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with an option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day, as deemed necessary by the investigator. | |

Primary: Number of participants with any treatment emergent adverse event (TEAEs), Serious AEs (SAEs), Deaths, Discontinuations Due to AEs, Treatment-related AEs

| | |
|-----------------|---|
| End point title | Number of participants with any treatment emergent adverse event (TEAEs), Serious AEs (SAEs), Deaths, Discontinuations Due to AEs, Treatment-related AEs ^[1] |
|-----------------|---|

End point description:

Adverse events (AEs) were defined as any new unfavorable/unintended signs/symptoms (including abnormal laboratory findings when relevant) or diagnosis or worsening of a pre-existing condition that occurs during the study. TEAEs were defined as the AEs that started or worsened in severity or seriousness following the first dose of GWP42003-P. Any AEs occurring between last dose of parent study (GWND18064) and this extension study visit 1 were not considered as TEAEs. The analysis was conducted on Safety Analysis Set defined as all participants who received at least one dose of GWP42003-P in the study.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 475 days (End of Treatment + 30 days)

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: Only descriptive statistics was planned for this primary safety endpoint.

| End point values | GWP42003-P | | | |
|----------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| TEAEs | 19 | | | |
| SAEs | 5 | | | |
| Deaths | 2 | | | |
| TEAEs leading to discontinuation | 3 | | | |
| Treatment-related TEAEs | 7 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Changes in the Indicated Clinical Laboratory Parameter From the Baseline at Any Time Post-dose

| | |
|-----------------|--|
| End point title | Number of Participants With Clinically Significant Changes in the Indicated Clinical Laboratory Parameter From the Baseline at Any Time Post-dose ^[2] |
|-----------------|--|

End point description:

Clinical significance was determined by the investigator. Numbers of participants with values outside the normal range for indicated biochemistry and hematology parameters were determined. The analysis was conducted in safety analysis set. ALT = Alanine aminotransferase, AT= alanine transferase (defined as aspartate aminotransferase (AST) or ALT in the study), ULN= upper limit of normal (ULN).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 442 days (End of Treatment)

Notes:

[2] - 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: Only descriptive statistics was planned for this primary safety endpoint.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| ALT >3xULN | 1 | | | |
| AT >3xULN | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Changes in the Indicated Vital Sign Values From the Baseline at Any Time Post-dose

| | |
|-----------------|--|
| End point title | Number of Participants With Clinically Significant Changes in the Indicated Vital Sign Values From the Baseline at Any Time Post-dose ^[3] |
|-----------------|--|

End point description:

Clinical significance was determined by the investigator. The change from baseline of randomized clinical trial (GWND18064-NCT03848832) at specific study days for vital signs parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate were calculated. The analysis was conducted in safety analysis set. mmHg=millimetres of mercury, bpm=beats per minute, EOT = End of Treatment

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 442 days (End of Treatment)

Notes:

[3] - 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: Only descriptive statistics was planned for this primary safety endpoint.

| | | | | |
|-------------------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Sitting SBP Change <-20mmHg, Day 29 | 2 | | | |

