Jazz Pharmaceuticals

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Statistical Analysis Plan			
Protocol:	GWND19189	**Version:**	1.0

Protocol Title: An exploratory, phase 2, randomized, double-blind, placebo-controlled trial to investigate the safety and efficacy of cannabidiol oral solution (gwp42003p; cbd-os) in children and adolescents with autism spectrum disorder

Protocol Number: GWND19189

Compound Number: GWP42003P

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List of Abbreviations

ABC	Aberrant Behavior Checklist Subscales
ABC-I	Aberrant Behavior Checklist Irritability Subscale
ADI-R	Autism Diagnostic Interview, Revised
ADOS-2	Autism Diagnostic Observational Schedule
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASD	Autism spectrum disorder
AST	Aspartate aminotransferase
b.i.d	Twice daily
BMI	Body mass index
[redacted]	[redacted]
CBD	Cannabidiol
CBD-OS	GWP42003-P, Cannabidiol oral solution
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impressions - Improvement
CGI-S	Clinical Global Impressions - Severity
CI	Confidence interval
COVID-19	Corona virus disease-19
CRF	Case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	12-Lead electrocardiogram
eCRF	Electronic case report form
EOT	End of Treatment
FAS	Full analysis set
GEE	Generalized estimating equation
GW	GW Research Ltd
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
LS	The least squares
MMRM	Mixed-effects repeated measures model
[redacted]	[redacted]
PP	Per protocol
PVD	Pharmacovigilance Department
[redacted]	[redacted]
RTSM	Randomization and Trial Management System
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SOC	System organ class
TEAE	Treatment-emergent adverse event
THC	Δ9-Tetrahydrocannabinol

ULN	Upper limit of normal
VABS-3	Vineland Adaptive Behavior Scales, 3rd Ed., comprehensive interview form
VAS	Visual analog scale
WASI-II	Wechsler Abbreviated Scale of Intelligence Scale Second Edition
WD	Withdrawal

CONTENTS

1. Introduction

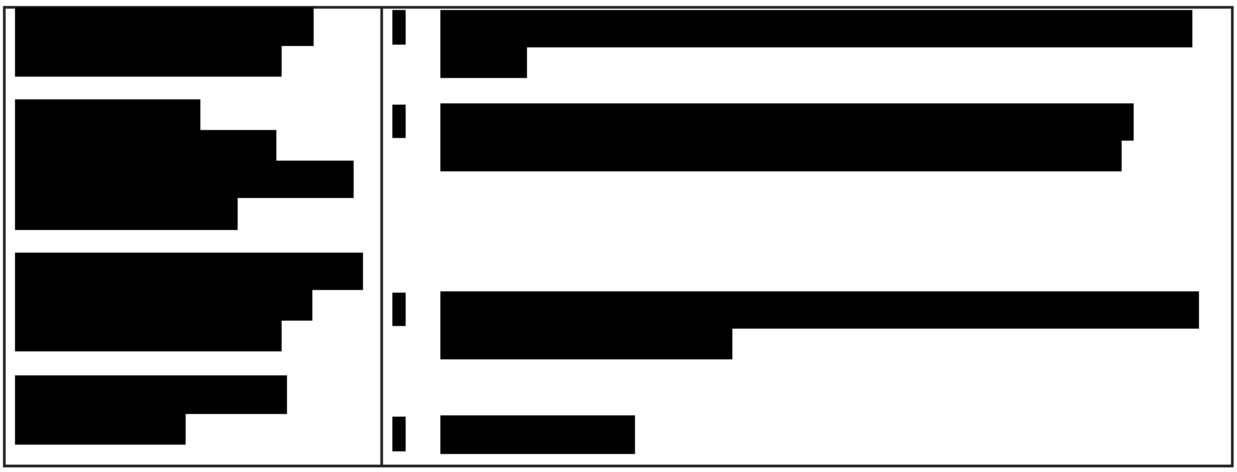
The protocol for study GWND19189 describes the general approach to analysis of data from the study. This analysis plan describes in detail the statistical methodology and planned analyses to be conducted for Protocol GWND19189 for inclusion in the CSR. Specifications for tables, figures, and listings are in a separate document.

2. Protocol Objectives and Endpoints

The objectives and endpoints for the study are outlined in Table 1.

Table 1 Protocol Objectives and Endpoints

Objectives	Endpoints
Efficacy	
To evaluate the efficacy of GWP42003-P, compared with placebo, in reducing symptom severity in children and adolescents.with ASD	Social Communication • Change from baseline to week 12 of the VABS-3 social and communication composite (arithmetic mean of the social and communication domain scores), the adaptive behavior composite, and individual domain scores. Behavior • Change from baseline to week 12 of the Aberrant Behavior Checklist Subscales. Overall condition • Proportion of patients with a score of “very much improved” or “much improved” on CGI-I at week 12. • Proportion of patients with a score of “very much improved”, “much improved” or “minimally improved” on CGI-I at week 12. • Change from baseline to week 12 of the CGI-S score.
Safety	
To evaluate the safety of GWP42003-P compared with placebo in children with ASD	Adverse events Clinical laboratory parameters Vital signs Physical examination procedures 12-lead ECG C-SSRS
[redacted]	
[redacted]	[redacted]



3. Study Design

3.1 Design Overview

This is an exploratory, Phase 2, double-blind, randomized, placebo-controlled, multisite trial, which will compare the safety and efficacy of a 10 mg/kg/day dose of GWP42003-P versus placebo in children and adolescents with ASD.

