# OVID THERAPEUTICS, INC.

# STATISTICAL ANALYSIS PLAN

**A Phase 2 Angelman Syndrome Clinical Trial: A Randomized, Double-blind, Safety and Efficacy Study of Gaboxadol (Short Name: STARS)**

OV101-15-001

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## LIST OF ABBREVIATIONS

| Abbreviation | Full Term |
|---|---|
| ABC-C | Aberrant Behavior Checklist- Community |
| ABC-I | Aberrant Behavior Checklist- Irritability Subscale |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| AE | Adverse Event |
| AGG_MENT | Aggregate Mental |
| AGG_PHYS | Aggregate Physical |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| AS | Angelman Syndrome |
| ATC | Anatomical Therapeutic Class |
| BID | Bis in die in Latin meaning twice a day |
| BMI | Body Mass Index |
| BP | Bodily pain |
| bpm | Beats per minute |
| [redacted] | [redacted] |
| CGI-I | Clinical Global Impressions-Improvement |
| CGI-S | Clinical Global Impressions-Severity |
| [redacted] | [redacted] |

| | |
|---|---|
| CI | Confidence Interval |
| cm | centimeter |
| COA | Clinical Outcome Assessments |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| EEG | Electroencephalogram |
| EQ-5D-5L | EuroQOL-5L |
| FAS | Full Analysis Set |
| GH | General health |
| HLGT | High Level Group Term |
| HLT | High Level Term |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ITT | Intent-to-Treat |
| IWRS | Interactive Web Response System |
| kg | Kilograms |
| MCS | mental component scores |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |
| mmHG | Millimeter of mercury |
| MH | Mental health |
| MMRM | Mixed Model Repeated Measures |

| | |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| NA | Nocturnal Awakenings |
| ODS | Output Delivery System |
| PCS | physical component scores |
| [redacted] | [redacted] |
| PGI | Parent's Global Impression |
| PF | Physical functioning |
| PP | Per Protocol |
| PT | Preferred Term |
| Q1 | Quartile 1 |
| Q3 | Quartile 3 |
| QD | Quaque die in Latin meaning one a day |
| RE | Role limitations due to emotional problems |
| RP | Role limitations due to physical health |
| RTF | Rich Text Format |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| sec | second |
| SF | Social functioning |
| [redacted] | [redacted] |

| [redacted] | [redacted] |
|---|---|
| SOC | System Organ Class |
| SOL | Sleep Onset Latency |
| SS | Safety Set |
| TEAE | Treatment Emergent Adverse Event |
| TST | Total Sleep Time |
| USA | United States of America |
| VT | Vitality |
| WASO | Wake After Sleep Onset |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the data-handling and statistical procedures to be used for the statistical analysis and reporting of efficacy and safety data collected under the Ovid Protocol OV101-15-001 Amendment 3 (September 7, 2017). The methods of analysis in this SAP expand on statistical considerations identified in the protocol; where considerations are substantially different, they will be identified as such in this document. This SAP has been developed and finalized prior to locking the clinical database for the primary analysis. Any additional analyses required to supplement the analyses specified in this SAP will be considered exploratory and will be identified in the Clinical Study Report (CSR).

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principals for Clinical Trials" and the most recent ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports."

# 2 STUDY SUMMARY

## 2.1 STUDY OBJECTIVES

The primary objective of the study is to evaluate the safety and tolerability of OV101 from Baseline to Week 6 and Week 12 in adult and adolescent subjects with Angelman Syndrome (AS) across different dose levels and in 2 dosing schedules.

The following dosing schedules will be assessed against placebo:

- Once daily (QD): Morning dose of placebo and an evening dose OV101 titrated to the target dose of 15 mg unless not tolerated
- Twice daily (BID): Evening and morning doses of OV101 titrated to the target doses of 15 mg evening dose and 10 mg morning dose unless not tolerated.
- Placebo only: Evening and morning dose of placebo.

The secondary objective is the identification of a set of parameters that may best characterize the efficacy of OV101 in adult and adolescent AS subjects for subsequent efficacy studies. These clinical outcomes assessments (COA) are administered at 3 full day study center visits (Baseline, Interim, and End of Treatment) by an appropriately trained professional to the adult and adolescent AS subjects or their caregivers, as appropriate. Assessments are based on direct observation from study center personnel observations and/or caregiver(s).

[redacted]

## 2.2 STUDY DESIGN

This is a multicenter, Phase 2, randomized, parallel (3 arm), double-blind, placebo-controlled study of OV101 in adult and adolescent subjects with AS to assess safety of OV101. Multiple efficacy endpoints are assessed to identify the most appropriate and sensitive outcome measures for future efficacy studies. The study compares 3 different treatment/dosing schedules (15 mg evening dose only [QD], 15 mg evening dose plus 10 mg morning dose [BID], or placebo) for 12 weeks.

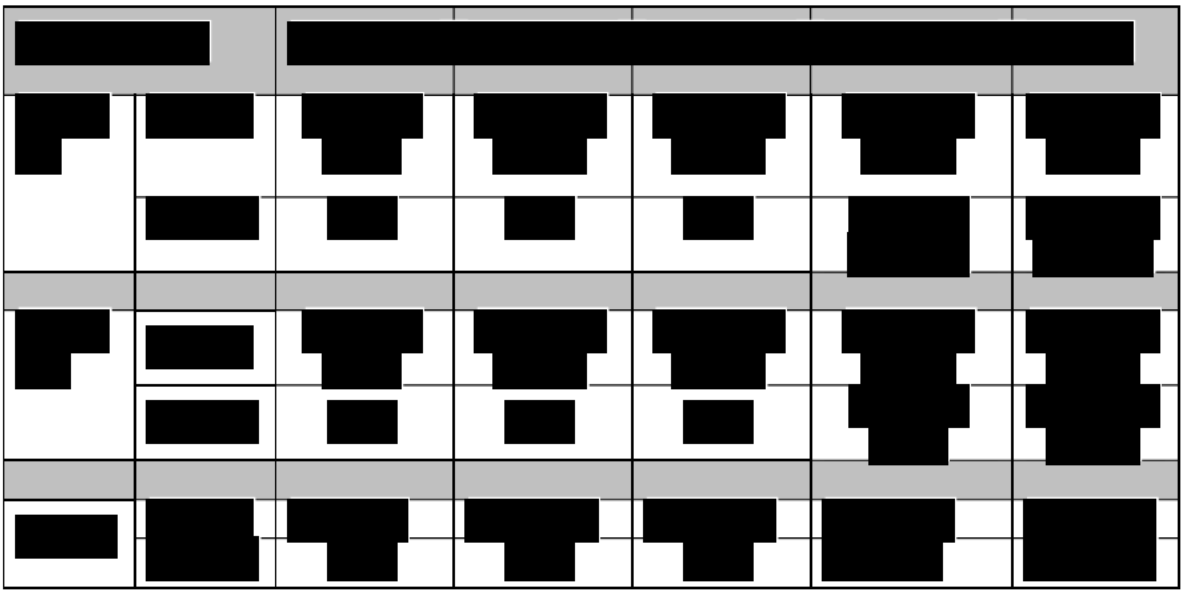
Approximately 75 subjects will be enrolled at approximately 15 study centers in the United States of America (USA) and Israel. At the completion of the study, there will be approximately 25 subjects in each of the 3 treatment groups: A) single evening dose, B) morning and evening dose, and C) placebo.

Adults aged 18 to 49 years and adolescents aged 13 to 17 at the time of informed consent with a molecular confirmation of AS are eligible for inclusion.

The study comprises a screening period of up to 4 weeks; a baseline visit for treatment randomization; a 12-week treatment period comprised of a 14-day titration period where treatment doses are progressively increased and a 6-week and 12-week visit for safety and efficacy assessments. The final study visit is for the end of treatment visit procedures followed by a 2-week telephone follow-up period to monitor safety.

All subjects receive a morning dose and an evening dose during the entire duration of treatment. Doses are progressively increased in 5 mg increments (OV101 or Placebo) to a target of 15 mg (3 capsules) in the evening for the OV101 groups and 10 mg (2 capsules) in the morning for the OV101 BID group. This up-titration to the target dose occurs unless this target dose is not tolerated. All subjects receive treatment for a maximum of 12 weeks at their highest tolerated dose. Modifications may be made per investigator judgement on urgent need or medical necessity. If tolerability is not acceptable after a previous up-titration step or during the course of the 12 weeks of

treatment, dose can be reduced to the previous tolerated level or even further. Once the tolerable dose has been reached, it shall remain constant for the duration of the treatment period.



*to end of study treatment period

### 2.2.1 Number of Subjects

Approximately 75 subjects will be enrolled and randomized into one of 3 treatment groups:

- OV101 QD: morning dose of placebo and evening dose of OV101
- OV101 BID: morning and evening dose of OV101
- Placebo: morning and evening dose of placebo

### 2.2.2 Randomization and Blinding Procedures

Subjects are randomized centrally via Interactive Web Response System (IWRS) with a 1:1:1 treatment allocation. Investigators, study staff, and study subjects are blinded to the randomized study treatment assignments.

### 2.2.3 Exploratory Efficacy Assessments

### 2.2.4 Safety Assessments

- Adverse Events (AE) collected continuously throughout the study
- Physical Examinations collected at Baseline, Day 43 (week 6) and Day 84 (week 12)
- Vital Signs collected at Baseline, Day 43 (week 6) and Day 84 (week 12)
- Laboratory parameters (electrolytes, lipids, glucose, renal, hepatic and pancreatic function tests, and hematology) collected at Baseline, Day 43 (week 6) and Day 84 (week 12)
- Electroencephalogram (EEG) collected at Baseline and Day 84 (week 12)
- Suicidality measured by the irritability sub-scale from the community ABC-C scale is collected at Baseline, Day 43 (week 6) and Day 84 (week 12)
- Caregivers' electronic seizure diary (Note: any clinically important changes, including changes in seizure medication, is reported as a safety event)

### 2.2.5 Other Assessments

- Concomitant Medications collected continuously throughout the study
- Blood draws for Biomarkers that will be evaluated externally

## Table 1 Schedule of Assessments

| Visit Name | Screening | Baseline | Unscheduled | Phone Titrate | Phone Safety | Interim | Phone Safety | End of Treatment | Follow-up Phone* |
|---|---|---|---|---|---|---|---|---|---|
| Window | | | Any Time | +2 Days | ± 2 Days | ± 3 Days | ± 2 Days | + 3 Days | ± 2 Days |
| | D--28 to D 0 | D 1 | Any Time | D 3, 7, 10, 14 | D 31 | D 43 | D 57, 71 | D 84 | D 98 |
| Week | | 1 | | | | 6 | | 12 | 14 |
| ICF and Assent (Separate for Caregiver and Subject) | X | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | | | | |
| Medical History | X | X | | | | | | | |
| Clinical Assessment† | X | X | | X | X | X | X | X | X |
| Biomarker Plasma‡ | | X | | | | | | X | |
| Biomarker DNA‡ | | X | | | | | | | |
| Molecular AS Test§ | X | | | | | | | | |
| Dose Titration | | | | X | X# | X# | X# | | |
| Physical Exam | X | X | | | | X | | X | |
| Vital Signs | X | X | | | | X | | X | |
| Clinical Laboratory Tests | X | X | | | | X | | X | |
| Serum Pregnancy Test** | X | X | | | | X | | X | |
| EEG | | X | | | | | | X | |
| Adverse Events | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X |
| Check Scales Completed by Clinician: | | | | | | | | | |
| CGI-S scale (in Sub-Domains and Global) | | X | | | | X | | X | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CGI-I scale (in Sub-Domains and Global) | | X | | | | X | | X | |
| | [redacted] | | [redacted] | | | | | | [redacted] | |
| | [redacted] | | [redacted] | | | | | | [redacted] | |
| | ABC-I (ABC-C Irritability Subscale) | See Caregiver ABC-C (Factor I) Score | X | X | X | X | X | X | X | X |
| Check Scales Completed by Caregiver: | | | | | | | | | | |
| | [redacted] | [redacted] | [redacted] | | | | [redacted] | | [redacted] | |
| | [redacted] | [redacted] | [redacted] | | | | [redacted] | | [redacted] | |
| | CGI-S | X | X | | | | X | | X | |
| | [redacted] | [redacted] | [redacted] | | | | [redacted] | | [redacted] | |
| | [redacted] | [redacted] | [redacted] | | | | [redacted] | | [redacted] | |
| | [redacted] | | [redacted] | | | | [redacted] | | [redacted] | |
| | [redacted] | [redacted] | [redacted] | | | | [redacted] | | [redacted] | |
| | [redacted] | | [redacted] | | | | [redacted] | | [redacted] | |
| | [redacted] | | X | | | | | | X | |
| | eDiary of Sleep Pattern†† | X | X | | | | X | | X | |
| | eDiary of Seizure Activity†† | X | X | | | | X | | X | |
| | eDiary of Medication Compliance†† | | X | | | | X | | X | |
| Check Other Assessments Completed | | | | | | | | | | |
| | [redacted] | | [redacted] | | | | | | [redacted] | |
| | [redacted] | [redacted] | [redacted] | | | | [redacted] | | [redacted] | |

Abbreviations: ABC-C = Aberrant Behavior Checklist – Community; ABC-C-Irritability Subscale = Aberrant Behavior Checklist – Community – Irritability Subscale; [redacted] CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – Severity; EEG = Electroencephalogram; [redacted] ICF = Informed Consent Form; [redacted]

* Safety follow-up phone visit 2 weeks after End of Treatment.

† Signs and symptoms of the syndrome.

‡ Only if separate ICF was signed.

§ Only if no written evidence for molecular diagnosis in subject records available.

# Ongoing up-titration if target dose could not be reached until Day 14. Down-titration for non-tolerability should be discussed with the Sponsor MM or his/her delegates if necessary.

** For women of child-bearing potential.

†† Continuous use and documentation; [redacted] electronic subject reported outcomes data will be downloaded by study center staff at baseline, interim, and End of Treatment visits. [redacted]

# 3 STATISTICAL METHODS

## 3.1 General Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher for Windows.

All clinical study data will be presented in subject data listings. In by-treatment group descriptive presentations, the 3 randomized treatment groups (15 mg evening dose only [QD], 15 mg evening dose plus 10 mg morning dose [BID], placebo) will be presented separately as well as a combined treatment group for OV101 QD and BID dosing.

Descriptive statistics (n, mean, standard deviation, Q1, median, Q3, minimum, and maximum) will be calculated by treatment group for continuous variables. Confidence intervals will be provided where appropriate.

Frequencies and percentages will be presented by treatment group for categorical variables. If there are missing values, the number missing will be presented, but without a percentage.

Means, medians, and confidence intervals will be reported to one decimal place more than the data reported on the Case Report Form (CRF) or by the laboratory/vendor. Standard deviations will be reported to two decimal places more than the data reported. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor. P-values will be reported to 4 decimal places.

Unless otherwise specified, all tests will be 2-tailed using a 0.05 level of significance. All confidence intervals (CIs) will be 2-sided 95% CIs.

### 3.1.1 Baseline Value and Change from Baseline (if applicable)

A Baseline value is defined as the most recent non-missing value obtained immediately prior to administration of first dose. Change from baseline will be calculated by subtracting the baseline value from the post-dose assessment for each subject (i.e., post-dose – baseline).

### 3.1.2 Handling of Missing/Incomplete Values

Selected efficacy analyses of Week12 endpoints will include missing value adjustments, if possible, by using the corresponding Week 6 observations either implicitly (in MMRM analyses) or by simple imputation (for binary endpoints).

These selected analyses are detailed below. For all other analyses, observed case data will be used and no imputations for missing data will be performed.

## 3.2 Analysis Populations and Subgroups

### 3.2.1 Definition of Analysis Populations

**Safety Analysis Set**
The Safety Analysis Set consists of all subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment they actually received. The Safety Analysis Set will be the analysis set used for all safety analyses.

**Intent-to-Treat Set**
The Intent-to-Treat set (ITT) consists of all subjects who are randomized, whether or not study drug is received. Subjects will be analyzed according to their randomized group.

**Full Analysis Set (also considered the modified Intent-to-Treat set)**
The Full Analysis Set (FAS) or modified Intent-to-Treat set (mITT) consists of all randomized subjects who receive at least 1 dose of study drug, and have at least 1 efficacy evaluation after receiving study drug. Subjects will be analyzed according to their randomized group. The FAS will be the primary analysis set for efficacy analyses.

**Per Protocol Set**
The Per Protocol Set (PP) is a subset of the FAS that includes all subjects who complete the Week 12 visit and have no major protocol deviations that are deemed to impact efficacy. These violations include but are not limited to violations of inclusion/exclusion criteria deemed to impact efficacy, inadequate study drug compliance over the dosing period as determined from the dosing information in the eCRF, usage of prohibited concomitant medications, and incorrect randomization. Subjects will be analyzed according to their randomized treatment group. The PP set will be used for the analysis of the key efficacy endpoints only.

Prior to database lock and unblinding, there will be a meeting to review protocol deviations. The threshold for percent compliance that would be considered inadequate and would result in exclusion from the per protocol set will be determined in this meeting following review of the relevant compliance information. In addition to the deviations listed above, other relevant protocol deviations, like early termination of treatment, may be identified for review.

### 3.2.2 Definition of Subgroups

The major sub-groups of interest are defined by age group 1: adolescent (subjects less than 18 years of age) versus adult (subjects 18 years of age and older). Additional subgroups of age (age group 2) will also be defined as follows: subjects less than 18 years of age, subjects 18 years and less than 25 years of age, and subjects 25 years and older.

## 3.3 Analysis Variables

### 3.3.1 [redacted]

- [redacted]

### 3.3.3 Safety Endpoints

- Incidence of adverse events
- Change in clinical laboratory parameters from Baseline to each post-baseline assessment
- Shift in clinical laboratory parameters from Baseline to each post-baseline assessment
- Change in vital sign measurements from Baseline to each post-baseline assessment
- Change in physical exam parameters from Baseline to each post-baseline assessment
- Change in EEG from baseline to the end of treatment
- Change in irritability from ABC-C from Baseline to each post-baseline assessment.
- Clinically important changes in seizure medication from the electronic seizure diary

### 3.3.4 Other Variables

- Incidence of discontinuations and reasons for discontinuations from the study
- Incidence of concomitant medications used
- Compliance, days on treatment, and total number of capsules taken

## 3.4 Subjects Disposition and Evaluability

### 3.4.1 Subject Disposition

Subject disposition (screening, randomization, study completion) will be presented overall and by treatment group. The number and percentage of subjects evaluated for each subject population will be presented overall and by treatment group. The numbers of subjects completing and not completing the study, as well as reasons for subject discontinuations will also be summarized overall and by treatment group.

### 3.4.2 Protocol Deviations

For subjects excluded from the Per Protocol Set, all deviations will be shown in a subject listing by treatment group.

## 3.5 Demographics and Baseline Characteristics

### 3.5.1 Demographics

Subject demographics and baseline characteristics will be summarized by treatment group and overall for all subject populations.

Descriptive statistics will be displayed for age, height, weight, and body mass index (BMI).

Age is calculated as (date of informed consent - date of birth + 1) / 365.25 and is truncated to complete years. Height, weight and BMI will be summarized with the data collected at the baseline visit.

Frequencies and percentages will be tabulated for sex, race, ethnicity, age group, childbearing potential, enrollment by study center, and country. To assess potential baseline imbalances, the randomized treatment groups will be compared with respect to demographics at baseline using an analysis of variance model (ANOVA) with treatment group as the only independent variable and using a chi square test of independence for the categorical variables.

### 3.5.2 Medical and Surgical History

Medical and surgical history will be summarized by body system for each treatment group as well as overall for all subject populations. Body system will be presented in descending order for all subjects.

## 3.6 Prior and Concomitant Medications

Therapies started and stopped prior to the start of study treatment are referred to as prior therapies. Therapies that started prior to treatment and continued on treatment as well as those that started during treatment are referred to as concomitant therapies. In order to define whether a medication with missing start or stop dates is a concomitant medication, refer to the following additional criteria.

- if both the start and stop dates of a particular medication are missing, that medication will be considered concomitant;
- if the start date of a medication is missing and the stop date of that medication falls on or after the dose date, that medication will be considered concomitant;
- if the start date of a medication is missing and the stop date of the medication is prior to the dose date, that medication is considered *not* concomitant;
- If the start date of a medication is prior to the dose date and the stop date of the medication is missing, that medication is considered concomitant.

Prior and concomitant medications will be coded using WHO Drug Dictionary Enhanced version June 2016 and will be classified by Anatomical Therapeutic Class (ATC) level 4 and preferred term (PT) for the Safety Analysis Set. For the presentation of concomitant medications, the ATC level 4 terms will be sorted alphabetically, and within ATC level 4 term, the PT will be used and presented by decreasing total frequency overall.

Frequencies and percentages of subjects using each concomitant medication will be presented for the Safety Analysis Set overall, and by treatment group.

All medication use will be listed regardless of the timing of the start of the medication.

## 3.7 Treatment Compliance and Exposure

Subjects will receive 1 kit at Baseline and 1 kit at Day 43 (Interim visit). Each kit will contain a bottle for morning doses and a bottle for evening doses. Each morning bottle will contain 90 capsules and each evening bottle will contain 140 capsules.

### 3.7.1 Compliance to Study Treatment

Compliance, days on treatment, and total capsules taken will be summarized descriptively by treatment group and presented by subject in a listing.

Total capsules taken will be derived as the total number of capsules dispensed minus the total number of capsules returned minus the total number of capsules not taken and not returned.

Expected days capsules taken will be based on the first and last expected days for taking study medication, using all available dosing information on the eCRF. The calculation formula is (last dose date - first dose date + 1).

Compliance will be calculated using the following method based on the number of capsules taken, as reported in the eCRF. The formula for % Compliance is based on the planned titration schedule, and depends on the duration of Expected days capsules taken, as shown:

| Expected Days Capsules Taken | % Compliance (as a function of Expected Days Capsules Taken, DAYS) |
|---|---|
| 1-2 Days | = 100 * Total Number Capsules Taken / DAYS |
| 3-6 Days | = 100 * Total Number Capsules Taken / [((DAYS – 2) * 2) + 2] |
| 7-9 Days | = 100 * Total Number Capsules Taken / [((DAYS – 6) * 3) + 10] |
| 10-13 Days | = 100 * Total Number Capsules Taken / [((DAYS – 9) * 4) + 19] |
| 14 Days to End of Treatment | = 100 * Total Number Capsules Taken / [((DAYS – 13) * 5) + 35] |

For example, if a subject was on treatment for 2 days and took one capsule during that time, then % Compliance = 100 * 1/2 = 50%. If a subject was on treatment for 21 days and took 60 capsules during that time, then % Compliance = 100 * 60/75 = 80%.

## 3.8 [redacted]

[redacted]

[redacted]

### 3.8.2 [redacted]

[redacted]

[redacted]

[redacted]

### 3.8.3 Analyses of the Exploratory Efficacy Endpoints

[redacted]

[redacted]

### 3.8.4 Subgroup Analyses

[redacted]

## 3.9 Safety Analysis

All safety data analyses will be conducted using the Safety Analysis Set.

### 3.9.1 Adverse Events

All adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 19.1 and will be classified by MedDRA system organ class (SOC), high level group term (HLGT), high level term (HLT), and preferred term (PT). Analyses of adverse events will be performed using the Safety Analysis Set.

Treatment emergent adverse events (TEAEs) are any adverse events occurring or worsening in severity after the first administration of study medication. The following imputation rules will be used for missing or incomplete AE start dates:

- Missing AE start day:
  - If the partial date contains a different month from the date of first study dose, then impute it as the first day of the month.
  - If it contains the same month as the date of first dose, then impute it as date of first dose.
- Missing AE start day and month:
  - If the partial date contains a different year from the date of first dose, then impute the missing day and month as Dec 31.
  - If it contains the same year as the date of first dose, then impute the missing day and month as day and month of first dose.
- Completely missing AE date:
  - Impute the missing date as the date of first dose.

The TEAE incidence will be presented by treatment group for all subjects in the Safety Analysis Set. The number and percentage of subjects who experience at least one TEAE and the number and percentage of subjects who experience at least one TEAE within each specific SOC and PT will be presented by treatment group (placebo, combined OV101 and separate dose groups). Additionally, the incidence of TEAE within each specific SOC, HLGT, and PT and specific SOC, HLT, and PT will be presented. The 95% CIs will be displayed for the frequency of TEAEs. Treatment-related AEs will be considered those at least possibly related to investigational product based on the investigator's assessment. The number and percentage of subjects reporting serious AEs, treatment-related AEs, and AEs leading to treatment discontinuation will also be summarized for each treatment group by MedDRA SOC and PT.

The AEs of Special Interest include Dizziness, Somnolence, Nausea, Vomiting PTs, and will be reported separately.

All adverse event data including baseline adverse events will be displayed in subject data listings.

### 3.9.2 Clinical Laboratory Evaluation

Blood samples will be collected for routine clinical laboratory safety evaluations at Screening, Baseline, Day 43 (week 6) and Day 84 (week 12). Additional laboratory safety evaluations will be performed at other times, if judged to be clinically

appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required.

Laboratory parameters include electrolytes, lipids, glucose, renal, hepatic and pancreatic function tests, and hematology.

Clinical chemistry and hematology tests are presented below:

Clinical Chemistry and Hematology Tests

| Clinical Chemistry | Hematology |
|---|---|
| Albumin | Basophils (absolute) |
| Alkaline phosphatase | Eosinophils (absolute) |
| Alanine aminotransferase | Lymphocytes (absolute) |
| Aspartate aminotransferase | Monocytes (absolute) |
| Bicarbonate | Neutrophils (absolute) |
| Calcium | Basophils |
| Chloride | Eosinophils |
| Cholesterol | Hematocrit |
| Creatine kinase | Hematology slide |
| Creatine, enzymatic | Hemoglobin |
| Direct bilirubin | Lymphocytes |
| Glucose, random, serum | Monocytes |
| High density lipoprotein cholesterol | Neutrophils |
| Indirect bilirubin | Platelets |
| Lactate dehydrogenase | Red blood cells |
| Low density lipoprotein cholesterol, calculated | White blood cells |
| Phosphorous | |
| Potassium | |
| Sodium | |
| Total bilirubin | |
| Total protein | |
| Triglyceride | |
| Urea (blood urea nitrogen) | |
| Uric acid | |
| Total cholesterol | |
| Magnesium | |
| Thyroid stimulating hormone | |

Continuous laboratory data will be examined for trends using descriptive statistics of actual values and changes from baseline over time. These data will also be categorized as low, normal or high based on the reference ranges of the central

laboratory. Shift tables from baseline to each post baseline time point will be presented.

### 3.9.3 Vital Signs and Other Physical Findings

The following vital signs will be collected at Screening, Baseline, Day 43 (week 6) and Day 84 (week 12):

- Systolic and Diastolic blood pressure (mmHg)
- heart rate (bpm)
- body temperature (◦F)
- weight (kg)

Summary statistics will be presented for actual values and change from Baseline values by treatment group.

### 3.9.4 EEG

EEG is collected at Baseline and Day 84 (week 12). Occipital rhythm, rhythmic theta, rhythmic delta, epileptiform abnormalities, and sleep will be analyzed descriptively. For occipital rhythm, the categories are normal, slow, or absent, with undeterminable as a response option. For rhythmic theta, the categories are <50% or >50%, with undeterminable as a response option. For these discrete variables, frequencies and percentages will be presented by treatment group for each visit. The sleep-related variables, total time of sleep recording in minutes, time asleep in minutes and percent time asleep will be summarized using descriptive statistics for each visit by treatment group.

### 3.9.5 Physical Examination

Physical exams will be evaluated by body system. Physical exam data are collected at Screening, Baseline, Day 43 (week 6) and Day 84 (week 12). The number and percentage of subjects in each treatment group with normal and abnormal physical examination results for each body system by visit will be presented. For each body system, shifts from baseline to final visit (no change, normal to abnormal or abnormal to normal) will also be presented.

### 3.9.6 Biomarkers

Blood will be drawn at Baseline and Day 84 (week 12) for Biomarker analysis. Analyses will not be performed at this time.

### 3.9.7 Suicidality

Suicidality is measured by the irritability scale from the ABC-C, also referred to as ABC-I. It is collected at Baseline, day 43 (week 6), and day 84 (week 12), and additionally at Phone Titrate, Phone Safety, Unscheduled, and Follow-up Phone visits. The ABC-I Completed by Clinician assessment described in the protocol consisted of the clinician completing the questionnaire based on the caregiver's response. In the protocol Schedule of Assessments, both ABC-I Clinician and ABC-C Caregiver were noted to be completed during clinic visits. However, in practice during the study, the ABC-I Clinician assessment was often not entered during clinic visits. Since the information is captured in the ABC-C Caregiver assessment, this data will be used to supplement the ABC-I assessment if missing at clinic visits.

Descriptive statistics for the ABC-I subscale and individual item scores will be presented by treatment group for each visit.

## 3.10 Interim Analysis

## 3.11 Changes from Protocol

Description of Caregiver:

During development of the study eCRFs, the relationship of the caregiver to the subject was collected in order to identify type of relationship as: parent, grandparent, friend, or other (like a group home resident).

Criteria for Per Protocol Determination:

Prior to database lock and unblinding, there will be a meeting to review protocol deviations. The threshold for percent treatment compliance that would be considered inadequate and would result in exclusion from the per protocol set will be determined in this meeting following review of the relevant compliance information. In the study

protocol 80% treatment compliance was specified as the threshold defining the per protocol exclusion, however, due to the allowance of down-titration in this study, it was determined that treatment compliance cannot be assessed with sufficient accuracy to warrant a strict 80% threshold. A lower threshold may be considered in the abovementioned meeting. If it is decided to lower the compliance threshold, this change will be documented in the CSR.

[redacted]

ABC-I Assessment at Clinic Visits:

The ABC-I is the irritability scale from the ABC-C. The ABC-I Completed by Clinician assessment described in the protocol consisted of the clinician completing the questionnaire based on the caregiver's response. In the protocol Schedule of

Assessments, both ABC-I Clinician and ABC-C Caregiver were noted to be completed during clinic visits. However, in practice during the study, the ABC-I Clinician assessment was often not entered during clinic visits. Since the information is captured in the ABC-C Caregiver assessment, this data will be used to supplement the ABC-I assessment if missing at clinic visits.

The hypothesized treatment effects on efficacy have shifted based on results from related studies that have been reported after the protocol was developed.

Primary Comparisons of Interest:

The protocol states that the primary comparisons of interest are between each active treatment group (dose group) and placebo group. In the SAP, it is determined that the primary comparisons of interest are between the combined OV101 group and placebo, in order to increase statistical power.

# 4 DATA HANDLING

## 4.1 Derived Endpoints and Data Handling

### 4.1.1 Handing of Repeated Assessments

If multiple results are reported for an assessment at the same post-baseline visit, then the first record will be used in analysis.

### 4.1.2 Aberrant Behavior Checklist-Community (ABC-C)

Five factors are defined as follows:

| Factor | Sum of Questions |
|---|---|
| Irritability, Agitation, Crying | 2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57 |
| Lethargy, Social Withdrawal | 3, 5, 12, 16, 20, 23, 26, 30, 32, 37, 40, 42, 43, 53, 55, 58 |
| Stereotypic Behavior | 6, 11, 17, 27, 35, 45, 49 |
| Hyperactivity, Non Compliance | 1, 7, 13, 15, 18, 21, 24, 28, 31, 38, 39, 44, 48, 51, 54, 56 |
| Inappropriate Speech | 9, 22, 33, 46 |

### 4.1.3 [redacted]

| [redacted] | [redacted] |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

Gross Total = Sum of Composites

### 4.1.4 [redacted]

[redacted]

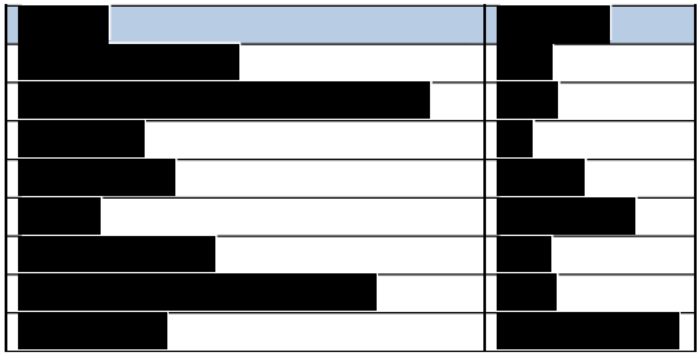
| [redacted] | [redacted] |
|---|---|
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

[redacted]

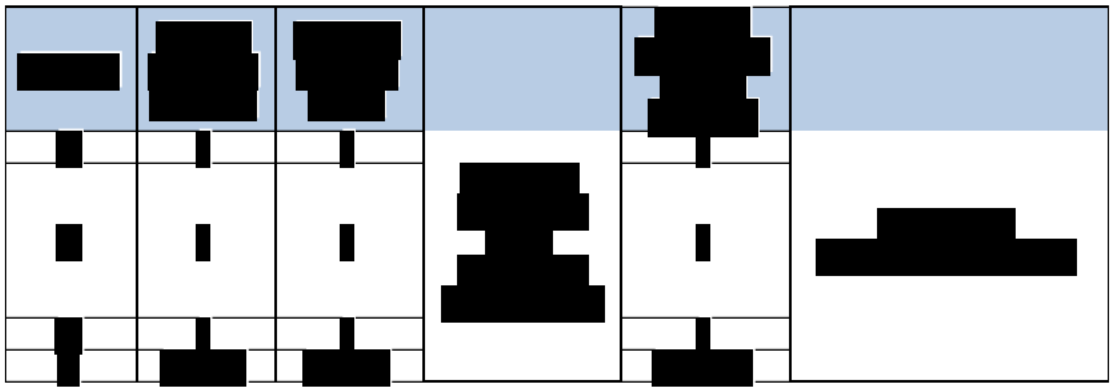
### 4.1.7 [redacted]

[redacted]

[redacted]



[redacted]



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### 4.1.8 EEG

Some of the EEG questions will be combined into one question:

- The 3 back ground questions of mild slowing, moderate slowing and severe slowing will be combined into one questions of Background slowing with 1=Mild, 2=Moderate or 3=severe responses
- The 3 Occipital Rhythm questions of normal for age, slow for age or absent will be combined into one question of Occipital Rhythm with responses of normal for age, slow for age or absent.
- The 2 rhythmic theta questions of <50% of the time and >50% of the time will be combined into one question of Rhythmic theta with responses of 1: <50% of the time or 2: >50% of the time.

## 4.2 Computation of Derived Data

### 4.2.1 Time Points and Duration

Standard calculations used across many assessments:

- Changes from baseline = Post Baseline value – Baseline value
- Percentage change from baseline = [(Post Baseline value – Baseline value)/Baseline Value]*100

### 4.2.2 Other Data Derivations

Body Mass Index BMI = Weight in Kg / (Height in meter)$^2$

Age is calculated as (date of informed consent - date of birth + 1) / 365.25 and is truncated to complete years.

# 5 Programming Specifications

It is suggested that computer-generated table output adhere to the following specifications.

1. Unless otherwise specified, all computer-generated tables and listings should be produced in landscape mode using SAS® ODS to create RTF output which can be imported by Microsoft® Word in table format. All output should have the following two-line header at the upper left margin:

   ```
   Sponsor Company Name
   Study Protocol Name
   ```

   and the following header at the upper right margin:

   ```
   Page x of y
   ```

2. Each table should be identified by in a sequential numeric order, and the table designation should be centered above the title. A decimal system within the numeric numbering (i.e., x.y and x.y.z) should be used to identify tables and listings with related contents. The title is centered in initial capital characters and should include the population type analyzed (e.g. Safety Population). The title and table designation are single-spaced, but are separated from the table by at least a double space.

   ```
                                   Table No.

                            First Line of Title
                        Second Line of Title (if needed)
                            Population Type Analyzed
   ```

3. Column headings should be in initial upper-case characters.
4. For variables with numeric values, include “unit” in column heading when appropriate.
5. Footnotes should be single spaced, but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table. All output should have at least the footnote about the program name and date of the program run.

   ```
   [1] Footnote 1
   ```

```
[2] Footnote 2
[3] Footnote 3

PROGRAM: program file name                                  DDMMMYYYY HH:MM
```

6. Unless specified otherwise, all data listings should be sorted by subject number with the investigation site, and by visit date within subject where appropriate.
7. For tables that summarize categorical (discrete) data, an Unknown or Missing category should be added to any parameters for which information is not available for any subject.
8. Unless otherwise specified, the estimated mean and median for a set of values should be printed out to one more decimal place than the raw (observed) data and rounded appropriately. Standard errors (or standard deviations) should be printed out to two additional decimal places than the raw (observed) data and rounded appropriately. For example, for age (with raw data in whole years):

```
n              xx
Mean (SD)      xx.x (xx.xx)
Median         xx.x
Min, Max       xx,xx
```

9. The p-values will be printed in the tables rounded appropriately to 4 decimal places and formatted as '0.xxxx'. P-values less than 0.0001 will be formatted in the tables as '<0.0001'.
10. All fractional numeric values should be printed with a zero to the left of the decimal point (e.g., 0.12, 0.3).
11. Unless otherwise specified, percentage values should be printed with one digit to the right of the decimal point (e.g., 12.8%, 5.4%).
12. Missing data should be represented on subject listings as either a hyphen (“-“).
13. Dates printed as a result in the table, listing, or graph should be printed in SAS DATE9. format (“DDMONYYYY”: 01 JUL 2002). Missing portions of dates should be represented on subject listings as dashes (-- JUL 99). Dates that are missing because they are not applicable for the subject should be listed as “N/A”, unless otherwise specified.

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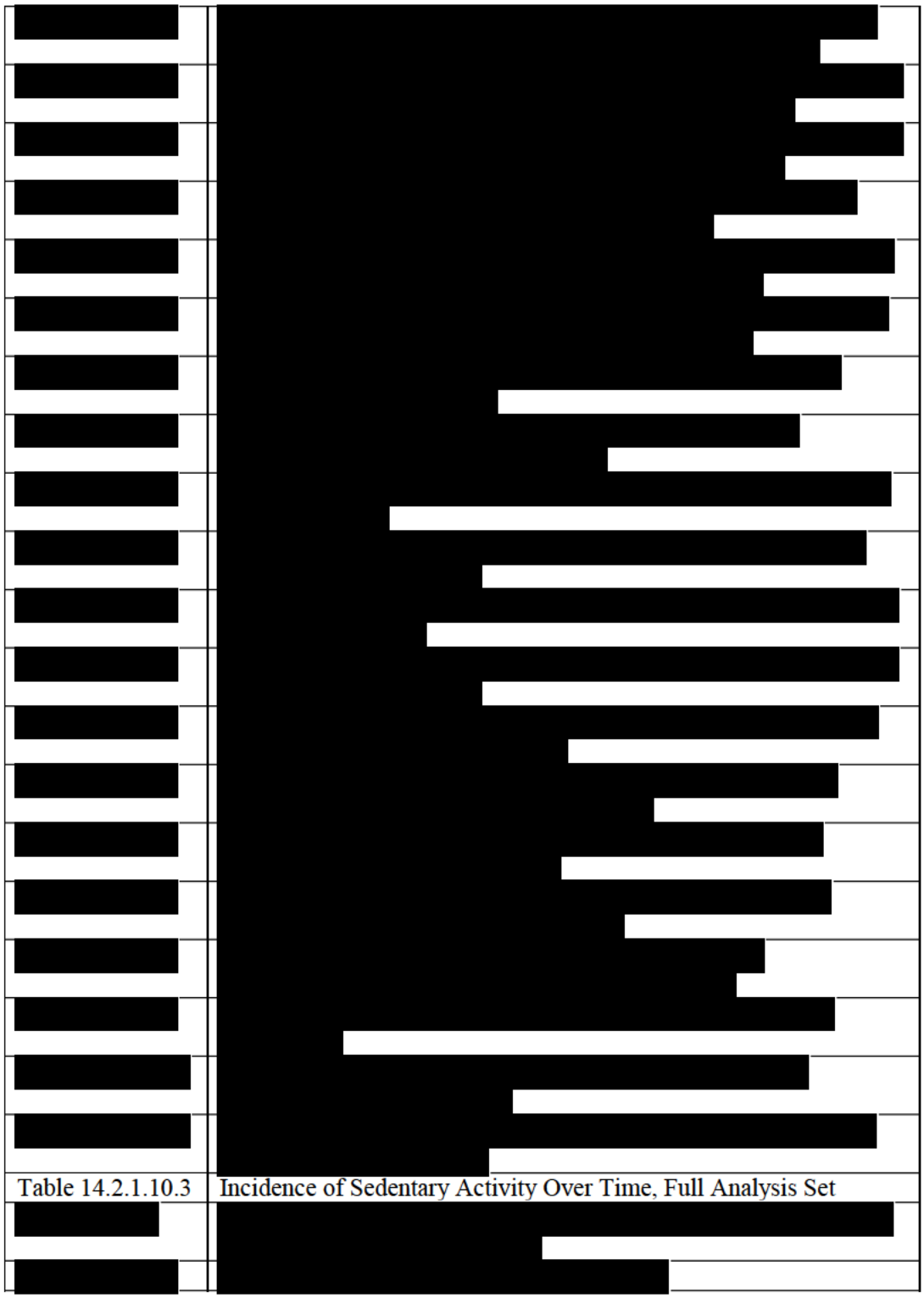

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|---|---|
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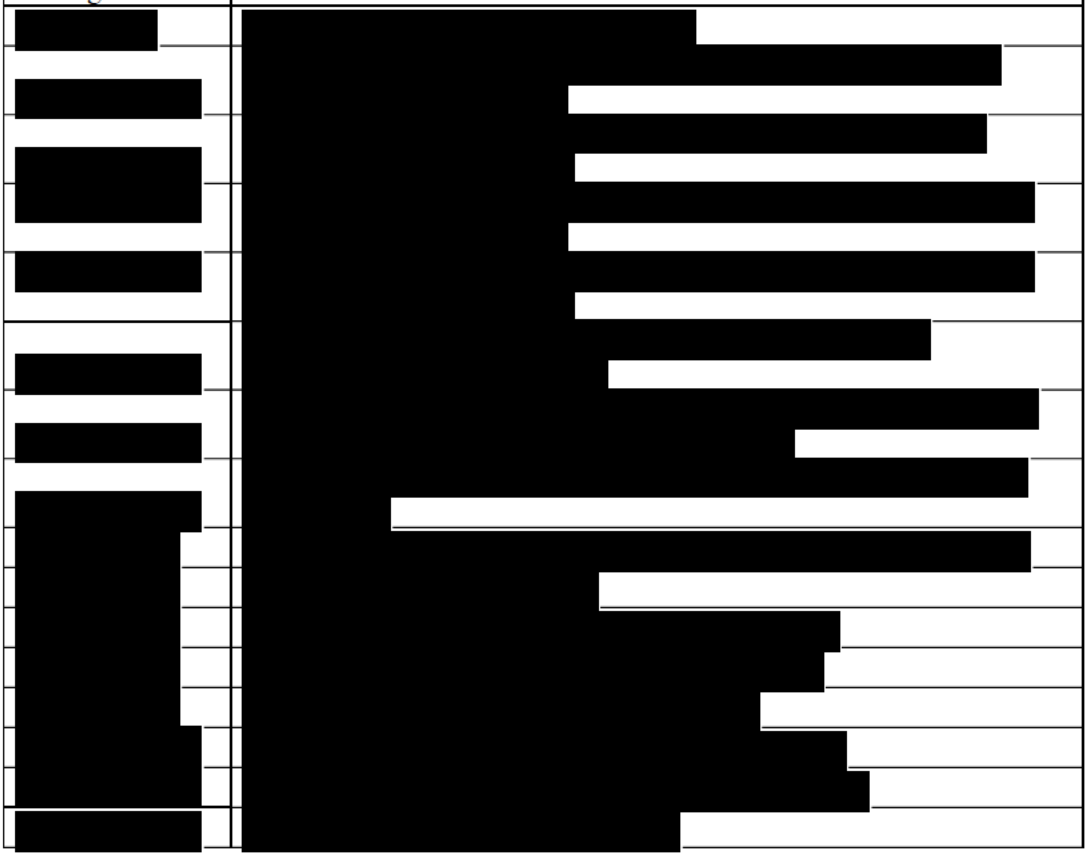

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