| | | | | |
|--|---|--|--|--|
| Sitting SBP Change <-20mmHg, Day 57 | 1 | | | |
| Sitting SBP Change <-20mmHg, Day 85 | 1 | | | |
| Sitting SBP Change <-20mmHg, Day 141 | 2 | | | |
| Sitting SBP Change <-20mmHg, Day 197 | 2 | | | |
| Sitting SBP Change <-20mmHg, EOT | 1 | | | |
| Sitting SBP Change >20mmHg, Day 29 | 1 | | | |
| Sitting SBP Change >20mmHg, Day 57 | 3 | | | |
| Sitting SBP Change >20mmHg, Day 85 | 2 | | | |
| Sitting SBP Change >20mmHg, EOT | 2 | | | |
| Sitting DBP Change <-10mmHg, Day 29 | 4 | | | |
| Sitting DBP Change <-10mmHg, Day 57 | 4 | | | |
| Sitting DBP Change <-10mmHg, Day 85 | 2 | | | |
| Sitting DBP Change <-10mmHg, Day 141 | 3 | | | |
| Sitting DBP Change <-10mmHg, Day 197 | 3 | | | |
| Sitting DBP Change <-10mmHg, EOT | 3 | | | |
| Sitting DBP Change >10mmHg, Day 29 | 9 | | | |
| Sitting DBP Change >10mmHg, Day 57 | 4 | | | |
| Sitting DBP Change >10mmHg, Day 85 | 4 | | | |
| Sitting DBP Change >10mmHg, Day 141 | 3 | | | |
| Sitting DBP Change >10mmHg, Day 197 | 1 | | | |
| Sitting DBP Change >10mmHg, EOT | 5 | | | |
| Pulse Rate Change <-10beats/min, Day 29 | 8 | | | |
| Pulse Rate Change <-10beats/min, Day 57 | 7 | | | |
| Pulse Rate Change <-10beats/min, Day 85 | 7 | | | |
| Pulse Rate Change <-10beats/min, Day 141 | 2 | | | |
| Pulse Rate Change <-10beats/min, Day 197 | 5 | | | |
| Pulse Rate Change <-10beats/min, Day 281 | 1 | | | |
| Pulse Rate Change <-10beats/min, Day 365 | 1 | | | |
| Pulse Rate Change <-10beats/min, EOT | 6 | | | |
| Pulse Rate Change >10beats/min, Day 29 | 2 | | | |
| Pulse Rate Change >10beats/min, Day 57 | 3 | | | |
| Pulse Rate Change >10beats/min, Day 85 | 3 | | | |
| Pulse Rate Change >10beats/min, Day 141 | 3 | | | |
| Pulse Rate Change >10beats/min, Day 197 | 1 | | | |
| Pulse Rate Change >10beats/min, EOT | 4 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Changes in the Indicated Physical Examination Parameters From the Baseline at Any Time Post-dose

| | |
|-----------------|--|
| End point title | Number of Participants With Clinically Significant Changes in the Indicated Physical Examination Parameters From the Baseline at Any Time Post-dose ^[4] |
|-----------------|--|

End point description:

Clinical significance was determined by the investigator for body weight and height parameters. Percent change in body weight ($\leq 7\%$ change or $\geq 7\%$ change) was calculated. Percentages were calculated as $100 \times n/\text{number of participants present at the study visit}$. The analysis was conducted in safety analysis set. EOT = End of Treatment

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 442 days (End of Treatment)

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: Only descriptive statistics was planned for this primary safety endpoint.

| End point values | GWP42003-P | | | |
|------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Weight Change $\leq 7\%$, Day 29 | 2 | | | |
| Weight Change $\leq 7\%$, Day 85 | 1 | | | |
| Weight Change $\leq 7\%$, Day 197 | 1 | | | |
| Weight Change $\leq 7\%$, EOT | 1 | | | |
| Weight Change $\geq 7\%$, Day 29 | 7 | | | |
| Weight Change $\geq 7\%$, Day 85 | 9 | | | |
| Weight Change $\geq 7\%$, Day 197 | 5 | | | |
| Weight Change $\geq 7\%$, Day 291 | 1 | | | |
| Weight Change $\geq 7\%$, Day 365 | 1 | | | |
| Weight Change $\geq 7\%$, EOT | 10 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Electrocardiogram (ECG) Values at Any Time Post-dose

| | |
|-----------------|--|
| End point title | Number of Participants With Clinically Significant Electrocardiogram (ECG) Values at Any Time Post-dose ^[5] |
|-----------------|--|

End point description:

Clinical significance was determined by the investigator. The analysis was conducted in safety analysis set. QTcB = corrected QT interval with Bazette correction. QTcF = QTc corrected by Fridericia, EOT = End of Treatment

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 442 days (End of Treatment)

Notes:

[5] - 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: Only descriptive statistics was planned for this primary safety endpoint.