Approximately 160 subjects who meet eligibility criteria and consent to participate in the study are randomly assigned in a 1:1 ratio to one of the following treatment groups:

- GWP42003-P
- Placebo

Patients will be stratified based on their age (6 to 11, 12 to 17), use of antipsychotics (on versus off), and region (North America versus Rest of the World). Patients will be administered 5 mg/kg/day GWP42003-P or matching volumes of placebo for 1 week and then 10 mg/kg/day GWP42003-P or matching volumes of placebo for 11 weeks. At the end of treatment, patients will taper the medication over 1 week.

Overall trial design is outlined in Figure 1.

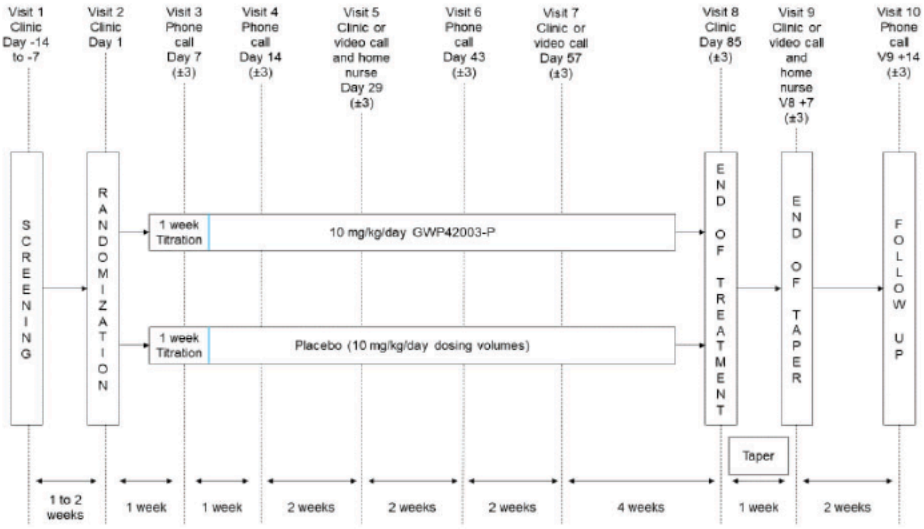


Figure 1 Trial Design and Treatment Schematic

Eligible patients may be randomized 7 to 14 days after the screening visit (Visit 1), once all required assessments have been completed and laboratory results have been reviewed; if required, screening assessments may be split over 2 visits; however, both visits must fall into the 7 to 14 day window prior to randomization (Visit 2). One week and 2 weeks following randomization, there will be 2 safety telephone visits (Visit 3 and 4). The patient will return to the clinic or video call and home nurse visit, 4 weeks after randomization (Visit 5). Six weeks after randomization, there will be another safety call (Visit 6), and then the patient will return for a clinic visit or video call visit (Visit 7) 8 weeks after randomization. The end of treatment visit will take place 12 weeks after randomization (Visit 8). If at any point it is decided to withdraw a patient from the trial, the patient should return to the clinic as soon as possible and complete Visit 8 procedures. At Visit 8, patients will commence to taper the medication (unless in case of withdrawal the medication was already discontinued or continued dosing is inadvisable, e.g., due to an AE). At the end of taper, the patient will return to the clinic or video call and home nurse visit (Visit 9). All patients will have a follow-up safety telephone visit, 14 days after Visit 9 or Visit 8 (in case the patient did not taper the medication).

Visit windows are allowed as defined in the schedule of assessment. Visit 3, 4, 5, 6, 7, and 8 days and windows are counted from the day of randomization (Visit 2). Visit 9 day and window is counted from the day of Visit 8. Visit 10 day and window is counted from the day of Visit 9, or the day of Visit 8 (if the patient did not enter the taper period).

3.2 Sample Size

[redacted]

3.3 Treatment Randomization

A permuted block randomization scheme was created to assign subjects in a 1:1 ratio to either of the two treatment groups. The scheme was stratified by age (6 to 11 years; 12 to 17 years), use of anti-psychotics (on; off), and region (North America; Other). At visit 2, randomization will be performed for each consenting eligible subject using [redacted].

3.4 Assessment Schedule

The assessments and procedures that will be conducted during this study are presented in the Schedule of Assessments (SoA) in Appendix 1 of the study protocol.