| | | | | |
|--|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| QTcB Interval, Aggregate > 450msec, Day 29 | 4 | | | |
| QTcB Interval, Aggregate > 450msec, Day 85 | 4 | | | |
| QTcB Interval, Aggregate > 450msec, EOT | 4 | | | |
| QTcB Interval, Aggregate > 480msec, Day 85 | 1 | | | |
| QTcB Interval, Aggregate > 480msec, EOT | 1 | | | |
| QTcF Interval, Aggregate > 450msec, Day 85 | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Changes in Tanner Staging at the Baseline and at End of Treatment

| | |
|--|--|
| End point title | Number of Participants With Changes in Tanner Staging at the Baseline and at End of Treatment ^[6] |
| End point description: The pubic hair growth and breast development of all adolescent participants were assessed by the investigator or the caregiver using Tanner Staging categorization from 1 to 5. The analysis was conducted in safety analysis set. | |
| End point type | Primary |
| End point timeframe: Up to approximately 442 days (End of Treatment) | |

Notes:

[6] - 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: Only descriptive statistics was planned for this primary safety endpoint.

| | | | | |
|--------------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Baseline, Tanner Stage 1, n=21 | 6 | | | |
| Baseline, Tanner Stage 2, n=21 | 3 | | | |
| Baseline, Tanner Stage 3, n=21 | 1 | | | |
| Baseline, Tanner Stage 4, n=21 | 2 | | | |

| | | | | |
|--|---|--|--|--|
| Baseline, Tanner Stage 5, n=21 | 4 | | | |
| Baseline, Tanner Stage Missing, n=21 | 5 | | | |
| End of Treatment, Tanner Stage 1, n=18 | 4 | | | |
| End of Treatment, Tanner Stage 2, n=18 | 2 | | | |
| End of Treatment, Tanner Stage 3, n=18 | 1 | | | |
| End of Treatment, Tanner Stage 4, n=18 | 3 | | | |
| End of Treatment, Tanner Stage 5, n=18 | | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Suicidal Ideation or Behaviour at End of Treatment

| | |
|-----------------|--|
| End point title | Number of Participants With Clinically Significant Suicidal Ideation or Behaviour at End of Treatment ^[7] |
|-----------------|--|

End point description:

Suicidal ideation and behaviour was assessed by the investigator via a clinical interview with the caregiver. The questionnaire included following questions: Has the child expressed any wish to be dead?, Has the child made any suicide attempts?, Has the child shown any non-suicidal self-injurious behavior? The responses were recorded as Yes/No. The analysis was conducted in safety analysis set.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 442 days (End of Treatment)

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: Only descriptive statistics was planned for this primary safety endpoint.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Clinically Significant Effects on their Menstruation Cycle at End of Treatment

| | |
|-----------------|---|
| End point title | Number of Participants With Clinically Significant Effects on their Menstruation Cycle at End of Treatment ^[8] |
|-----------------|---|

End point description:

Participants were evaluated for any changes to typical menstrual cycles, duration of menstrual cycles

and typical strength of the menstrual cycles during the study. Clinical significance was determined by the investigator. The analysis was conducted in safety analysis set.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to approximately 442 days (End of Treatment)

Notes:

[8] - 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: Only descriptive statistics was planned for this primary safety endpoint.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: participants | | | | |
| number (not applicable) | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Clinical Global Impressions-Improvement (CGI-I) Continuous Score

| | |
|-----------------|---|
| End point title | Mean Clinical Global Impressions-Improvement (CGI-I) Continuous Score |
|-----------------|---|

End point description:

CGI-I is a 7-point scale that requires the clinician to assess how much a participant's illness has improved or worsened relative to a Baseline state at the beginning of the intervention. This was rated as: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; or 7 = very much worse. Baseline of the parent study GWND18064 (NCT03848832) was used as baseline. This analysis included participants of safety set without baseline assessment but with post-baseline assessment. At each visit, all participants without missing assessment were included.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Day 442 (End of Treatment)

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 3.3 (\pm 1.15) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Rett Syndrome Behaviour Questionnaire (RSBQ) Overall score at End of Treatment

| | |
|-----------------|--|
| End point title | Change from Baseline in Rett Syndrome Behaviour Questionnaire (RSBQ) Overall score at End of Treatment |
|-----------------|--|

End point description:

RSBQ is a caregiver-completed questionnaire that assess the overall condition (45 items) in individuals with Rett Syndrome. Each item (except Item 31) is rated on a 3-point scale (0-2); 0 indicating an item that is "not true as far as you know," 1 indicating an item is "somewhat or sometimes true," and 2 indicating an item that is "very true or often true". Item 31 is to be reverse scored. The total summed score ranges from 0 to 90, and higher total scores represent greater severity. Baseline of the randomized clinical study (GWND18064 - NCT03848832) was used as baseline for the change from baseline calculation. Change from baseline at one specific visit included all participants without missing baseline and missing assessment at this specific visit. This analysis includes participants of safety set without baseline assessment but with post-baseline assessment. At each visit, all participants without missing assessment were included.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Treatment (up to Day 442)

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 46.7 (± 12.05) | | | |
| CFB at End of Treatment | -7.4 (± 14.93) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Clinician Global Impressions - Severity Scale (CGI-S) Continuous Score at End of Treatment

| | |
|-----------------|---|
| End point title | Change from Baseline in Mean Clinician Global Impressions - Severity Scale (CGI-S) Continuous Score at End of Treatment |
|-----------------|---|

End point description:

CGI-S is a 7-point scale that requires the clinician to rate the severity of the participant's illness at the time of assessment relative to the clinician's experience with participants who had the same diagnosis. This was rated as: 1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; or 7 = extremely ill. Baseline of the parent study- GWND18064 (NCT03848832) was used as baseline for the change from baseline calculation. Change from baseline at one specific visit included all participants without missing baseline and missing assessment at this specific visit. This analysis included participants of safety set without baseline assessment but with post-baseline assessment. At each visit, all participants without missing assessment were included.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Treatment (up to Day 442)

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 4.4 (± 0.93) | | | |
| CFB at End of Treatment | -0.1 (± 0.48) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Children's Sleep Habits Questionnaire (CSHQ) Total Score at End of Treatment

| | |
|-----------------|---|
| End point title | Change from Baseline in Mean Children's Sleep Habits Questionnaire (CSHQ) Total Score at End of Treatment |
|-----------------|---|

End point description:

The CSHQ is a caregiver-completed sleep screening instrument designed for school-aged children, including 33 items within 8 subscales: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep-disordered breathing, daytime sleepiness. Item scores range from 1-3: where 3=usually; for 5 or more times a week, 2=sometimes; for 2-4 times a week, 1=rarely; for never or 1 time/week, while 5 items are reverse scored. Total summed score range: 33-99; higher scores reflect more disturbed sleep behavior. Baseline of the parent study GWND18064 (NCT03848832) was used as baseline for the change from baseline calculation. Change from baseline (CFB) at one specific visit included all participants without missing baseline and missing assessment at this specific visit. This analysis included participants of safety set without baseline assessment but with post-baseline assessment. At each visit, participants without missing assessment were included.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Treatment (up to Day 442)

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 49.6 (± 7.57) | | | |
| CFB at End of Treatment | -3.0 (± 6.87) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in 9-item Mean Motor Behavioral Assessment (MBA-9) Total Score at End of Treatment

| | |
|-----------------|---|
| End point title | Change from Baseline in 9-item Mean Motor Behavioral Assessment (MBA-9) Total Score at End of Treatment |
|-----------------|---|

End point description:

MBA-9 is derived from the full MBA scale (37 Rett syndrome symptoms) by selecting the items deemed amenable to change and which reflected areas of meaningful clinical change. The severity of current symptoms is rated by the investigator on a 5-point numerical scale; (0 =normal or never; 1 =mild or rare; 2 =moderate or occasional; 3 =marked or frequent; 4 =very severe or constant). The MBA-9 total score is calculated by summing the scores of the 9 individual items. Total score range: 0-36; higher total scores represent greater severity. Baseline of the parent study- GWND18064 (NCT03848832) was used as baseline for the change from baseline calculation. Change from baseline (CFB) at one specific visit included all participants without missing baseline and missing assessment at this specific visit. This analysis includes participants of safety set without baseline assessment but with post-baseline assessment. At each visit, all participants without missing assessment were included.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, End of Treatment (up to Day 442)