3.5 Interventions

GWP42003-P or placebo will be administered orally b.i.d. (morning and evening) using the syringe(s) provided, preferentially with food i.e., within 30 minutes after the end of a meal/snack. The first dose of GWP42003-P or placebo is taken at home in the evening. The time of IMP administration in relation to food should be kept consistent throughout the trial.

Patients will be administered 5 mg/kg/day GWP42003-P or matching volumes of placebo for 1 week and then 10 mg/kg/day GWP42003-P or matching volumes of placebo for 11 weeks. At the end of treatment, patients will taper the medication in steps of -2.5 mg/kg/day every 2 days over 1 week.

4. General Study Level Considerations

4.1 Data Sources

Data are recorded on electronic case report forms (eCRFs). Central laboratory data and [redacted] will be provided via electronic data transfers. Electronic devices are used to capture dosing diary, medications, and questionnaire data.

Section 16.3 of the protocol provides additional details describing data collection.

4.2 Definition of Baseline and Change from Baseline

Baseline for analysis purposes is defined as the last available observation prior to the first administration of the study drug at home in the evening of Visit 2.

4.3 Study Day

Study day 1 is defined as the date of the first dose, and the day immediately prior to study day 1 is study day -1. For any events on or after the first administration of the study drug, study day is calculated as:

event date – date of first administration of study drug + 1.

For any events before the first administration date, study day is calculated as:

event date – date of first administration of study drug.

4.4 Analysis Visit Window

No analysis visit windowing will be performed for this study.

For by-visit summaries, data recorded at the nominal visit will be presented. Subjects who withdraw early will be mapped to the nearest scheduled visit considering missed previous visits (if previous visit is not missing, then consider the next visit). Unscheduled measurements will not be included in by-visit summaries but will contribute to the baseline timepoint (if baseline is missing) and/or worst-case value where required (e.g. shift tables or summaries involving worst-case values at any time post-Baseline).

Listings will include scheduled, unscheduled, retest and early discontinuation data.

4.5 Missing Data and Partial Dates

Unless stated otherwise, missing data will not be replaced with imputed values.

Partial start or stop dates (month or day) are allowed on CRF for adverse events, concomitant medication, antipsychotic medication, and medical history. An entry for the year is required in the eCRF system for each of these dates. Only the month and day may be entered as unknown. Dates from these forms will be reported in listings as collected. Every effort will be made to query missing dates.

For records with a partial start date, the following procedure will be employed in determining if an AE is treatment emergent AE:

- Dates with missing day and non-missing month will be assumed to occur on the first day of the non-missing month, except for assessments/events occurring in the first month of dosing, in which case the date will be the first day of dosing.

- Dates with missing month will be assumed to occur on the first day of the non-missing year (i.e. January 1), except for assessments/events occurring in the first year of dosing, in which case the date will be the first day of dosing.

4.6 Multiple Study Centers

The study will be conducted at multiple centers in North America and Rest of the World. Data from all sites will be pooled for all analyses. For efficacy analyses, region (North America, Rest of the World) will be included as a stratification factor.

5. Statistical Analysis

5.1 Hypothesis testing

Statistical hypothesis testing will be performed on the efficacy and exploratory endpoints as appropriate with no inferential statistical decision drawn as this is an exploratory trial. Statistical hypotheses will be tested using 2-sided tests at a 5% significance level. P-values and 95% confidence intervals will be provided where appropriate.

5.2 Analysis Populations

Five analysis populations will be defined for use with various analyses. Table 2 illustrates the relationship between each population and the analyses for which the data from the population will be used.

Table 2 Analysis Populations

Analysis		Analysis Population			
	Screened Analysis Set	Full Analysis Set	Safety Analysis Set	Per Protocol Analysis Set	[redacted]
Subject disposition	X		X		
Population inclusion	X	X			
Medical history		X			
Autism history		X			
Caregiver		X			
Demographics and baseline characteristics		X	X	X	
Protocol deviations	X	X			
Efficacy endpoints		X		X	
[redacted]					[redacted]
Safety endpoints			X		

5.2.1 Screened Analysis Set

The Screened analysis set includes all subjects who are enrolled (i.e, screened in the trial by providing written informed consent/assent).

5.2.2 Full Analysis Set (FAS)

All patients who have been randomized to study treatment and receive at least 1 dose of IMP will be included in the full analysis set (FAS) irrespective of their protocol adherence and continued participation in the study. Patients will be analysed according to their randomized IP assignment, irrespective of the treatment actually received.

5.2.3 Safety Analysis Set

All patients who receive at least 1 dose of IMP in the trial will be included and analyzed according to the treatment received. Only patients for whom it has been confirmed that they did not take any IMP will be excluded from the safety analysis set.

5.2.4 Per Protocol (PP) Analysis Set

The PP set is defined as all patients that are a subset of the FAS who have no major protocol deviations deemed to compromise the assessment of efficacy. Major protocol deviations will be identified and fully defined prior to unblinding of the trial based on the blinded data. A patient may be considered to be excluded from the PP set if any of the following criteria are met:

- Not meeting Inclusion criteria, or meeting Exclusion criteria
- Usage of restricted medications/treatments that may affect interpretation of the efficacy endpoints
- Noncompliance with the trial treatment regimen
- Incorrect treatment administered to/taken by subject

Alternate criteria for exclusion from the PP set may be applied to accommodate unforeseen events that occurred during the conduct of the study. The subjects belonging to PP analysis set are defined prior to breaking the blind of the study in a blind data review meeting.

[redacted]

[redacted]

6. Data Display Characteristics

Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values (n), mean, standard deviation (StdDev), minimum (min), median, and maximum (max). Categorical variables will be summarized by the frequency and proportion of participants falling into each category.

Unless stated otherwise, data listings will be produced for all recorded data. Data listings will be ordered by treatment, site, subject number, and time of assessment. When expedient, additional levels of ordering hierarchy may reflect subsets of assessments within subject. Additional data listings will be produced for outcome measures that involve extensive procedures to derive the analyzed outcomes.

Figures will be produced when specified in sections to follow.

Details of the display format and numbering will be described in a separate TLF shells document.

The MedDRA version used for coding AEs, prior/concomitant medications and laboratory parameters will be included in the relevant outputs as a footnote.

All summaries, statistical analyses, data listings, and figures will be completed using SAS version 9.4 of the SAS Institute (North Carolina, USA) unless otherwise noted. Each summary, figure, or data listing will include the data cutoff date in addition to the production date.

6.3 Subject Accountability

6.3.1 Disposition

The presentation of patient disposition will include information on enrolment, randomization, receiving at least one dose of IP, completing Week 4, Week 8 and Week 12 of treatment and study discontinuations and completing the study. Number of subjects completed the follow up period and tapered the medication will be included. It will summarise whether a subject did or did not experience these milestones and, if not, the reason. The presentation will also include the number of subjects with complete follow-up of each efficacy endpoint and vital status of subjects at the end of the study (dead, alive or unknown).The tabulation will include an overview

of the number and percentage of subjects experiencing a particular disposition event, per treatment arm and in total, with number of randomized subjects in the respective treatment group, and in total, used as the denominator for the percentage calculation. Number of subjects enrolled, but not randomized, as well as number of subjects with a certain reason for not being randomized will only be displayed for all subjects combined, with no percentage calculated. The number and percentage of subjects discontinuing treatment and discontinuing study due to COVID-19 will also be presented.

The disposition data mentioned above will be listed for all patients.

6.3.2 Subject Characteristics

Data collected about the following subject characteristics at the Baseline visit (Visit 2) will be summarized for populations as in Table 2.

Demographics

The following demographic and baseline characteristics data will be summarized by treatment group and overall using the safety set.

Demographic characteristics: age at randomization, age group (6 to 11, 12 to 17), sex at birth, if female, childbearing potential, race and ethnicity.

Baseline characteristics: height (cm), weight (kg), body mass index (BMI) (kg/m2). use of antipsychotics, region and WASI-II (verbal comprehension index score (VCI); perceptual reasoning index score (PRI); intelligent quotient score (FSIQ-2)).

Medical history

Previous and current medical conditions (excluding autism history) will be summarized as the numbers and percentages of subjects for the FAS by system organ class (SOC) and preferred term (PT).

Autism history and diagnosis

Autism diagnosis will be summarized for the FAS as per eCFR form “Autism History” and in addition, assessment used to confirm diagnosis (ADOS-2, ADI-R). Time since initial diagnosis (number of years from date of original diagnosis to the date of informed consent/assent) will also be presented.

- ADOS-2. Module administered; Social Affect Total; RBR/RRB Total; Overall Total;
- ADOS-2 Comparison Score; ADOS-2 Classification.
- ADI-R. Scores for A, B, C, D.

Autism history events will be summarized as per cetegories presented in the eCRF.

Main caregiver and caregiver update

Caregiver information as collected at Visit 1 on the “Main Caregiver” eCRF will be summarized using FAS. Changes to caregiver collected at each visit will be summarise and also will present how many patients had changed the caregiver.

6.3.3 Protocol Deviations and Population Inclusions

All screened patients will be displayed in a listing that includes eligibility for each analysis set, protocol version for which patient was enrolled, dates of informed consent/assent and screening.

All protocol deviations are recorded in the Clinical Trial Management System, InfoLink2, and will be included in a data listing of deviations.

Major protocol deviations resulting in FAS subjects being excluded from the PP set will be summarized by deviation category.

7. Efficacy Analyses

Efficacy analyses, constituting the comparison of GWP42003-P against placebo in reducing symptom severity in children with ASD, will use data from the FAS and the PP analysis set as specified in Table 2.

Statistical hypothesis testing will be performed with no inferential statistical decision drawn as this is an exploratory trial. Unless otherwise specified, for all analyses for which a statistical test is performed, the null hypothesis corresponds to no difference between GWP42003-P and Placebo treatment arms.

Example SAS-codes provided may be modified without amendment to this SAP.

7.1 Statistical Models

7.1.1 MMRM analysis

The change from baseline of the VABS, ABC and RBS endpoints will be analyzed using an MMRM model. The corresponding model will include randomization stratification factors, baseline score, visit, treatment arm, visit by treatment arm interaction, visit by baseline interaction as fixed effects, and visit repeated within each patient as a repeated effect.

LS mean estimates for each treatment arm at each visit, along with the standard error and 95% CI will be presented separately. In addition, estimates of the treatment difference at each visit will be presented along with standard errors of difference and 95% CIs. The main comparison of interest is the estimate of the treatment difference at Week 12 (Visit 8).

The following provides sample code for implementing MMRM analysis using compound symetry covariance matrix:

7.1.2 GEE model

CGI-I and the change from baseline of CGI-S endpoints will be analyzed using an GEE model. Treatment arm and stratification factors as fixed effects and baseline response as a covariate. The model will also include a repeated statement that allows to model the correlation of the dependent variable at different time points.

An ordinal multinomial distribution with cumulative logit link is assumed in the model. Parameter estimates, standard errors and 95% confidence intervals will be presented which are based on empirical standard error estimates.

The following provides sample code for implementing GEE analysis using independent covariance matrix:

```
proc genmod data=test descending;
 class subjid trt visit agegr antipmed region;
 model chg = base trt visit trt*visit base*visit randager randrgn randpsy /
 dist=multinomial
 link=clogit type3 wald;
 repeated subject=subjid / withinsubject=visit type=indep corrw covb;
run;
```

Note: Model variables are same as in MMRM

7.1.3 Logistic regression model

The proportion of responders of CGI-I endpoint will be analysed using logistic regression. Treatment, stratification variables, and baseline score will be included as covariates. The odds ratio between treatment groups and its 95% confidence intervals at Week 12 will be presented. The following provides sample code for implementing logistic regression:

```
ods output oddsratios=ors parameterestimates=params;
proc logistic data=test descending;
 class trt randager randrgn randpsy/ param=ref;
 model response = base trt randager randrgn randpsy;
run;
```

where, response is the response variable.

7.1.4 ANCOVA model

An ANCOVA model with randomization stratification factors and treatment arm as factors and baseline score as a covariate will be used to analyze change from baseline to Week 12. The LS mean estimates for each treatment arm will be displayed together with standard errors and their corresponding 95% CIs. Treatment differences with 95% CIs will also be produced.

The following provides sample code for implementing ANCOVA analysis:

```
ods output lsmeans=lsmeans diffs=diffs;
proc mixed data=test;
  class trt randager randrgn randpsy;
  model chg = base trt randager randrgn randpsy / ddfm=kr cl
  alpha=0.05 solution;
  lsmeans trt / cl diff;
run;
```

7.1.5 Bayesian analysis

Bayesian analysis on the final data will be carried out as described in interim analysis plan.

7.2 Efficacy endpoints

7.2.1 Vineland Adaptive Behavior Scales, 3rd Edition (VABS-3)

The Vineland-3 assesses adaptive behavior in 3 domains: Communication, Daily Living Skills, and Socialization. Each domain has 3 subdomains: receptive, expressive, written (Communication domain); personal, domestic, community (Daily Living Skills domain); interpersonal relationships, play and leisure, coping skills (Socialization domain). The assessment are done at Visit 2, Visit 5, Visit 7, and Visit 8 EoT/WD.

Subdomain and domain scores will be calculated in the Rater Station. The Chronological Age at baseline is used to derived scores for the Vineland-3 throughout the study.
The social and communication composite score is a key interest and will be calculated as the arithmetic mean of the Socialization and Communication domain scores.

The adaptive behavior composite score is calculated as arithmetic mean of all 3 domain scores.

The change from baseline in subdomain, domain and composite scores will be summarized by visit. The change from baseline in social and communication composite score, adaptive behavior composite score, and individual domain scores will be analyzed using an MMRM model. Multiple analyses will carryout by including all observed data and using per protocol set. Normality assumption will be tested for Social and communication composite using Q-Q plot.

7.2.2 Aberrant Behavior Checklist (ABC)

The ABC contains items that resolve into 5 subscales: Irritability (15 items); Social Withdrawal (16 items); Stereotypic Behavior (7 items); Hyperactivity/Noncompliance (16 items); and Inappropriate Speech (4 items). Each item is scored as 0 (never a problem), 1 (slight problem), 2 (moderately serious problem), or 3 (severe problem). The assessment is done by the caregiver at Visit 1 (Screening), Visit 2, Visit 5, Visit 7, and Visit 8 EoT/WD.

Subscale score is calculated as the sum of the items belonging to each subscale. ABC-I (Irritability) subscale score is of the key interest.

Subscale	Items
ABC-I (Irritability)	2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57
Social Withdrawal	3, 5, 12, 16,, 20, 23, 26, 30, 32, 27, 40, 42, 43, 53, 55, 58
Stereotypic Behavior	6, 11, 17, 27, 35, 45, 49
Hyperactivity/Noncompliance	1, 7, 13, 15, 18, 21, 24, 28, 31, 38, 39, 44, 48, 52, 54, 56
Inappropriate Speech	9, 22, 33, 46

The change from baseline in ABC-I and other subscale scores will be summarized by visit. MMRM analysis as described in Section 7.2 will be used to analyze the change from baseline in ABC-I and other subscale scores.

Multiple analyses will carryout by including all observed data and using per protocol set. Normality assumption will be tested for ABC-I (irritability) score using Q-Q plot.

7.2.3 Clinical Global Impression – Severity and Improvement (CGI-S and CGI-I)

The CGI-S is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's experience with patients who have the same diagnosis. The clinician is asked: *Considering your total clinical experience with this particular population, how ill is the patient at this time?* This is 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. The questionnaire is done at Visit 1 (Screening), Visit 2, Visit 5, Visit 7 and Visit 8 EoT/WD.

The CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The clinician is asked: *Compared to the patient's condition at admission to the project, how much has the patient changed?* This is 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.

The questionnaire is done at Visit 5, Visit 7 and Visit 8 EoT/WD.

The frequency and proportions of patients within each category for the CGI-S and CGI-I scores will be produced separately by visit.

A GEE model will be fitted, for CGI-I (or change from baseline CGI-S) as the dependent variable, visit, treatment arm, stratification factors, baseline into visit interaction and treatment

into visit interaction as fixed effects and baseline response (CGI-S for both models) as a covariate.

Patients who achieve a score of 1 or 2 ('very much' or 'much' improved) on the CGI-I scale at Week 12 will be considered responders and the rest are considered non-responders. A logistic regression model will be used for analysing the responses. A second analysis similar to above will be done with subjects who achieve a score of 1, 2 or 3 ('very much', 'much', 'minimally' improved) at Week 12.

[redacted]

[redacted]

8. Safety Analyses

Safety analyses will use data from the Safety analysis set. For each safety analysis endpoint, GWP42003-P will be compared with placebo in all sections to follow.

8.1 Exposure and treatment compliance

Exposure

Exposure to GWP42003-P or placebo will be summarized using the following parameters:

- Treatment duration, calculated as the number of days subject received study drug, using the formula:
  (the date of the last dose – the date of the first dose +1). [CFR data]

  Treatment duration will be summarized overall and separately for treatment and taper period.
- Average dose (mg/kg/day) based on diary reported days by visit and overall

Diary compliance
Diary compliance (%) is calculated by:
Diary entries * 100/ expected diary entries.
Expected diary entries are derived from treatment duration.

Dose compliance based on Diary
Number of doses administered, as reported in the diary, and dose compliance percentage will be summarized overall and separately for treatment and taper period
Dose compliance based on Diary (%) is calculated by:
Number of doses administered * 100/ number of diary entries (am+pm)

Dose compliance based on CRF
Total expected volume since last dispensation, total volume actually taken since last dispensation and derived dose compliance (%) are captured on CRF at Visit 5, Visit 8 EoT/WD, and Visit 9/End of Taper; derived dose compliance will be summarized for each period.

Number and percentage of subjects compliant will be summarized for each period by treatment group and overall for following groups;
Compliant: ≥75% to ≤125%
Minor Compliance Deviations 50-75 & 125-50
Major Compliance deviations: <50 and >150

Consistency of dose administration in relation to meal timing (Yes, No) by visit will be summarized separately.

Dose adjustment and suspension
The number and percent of subjects with any dose adjustment (overall and by reason) as collected on Investigator Dose Adjustment CRF will be summarized.

8.2 Adverse Events

Adverse events will be collected from the date caregiver signs informed consent form up to the post-treatment safety follow-up visit. All AEs occurring during the trial, whether attributed to the IMP or not, observed by the investigator, or reported by the caregiver, will be recorded in the eCRF. AEs will be coded using the latest version of MedDRA at the time of reportig, associating lower-level terms with preferred terms and system organ classes by the primary hierarchy. Treatment-emergent AEs (TEAEs) are AEs that started, or worsened in severity or seriousness, following the first dose of IMP.

An AE profile for the Safety analysis set will be provided, which summarizes the subject incidence by treatment received, for the following information:

- Any TEAEs
- TEAEs related to treatment
- Serious TEAEs
- Serious TEAEs related to treatment
- TEAEs leading to withdrawal of IMP
- TEAEs related to treatment leading to withdrawal of IMP
- TEAE leading to death

AE summaries will include TEAEs. AE descriptions will be presented by decreasing frequency across all patients for a given SOC and Preferred Term. The tables will display counts and percentages of subjects who reported at least one AE in each system organ class represented in the AE data. Within each system organ class, the tables will display the counts and percentages of subjects reporting at least one AE, as designated by the preferred terms.

The following AE summaries will be produced:

- TEAEs by SOC and PT
- TEAEs related to treatment by SOC and PT. This table will include TEAEs that have a plausible relationship to the IMP as assessed by the investigator.
- TEAEs by SOC, PT, and maximum severity. On this table, treatment groups will be subdivided into three potential grades of AE severity— Mild, Moderate, Severe. TEAEs missing a severity grade will be imputed as 'Severe'.
- TEAEs by SOC, PT, and sex
- TEAEs by SOC, PT, and time of first onset (<1 week, 1-<4 weeks, 4-<12 weeks, >=12 weeks)
- TEAEs by SOC, PT, and time to AE resolution (<1 week, 1 week, 2 weeks, 3 weeks, 4 weeks, >=5 weeks, ongoing).
- Serious TEAEs by SOC and PT
- Serious TEAEs related to treatment by SOC and PT. The same approach applies as described for TEAEs related to treatment.
- TEAEs leading to study withdrawal by SOC and PT. This subset includes "Study Discontinuation" due to TEAEs.
- TEAEs leading to withdrawal of IMP by SOC and PT. This subset includes TEAEs with an Action Taken of "Drug Withdrawn." Withdrawal means permanent discontinuation of IMP.
- Treatment related TEAEs leading to withdrawal of IMP by SOC and PT. This subset includes TEAEs with an Action Taken of "Drug Withdrawn." Withdrawal means permanent discontinuation of IMP.
- TEAEs leading to dose reductions by SOC and PT. This subset includes TEAEs with an Action Taken of "Dose Reduced."
- TEAEs related to treatment leading to dose reductions by SOC and PT. This subset includes TEAEs with an Action Taken of "Dose Reduced."
- TEAEs leading to dose reductions and are resolved by SOC and PT. This subset includes TEAEs with an Action Taken of "Dose Reduced" and Outcome "Recovered/Resolved" or "Recovered/Resolved with Sequelae".
- TEAEs leading to dose interruptions by SOC and PT. This subset includes TEAEs with an Action Taken of "Dose Interrupted."
- TEAEs related to treatment leading to dose interruptions by SOC and PT. This subset includes TEAEs with an Action Taken of "Dose Interrupted."
- TEAEs leading to dose interruptions and are resolved by SOC and PT. This subset includes TEAEs with an Action Taken of "Dose Interrupted" and Outcome "Recovered/Resolved" or "Recovered/Resolved with Sequelae".
- Fatal TEAEs by SOC and PT. This subset includes TEAEs with Outcome "Fatal".

- Treatment-emergent AESIs by SOC and PT. The definition of AESI is described in Section 8.1.3.

The following AE listings will be prepared:

- All AEs
- Serious TEAEs
- TEAEs related to treatment
- TEAEs leading to drug withdrawal
- Fatal TEAEs
- Treatment-emergent AESIs

8.2.1 Adverse Events of Special Interest

[redacted]

Treatment-emergent AESIs will be summarized as described in Section 8.1.2.

8.3 Clinical Laboratory Results

Laboratory tests will include hematology, serum biochemistry, coagulation (Visit 1 only; thereafter only as an unscheduled assessment if ALT or AST > 3 x ULN), Clinical laboratory sample parameters are detailed in Table 9.1-1 in the study protocol.
Urinary data and the drug abuse data will only be listed.

In case of values <LLoQ or >ULoQ, LLoQ or ULoQ, respectively, will be used in summary tables.

All test results and abnormal laboratory values will be presented in data listings.

Summaries of actual values and changes from baseline for numeric test results will be presented for each assessment time point.

Shift tables will be summarizing the counts and percentages of subject's baseline CTCAE grade versus worst CTCAE grade at any postbaseline visit.

Potential Cases of Drug-Induced Liver Injury
A table will summarize the number of subjects by the following criteria.
At baseline:

- ALT > 1 x ULN
- AST > 1 x ULN
- ALT or AST > 1 x ULN
- TBIL > 1 x ULN
- ALT or AST or TBIL > 1 x ULN

At any time point after first dose of study treatment:

- ALT > N x ULN, where N=1, 2, 3, 5, 8
- AST > N x ULN, where N=1, 2, 3, 5, 8
- ALT or AST > N x ULN, where N=1, 2, 3, 5, 8
- ALP > 2 x ULN
- TBIL > 1 x ULN
- TBIL > 2 x ULN
- ALT or AST > 3 x ULN and TBIL > 2 x ULN
- ALT or AST>3 x ULN and INR > 1.5

The summary table will be done by sex, [redacted] and overall.

8.4 Vital Signs

Vital signs include body temperature, pulse rate, respiratory rate and blood pressure taken in a sitting position at rest for 5 minutes, and are measured at Visit 1 (Screening), Visit 2, Visit 5, Visit 8 EoT/WD, and Visit 9.

Summary of actual values and changes from baseline will be presented for each assessment time point.

The number and percentage of subjects with marked abnormalities post-baseline will be tabulated for each vital sign marked abnormality category. In the listings, the marked abnormalities are classified as high (H, HH) or low (L, LL) based on values occurring above the higher limit or below the lower limit, respectively. Only the most severe abnormality will be counted (e.g. a subject meeting the 'HH' criterion for a specific parameter will not be summarized under 'H' for this parameter. Percentages will be based on the number of subjects at risk for the parameter: those not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value. The vital signs marked abnormality categories are presented in the table below.

Table 4 Marked abnormalities for vital signs

Parameter (unit)	Abnormality
Weight (kg)	Decrease from baseline > 7% (L flag) Increase from baseline > 7% (H flag)
Body temperature (C)	< 36 (L flag) > 38 (H flag)
Pulse rate (beats/min)	< 60 (L flag) > 100 (H flag)
Respiratory rate (breaths/min)	< 12 (L flag) > 20 (H flag)
Systolic blood pressure (mmHg)	< 90 (L flag) > 140 (H flag) > 160 (HH flag)
Diastolic blood pressure (mmHg)	< 50 (L flag) > 90 (H flag) > 100 (HH flag)

8.5 Physical Examination

Physical examination findings for Visit 1 and Visit 8 EoT/WD, will be summarized as recorded. Height, weight, and BMI will be summarized as continuous variables. Categories of findings (normal, abnormal, not evaluated) on physical examination will be summarized as frequency and percentages.

8.6 12-lead ECG

A 12-lead ECG will be performed at Visit 1 and Visit 8 EoT/WD. Summaries of actual values and changes from baseline will be presented.

Marked abnormalities will be summarized, using a similar approach as described in Section 8.4.

Table 3 Marked abnormalities for 12-lead ECG

Parameter (unit)	Observed Values
QTcF (msec)	> 450 > 480 > 500

8.7 C-SSRS

The C-SSRS is a suicide risk assessment performed by the investigator at Visit 1 (Screening), Visit 2, Visit 5, Visit 7, Visit 8 EoT/WD, and Visit 9.

The number and percent of subjects with suicidal ideation by category, suicidal behavior by category and/or self-injurious behavior without suicidal intent will be tabulated. Percentages will be based on the number of subjects with at least one post-baseline C-SSRS assessment.

Shift from baseline showing any change in suicidal ideation and suicidal behavior will be provided. Subjects will be summarized under the worst of the following three categories: 1) No suicidal ideation of behavior; 2) suicidal ideation only; 3) suicidal ideation and behavior.

8.8 Concomitant Medications and Concomitant Therapy

Concomitant medications (CMs) will be coded using the September 2020 version of WHO Drug. Prior medications include any medications taken and stopped prior to start of treatment. Concomitant medications are defined as any medications that are ongoing or with stop dates on or after date of first IMP.

CM summary tables will display the anatomical main class of each coded CM and, within that, the pharmacological subgroup (3rd level) of the coded CM. Summary tables will display counts and percentages of subjects who reported using at least 1 CM in each represented pharmacological subgroup by treatment arm.

The following will be summarized:

- Prior (including antipsychotic) medications
- Concomitant (excluding antipsychotic) medications
- Concomitant antipsychotic medications
- Non-pharmacologic therapies and therapeutic diets prior and during the trial. These will be summarized by treatment arm.

The listing of CMs will display entries from Concomitant Medications and Concomitant Antipsychotic Medications forms, ordered within subject by the “Start Date.” The listing will display the recorded term from the CRF and the WHO Drug pharmacological subgroup.

8.9 Pregnancy monitoring

All female subjects of childbearing potential will take a pregnancy test at Visit 1 (Screening), Visit 8 EoT/WD if not tapering, and Visit 9. The test results are reported together with laboratory test results.
The information collected on Pregnancy Monitoring and Pregnancy Outcome CRFs will be displayed separately in listings.

Changes from the Protocol Planned Analysis

Protocol	SAP
[redacted]	ABC-I domain score is calculated for more than two time points, thus MMRM analysis will be used. [redacted] therefore ANVOCA analysis will be used

References

[1] Bolognani F, del Valle Rubido M, Squassante L, et al. A phase 2 clinical trial of a vasopressin V1a receptor antagonist shows improved adaptive behaviors in men with autism spectrum disorder. Sci. Transl. Med., 2019;11: eaat7838.

[2] Fung LK, Mahajan R, Nozzolillo A, et al. Pharmacologic treatment of severe irritability and problem behaviors in autism: a systematic review and meta-analysis. Pediatrics, 2016;137(s2):e20152851K.

[3] Bodfish, J. W., Symons, F. J., Parker, D. E., & Lewis, M. H. (2000). Varieties of repetitive behavior in autism: Comparisons to mental retardation. Journal of Autism and Developmental Disorders, 30(3), 237-243.

[redacted]