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | GWP42003-P | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 17.1 (± 6.36) | | | |
| CFB at End of Treatment | 0.7 (± 5.19) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 475 days (End of Treatment + 30 days)

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) are defined as the AEs that started or worsened in severity or seriousness following the first dose of GWP42003-P. Any AEs occurring between last dose of parent study (GWND18064) and this extension study visit 1 were not considered as TEAEs. The analysis was conducted in safety analysis set.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | GWP42003-P |
|-----------------------|------------|

Reporting group description:

Participants received GWP42003-P (5 mg/kg/day] for 1 week. Depending on clinical response and tolerability, the participants' dose was increased in weekly increments of 5 mg/kg/day up to 15 mg/kg/day GWP42003-P. Participant remained on a stable dose of GWP42003-P for the duration of the maintenance period of the trial (up to 104 weeks), with the option for doses to be decreased or increased to a maximum dose of 20 mg/kg/day based on clinical response and tolerability, as deemed necessary by the investigator.

| Serious adverse events | GWP42003-P | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | | |
| number of deaths (all causes) | 2 | | |
| number of deaths resulting from adverse events | 2 | | |
| Congenital, familial and genetic disorders | | | |
| Rett Syndrome | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nervous system disorders | | | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Status epilepticus | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory arrest | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | Additional description: The deaths were not considered to be treatment related by the investigator. | | |
| subjects affected / exposed | 2 / 21 (9.52%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Postoperative wound infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | GWP42003-P | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 21 (90.48%) | | |
| Investigations | | | |
| Mean cell volume increased | | | |

| | | | |
|--|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Monocyte count decreased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 21 (9.52%)</p> <p>2</p> <p>3 / 21 (14.29%)</p> <p>4</p> | | |
| <p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 21 (9.52%)</p> <p>2</p> | | |
| <p>Nervous system disorders</p> <p>Epilepsy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Seizure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Tremor</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 21 (9.52%)</p> <p>5</p> <p>3 / 21 (14.29%)</p> <p>5</p> <p>2 / 21 (9.52%)</p> <p>2</p> | | |
| <p>Blood and lymphatic system disorders</p> <p>Neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 21 (9.52%)</p> <p>4</p> | | |
| <p>General disorders and administration site conditions</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 21 (19.05%)</p> <p>4</p> | | |
| <p>Gastrointestinal disorders</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>4 / 21 (19.05%)</p> <p>5</p> <p>7 / 21 (33.33%)</p> <p>9</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> | | | |

| | | | |
|--|----------------------|--|--|
| Cough subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | | |
| Psychiatric disorders Bruxism subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | | |
| Irritability subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | | |
| Infections and infestations Otitis media subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 5 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 28 May 2020 | The purpose of the amendment was to define the entry criteria for participants who were affected by COVID-19 pandemic containment measures during their participation in the parent Study GWND18064: <ul style="list-style-type: none">• Allowance for participants to enroll into GWND19002 after the point of GWND18064 follow-up.• Allowance for participants who withdrew from GWND18064 due to COVID-19 pandemic containment measures to enroll into GWND19002 at a later date, when appropriate. |
| 11 November 2020 | The purpose of the amendment was to define the entry criteria for participants who were affected by COVID-19 pandemic containment measures during their participation in the parent study GWND18064 or withdrew from GWND18064 due to sponsor administrative decision: <ul style="list-style-type: none">• Allowance for participants to enroll into GWND19002 after the point of GWND18064 follow-up.• Allowance for participants who withdrew from GWND18064 due to COVID-19 pandemic containment measures or withdrew from GWND18064 due to sponsor administrative decision to enroll into GWND19002 at a later date, when appropriate. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This trial was terminated due to enrolment challenges and the COVID-19 pandemic. Due to early termination and participant's withdrawal, the number of participants was small, the length of treatment was reduced, which limited data interpretation.

Notes: