Protocol A9451181

A PHASE 4, RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO- AND ACTIVE-CONTROLLED, SINGLE-DOSE, FIVE-WAY CROSSOVER STUDY EVALUATING THE ABUSE POTENTIAL OF THREE DOSES OF NEURONTIN® TAKEN ORALLY IN HEALTHY, NON-DRUG DEPENDENT PARTICIPANTS WITH SEDATIVE DRUG ABUSE EXPERIENCE

Statistical Analysis Plan (SAP)

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/ 16 Nov 2020	Original 20 May 2020	N/A	N/A
1.1/21 Oct 2021	V2.0, 11 Dec 2020	To add the definition of the Modified Completer Population To incorporate other clarifications and typographical edits	• Section 4 Table 4: added definition of the Modified Completer Population • Section 4 Table 4: Evaluable Population will based on the Modified Completer Population, instead of Completer population • Section 5.2: specified that all PD analyses will be performed using the Modified Completer Population • Section 5.3: changed the heading to Potential Additional Analysis to match the contents better • Section 6.2: added description on how primary and secondary PD data will be summarized and presented • Other minor clarifications and typographical edits have been made in various sections
1.2/25 Oct 2021	N/A	To reflect scope of PK sample analysis and ensure the consistency within the section	• Section 6.2.3: removed 'if deemed necessary' for the Placebo and Diazepam PK sample analysis.
3.0 / 4 Jan 2023	V5.0 29 Apr 2022	Addional site added to the study Modify Evaluable Population Defining PK based Protocol Deviation Missing pre-dose VAS score	• Update the model due to additional site added. • Change the Evaluable Population to be based on Modified Completer Population • PK deviations are pre-defined based on PK results according to PK expection. • The neutral VAS score will be used as the baseline value for High Emax and

			all AUEC calculation when the pre-dose VAS is missing.
		Clarify the statistical model will be used in 6.2.2	• ANOVA was changed to linear mixed-effects model per FDA guidance and comment.
		Outline how to handle repeated VAS values.	• Repeated VAS values will be averaged for statistical analysis.
		Update the statistical models to be used in 6.2 and 6.2.2	• Updated the dependent and independent variable of the models
4.0 / 27 Jan 2023	V5.0 29 Apr 2022	Defining the calculatable PK parameter	• A subject/period must have at least 3 consecutive samples above LLOQ to be included in the PK parameter calculation.
		Defining nordiazepam based major protocol devistion	• A subject/period with significant measurable concentrations of the active metabolite of diazepam, N-desmethyldiazepam, that is not consistent with diazepam dosing in that period or the following period (carryover due to long half-life of the metabolite or possible poor metabolizers) will be defined as a major protocol deviation.

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study A9451181. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Neurontin® (gabapentin) is indicated for postherpetic neuralgia in adults, adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization in adults and pediatric patients 3 years and older with epilepsy.

Gabapentin does not exhibit affinity for benzodiazepine, opiate (mu, delta or kappa), or cannabinoid 1 receptor sites; however, gabapentin abuse has been reported at increasing

rates. Individuals abusing gabapentin describe experiences such as euphoria, improved sociability, relaxation and a marijuana-like "high".[1-8]

There are post-marketing reports of abuse and individuals experiencing withdrawal symptoms shortly after discontinuing higher than recommended doses of gabapentin used to treat illnesses for which the drug is not approved. Such symptoms included agitation, disorientation and confusion after suddenly discontinuing gabapentin that resolved after restarting gabapentin. Most of these individuals were taking higher than recommended doses of gabapentin for unapproved uses and had a history of poly-substance abuse or used gabapentin to relieve symptoms of withdrawal from other substances.

Epidemiological studies have shown that gabapentin may have abuse potential, particularly among individuals with a history of opioid abuse. Gabapentin abuse is reported both alone (i.e., without other drugs), and in conjunction with opioids to enhance the 'high' obtained from opioids. [1,4] Further, published data suggest that gabapentin is recorded on death certificates suggesting drug overdose, both as the primary and contributory causes of death, and reported with and without other drugs like opioids, benzodiazepines, and alcohol.[1,5-7] This clinical trial will evaluate gabapentin in a cross-over design with comparison to placebo and a positive control, diazepam, regarding abuse-related subjective responses, physiological responses (including an assessment of respiratory depression), and drug pharmacokinetics in a healthy non-drug dependent population with drug abuse experience with sedative drugs.

2.1. Study Objectives and Endpoints

Objectives	***Endpoints***
Primary:	***Primary:***
• *To assess the potential abuse liability of orally administered Neurontin® taken alone compared to placebo in a healthy non-drug dependent participants with drug abuse experience under fasted condition.*	• *Bipolar visual analog scale (VAS) for "Drug Liking" maximum effect (E_{max}) as obervered directly from the data without baseline correction*
Secondary:	***Secondary:***
• *To evaluate additional pharmacodynamic (PD) effect, pharmacokinetics (PK), and safety of Neurontin® or diazepam taken alone in a healthy non-drug dependent participants with drug abuse experience under fasted condition.*	***PD endpoints:*** • *Bipolar VAS for "Drug Liking" (Time for E_{max} [TE_{max}], area under the effect-time profile from time 0 to the time of the last quantifiable concentration [$AUEC_{last}$], and partial AUECs [$AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$]).* • *Unipolar VAS for "High" (E_{max}, TE_{max}, $AUEC_{last}$, and partial AUECs [$AUEC_1$, $AUEC_2$, $AUEC_3$, $AUEC_4$, $AUEC_8$]).* • *Bipolar VAS for "Take Drug Again" at 24, 36, 48, and 72 hour post-dose.*

Objectives	*Endpoints*
	• *Bipolar VAS for "Overall Drug Liking" at 24, 36, 48, and 72 hours post-dose.* • *Unipolar VAS for "Good Drug Effect".* • *Unipolar VAS for "Bad Drug Effect".* • *Unipolar VAS for "Any Drug Effect".* • *Observer-rated assessment of alertness/sedation.* ***PK endpoints:*** • *C_{max}, time for C_{max} (T_{max}), area under the effect-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last}) of gabapentin and, if deemed necessary for diazepam and its active metabolite (N-desmethyldiazepam).* • *Area under the plasma concentration-time profile from time 0 extrapolated to infinity time (AUC_{inf}), and terminal half-life ($t_{½}$), if data permits, of gabapentin and, if deemed necessary for diazepam and its active metabolite (N-desmethyldiazepam).* • *Partial AUCs (AUC_1, AUC_2, AUC_3, AUC_4, and AUC_8) of gabapentin and, if deemed necessary for diazepam and its active metabolite (N-desmethyldiazepam).* ***Safety endpoints:*** • *Vital signs (respiratory rate [RR], blood pressure [BP], pulse rate [PR]).* • *Oxygen saturation of hemoglobin (SpO_2).* • *Physical examination.* • *12-lead electrocardiogram (ECG).* • *Clinical lab and AEs.*
Tertiary/Exploratory:	***Tertiary/Exploratory:***
• *Exposure-response relationship between drug (gabapentin or diazepam) concentrations and selected PD effect.* • *To enable exploratory research through collection of banked biospecimens, unless*	• *Correlation between drug (gabapentin or diazepam) concentrations and selected PD endpoints (Bipolar VAS for "Drug Liking", Unipolar VAS for "High"), as data permit.*

Objectives	*Endpoints*
prohibited by local regulations or ethics committee decision.	• *Potential results from exploratory analysis of banked biospecimens (these results may or may not be generated in the context of the present study).*

2.2. Study Design

This will be a multi-center, randomized, double-blind, double-dummy, placebo- and active-controlled, 5-treatment, 10-sequence, 5-period crossover single-dose, Williams square design study in healthy adult, non drug-dependent male and female participants with drug abuse experience with sedative drugs. The study includes Screening, a Qualification Phase, a Treatment Phase and Follow-up. This study will randomize approximately 50 participants to ensure at least 32 participants complete the Treatment Phase of the study. Dropouts in the treatment phase for non-safety reasons may be replaced at the discretion of investigator in consultation with the sponsor.

The following study visits are required, see Figure 1 and the SoA (Table 1 and Table 2) of the protocol:

- Visit 1, Screening will occur within 28 days prior to Visit 2.
- Visit 2, Qualification Phase will require inpatient stay at the clinical research unit (CRU) for 3 nights:
    - Naloxone Challenge Phase, Day -1.
    - Drug Discrimination, Days 1 and 2 will require inpatient stay at the CRU for 2 nights.
    - End of Drug Discrimination requires an inpatient stay at the CRU overnight to ensure discharge occurs 24 hours after receiving diazepam or placebo.
    - Participant will proceed to Visit 3 after at least 14 and no more than 28-day washout.
- Visits 3 to 7, Treatment Phase:
- Each visit will require an inpatient stay at the CRU of 3 or 4 nights.
- Each visit will be separated by a washout period of at least 14 days.
- End of Study Assessments will be at the CRU 72 hours after completing the last study drug dosing at the end of period 5 or at the time of early withdrawal.
- For the entire study, 18 - 23 overnight inpatient stays will be required.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The following parameter will be calculated for VAS for "Drug Liking" during each Treatment Period:

- Maximum (peak) effect (E_{max}) as observed directly from the data.

3.2. Secondary Endpoint(s)

The following parameters will be calculated for VAS for "Drug Liking" and VAS for "High" during each Treatment Period:

Table 2. ***Derivation of Pharmacodynamic Parameters***

Parameter	*Definition*	*Method of Determination*
E_{max} (High only)	*Maximum* change from pre-dose response	*Observed directly from data. If Emax is less than 0 then 0 will be used as the E_{max} values.*
TE_{max}	*Time for E_{max}*	*Observed directly from data as time of first occurrence*
$AUEC_{last}$	*Area under the effect-time profile from time zero to the time of the last quantifiable effect (E_{last})*	*Linear trapezoidal method*
$AUEC_1$	*Area under the effect-time profile from time zero to 1 hour postdose*	*Linear trapezoidal method*
$AUEC_2$	*Area under the effect-time profile from time zero to 2 hours postdose*	*Linear trapezoidal method*
$AUEC_3$	*Area under the effect-time profile from time zero to 3 hours postdose*	*Linear trapezoidal method*
$AUEC_4$	*Area under the effect-time profile from time zero to 4 hours postdose*	*Linear trapezoidal method*
$AUEC_8$	*Area under the effect-time profile from time zero to 8 hours postdose*	*Linear trapezoidal method*

The additional endpoints of VAS for "Overall Drug Liking", "Take Drug Again", "Good Drug Effect", "Bad Drug Effect", and "Any Drug Effect" and the observer-rated assessment of alertness/sedation will be summarized by timepoints.

3.3. Other Endpoint(s)

PK parameters will be derived from the concentration-time profiles as shown in Table 3.

A subject/period must have at least 3 consecutive samples above LLOQ to be included in the PK parameter calculation.

Table 3. ***Derivation of Pharmacokinetic Parameters***

Parameter	*Definition*	*Method of Determination*
C_{max}	*Maximum plasma concentration*	*Observed directly from data*
T_{max}	*Time for* C_{max}	*Observed directly from data as time of first occurrence*
AUC_{last}	*Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration* (C_{last})	*Linear up/Log linear down trapezoidal method*
AUC_{inf}[a]	*Area under the plasma concentration-time profile from time zero extrapolated to infinity time*	$AUC_{last} + (C_{last}*/k_{el})$, *where* $C_{last}*$ *is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.*
AUC_1	*Area under the plasma concentration-time profile from time zero to 1 hour postdose*	*Linear up/Log linear down trapezoidal method*
AUC_2	*Area under the plasma concentration-time profile from time zero to 2 hours postdose*	*Linear up/Log linear down trapezoidal method*
AUC_3	*Area under the plasma concentration-time profile from time zero to 3 hours postdose*	*Linear up/Log linear down trapezoidal method*
AUC_4	*Area under the plasma concentration-time profile from time zero to 4 hours postdose*	*Linear up/Log linear down trapezoidal method*
AUC_8	*Area under the plasma concentration-time profile from time zero to 8 hours postdose*	*Linear up/Log linear down trapezoidal method*
$t_{1/2}$[a]	*Terminal elimination half-life*	$Log_e(2)/k_{el}$, *where* k_{el} *is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve. Only those data points judged to describe the terminal log-linear decline will be used in the regression.*

a. If data permit.

3.4. Baseline Variables

The pre-dose psychometric measurements of each period will be the baseline for calculating the changes in these parameters post dose.

When the pre-dose psychometric measures were not collected or missing, the neutral VAS point (50 for Drug liking, 0 for High) will be used as baseline for Emax (High only) and AUEC calculation purpose.

3.5. Repeated VAS values

For post-dose VAS data collection, when VAS evaluations were taken within a 10-minute window, the values will be treated as repeated measures. In this case, the mean value will be used for the VAS score; the median time will be used as the data collection time.

For pre-dose VAS data collection, when there were multiple VAS values collected, the values will be averaged to be the baseline values.

3.6. Safety Endpoints

Any adverse events (AEs) occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Adverse events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment.

Adverse events will be summarized by treatment and Phase of the study (i.e., Naloxone Challenge Phase, Drug Discrimination Phase, and Treatment Phase).

The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data (respiratory rate [RR], blood pressure [BP], pulse rate [PR]).*
- 12-lead electrocardiogram (ECG).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding, other than the Modified Completer Population and Evaluable Population which will be done after unblinding, and releasing the database and classifications will be documented per standard operating procedures.

Table 4. Analysis Sets

Population	Description
Safety	*The Safety Population will include all participants who receive at least one dose of study drug, beginning with the Naloxone Challenge. This population will be analyzed as treated.*
PK	*The PK population will include all enrolled participants treated who have at least 1 concentration in the Treatment Phase. The PK parameter analysis population will include all enrolled*

Table 4. Analysis Sets

Population	Description
	participants treated who have at least 1 of the PK parameters of interest.
Completer	*The Completer Population will include all randomized participants who complete all 5 periods of the Treatment Phase and who contribute post-dose PD data during each period.* These participants must have at least one post-dose response on the VAS for Drug Liking within 2 hours of Tmax for each treatment group: ie, at least one VAS response within the interval 0-3h postdose (assuming the Tmax of 20 mg diazepam is 1h) and at least one VAS response within the interval 1-5h postdose (assuming the Tmax of 600/1200/1800 mg gabapentin is 3h). *This population will be analyzed as randomized.*
Modified Completer	*The Modified Completer Population will include all randomized participants in the Completer Population, excluding any participants who meet either or both of the following criteria for Drug Liking VAS:* *1. E_{max} scores are within a 5 point difference across all five treatments (ie, Maximum E_{max} score – Minimum E_{max} score ≤5);* *2. $E_{max}(P) > 60$ AND $E_{max}(P) - E_{max}(Dia20) \geq 5$;* *where $E_{max}(P)$ and $E_{max}(Dia20)$ are the VAS E_{max} scores for placebo and diazepam 20 mg, respectively.* *This population will be analyzed as randomized.*
Evaluable	*The Evaluable Population will include all randomized participants in the Modified Completer Population who do not have major protocol violations or adverse events that would interfere with drug absorption, such as vomiting within 4 hours of study drug administration. Major protocol violations, including deviations related to study drug intake, are defined as those that could potentially affect the PD conclusions of the study. Prior to unblinding the Treatment Phase data, the Sponsor (or designee) will identify protocol violations or adverse events that would disqualify a participatnt from the evaluable population and determine which participants or participant visits will be excluded. This population will be analyzed as randomized.*

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

To assess the abuse potential of gabapentin, the following tests will be performed in the order they are given:

Study Validation:

The sensitivity and integrity of the study will be validated by comparing the mean responses of diazepam, the positive control (C), to the placebo (P):

$$H_0: \mu_C - \mu_P \leqslant \delta_1 \text{ versus } H_a: \mu_C - \mu_P > \delta_1 \text{ where } \delta_1 = 15.$$

Gabapentin versus diazepam:

1. Does gabapentin (T) produce mean responses that show less abuse potential than diazepam (C)?

$$H_0: \mu_C - \mu_T \leqslant \delta_2 \text{ versus } H_a: \mu_C - \mu_T > \delta_2 \text{ where } \delta_2 = 0.$$

Gabapentin versus placebo (Primary):

2. Does gabapentin (T) produce mean responses that show abuse potential similar to placebo (P)?

$$H_0: \mu_T - \mu_P \geqslant \delta_3 \text{ versus } H_a: \mu_T - \mu_P < \delta_3 \text{ where } \delta_3 = 11.$$

For each of the gabapentin hypotheses, the statistical significance of the test will be assessed for all doses of gabapentin.

The study will be considered validated if the one-sided p-value for the validation hypothesis test is less than 0.05.

5.2. General Methods

Statistically, the study will be evaluated as a safety study. Consequently, the null hypothesis for gabapentin will be constructed on the presumption that these treatments produce abuse potential similar to placebo. To demonstrate that these treatments have no abuse potential the null hypothesis will be statistically rejected.

All PD analyses will be performed using the Modified Completer Population and all available post-dose data; these will be the primary PD analyses.

5.3. Potential Additional Analysis

Key PD analyses may be repeated on the Evaluable Population using all available post-dose data.

6. ANALYSES AND SUMMARIES

6.1. Study Validity Analysis of Endpoints

Study validity will first be confirmed through the comparison of mean E_{max} for Drug Liking between diazepam 20 mg and placebo administered during the Treatment Phase. This comparison will be made using a mixed-effect model with site, sequence, site by sequence interaction, period, treatment and site by treatment interaction as fixed effects, and participant nested within site by sequence as a random effect. If site by treatment interaction is not signfiant by p level of 0.1 then the term will be dropped form the final model. If the treatment comparison of diazepam 20 mg vs. placebo is statistically significant by a margin of 15 (ie, one-sided $p \leqslant 0.05$) in the appropriate direction, it will confirm the sensitivity of the study. If study validity is not confirmed, comparisons between gabapentin and diazepam will not be performed.

6.2. Analysis of Primary and Secondary Endpoints

A linear mixed-effects model that includes site, sequence, site by sequence, period, treatment and site by treatment as fixed effects, and the participant nested within site by sequence as a random effect will be used, baseline will be used as covriate for High Emax calcualtion. If site by treatment interaction is not signfiant by p level of 0.1 then the term will be dropped form the final model. The primary analyses of abuse potential will be based on testing the differences between the means from the primary measure(s) at the peak of drug response effects (VAS Drug Liking E_{max}) produced by gabapentin, diazepam and placebo at a significance level of 0.05 (1-sided).

The primary PD endpoint is the Emax of bipolar VAS for “Drug Liking”.

The principal parameters for the primary and secondary endpoints will be summarized by treatment using descriptive statistics (mean, standard deviation [SD], median, first and third quartiles, minimum and maximum). These parameters will be analyzed using a mixed-effect model with site, sequence, site by sequence, period, treatment and sitey by treatment as fixed effects, and participant nested within the site by sequence as a random effect; site by treatment interaction will be tested first, the interaction term will be removed from the final model when the interaction test p value is less than 0.1. Analyses of endpoints (VAS Feel High E_{max}) with baseline (pre-dose) measurements will include the baseline measurement as a covariate in the model. Least squares means, standard errors, and 90% confidence intervals will be provided for each treatment and for the difference between treatments. Data will be summarized graphically, where appropriate.

The treatment comparison to test for study validity will be:

- diazepam 20 mg vs. placebo; (This comparison is used for validation of the study and adjustments for multiple comparisons will not be applied for this treatment comparison).

Comparisons of gabapentin versus diazepam will be:

- gabapentin 600 mg vs. diazepam 20 mg;

- gabapentin 1200 mg vs. diazepam 20 mg;
- gabapentin 1800 mg vs. diazepam 20 mg.

Comparisons of gabapentin versus placebo will be (Primary):

- gabapentin 600 mg vs. placebo;
- gabapentin 1200 mg vs. placebo;
- gabapentin 1800 mg vs. placebo.

Statistical significance of all treatment differences will be reported. All statistical tests will be conducted using one tailed significance criteria. These comparisons will be used to assess the primary study objective.

The additional endpoints of VAS for "Overall Drug Liking", "Take Drug Again", "Good Drug Effect", "Bad Drug Effect", and "Any Drug Effect" and the observer-rated assessment of alertness/sedation will be summarized by timepoints.

Mean time plots (linear scale) against nominal time postdose by treatment (all treatments on the same plot) of VAS for"Drug Liking", "High", "Overall Drug Liking", "Take Drug Again", "Good Drug Effect", "Bad Drug Effect", and "Any Drug Effect" will be presented.

6.2.1. Sensitivity/Supplementary Analyses

Regression diagnostics will be performed to verify model assumptions and adequacy of the fitted linear models for the primary endpoints. Levene's test will be used to diagnose potential heterogeneity of variance and the Shapiro–Wilk test will be used to diagnose potential non-normality of the model residuals.

If the resulting p-value from Levene's test is $\leqslant 0.05$, the null hypothesis of equal variances is rejected and it will be concluded that there is a difference between the treatment group variances. An unequal variance model will then be applied using the Satterthwaite method in order to produce an accurate F-approximation.

If the resulting p-value from the Shapiro-Wilk test is $\leqslant 0.05$, symmetry of the distribution of paired differences will be tested using the Triples Test and either the t-test (symmetry) or sign test (asymmetry) will be performed.

If needed (Shapiro-Wilk test has a p-value $\leqslant 0.05$), symmetry will be tested for each of the primary comparisons using the Triples Test in the following manner:

1. Calculate the paired differences of the treatments being compared
2. Calculate T as follows:

[redacted]

[redacted]

4. Calculate the test statistic [redacted]

5. If [redacted] then the distribution of the differences in responses will be considered asymmetric, otherwise they will be considered symmetric.

The test for median of differences for each treatment comparison and endpoint (Emax) will be determined by the t test if the paired differences are symmetric, or by the Sign Test if the paired differences are asymmetric.

6.2.2. Pharmacodynamic Analysis

For PD parameter values are not analyzed in primary and secondary endpoints., Descriptive statistics will be reported by treatment and by hours . The values will be analyzed with linear mixed-effect model consisting of: Site, Sequence, Site*Sequence, Period, Treatment, Time, Period*Time, Treatment*Time, and site by treatment terms as fixed effects, and a participant (site*Sequence) term as a random effect; site by treatment interaction will be tested first, the interaction term will be removed from the final model when the interaction test p value is less than 0.1. To accommodate the repeated measures aspect of the design, a compound symmetric covariance matrix will be employed, with the participant set to Participant (Site*Sequence). The Treatment*Time least-squares means and differences among them will be assessed for trends likely to be of clinical relevance.

Descriptive statistics of the mean, standard error, and other summary statistics such as minimum, first quartile (Q1), median, third quartile (Q3) and maximum for each subjective measure, each treatment and each paired difference among treatments will be calculated and used to create tables and graphs.

As an exploratory analysis, the time course of the different subjective measures in relation to each other (and to abuse-related AEs) will evaluate the outcome of positive or negative assessments of the drug before, during and after the peak of drug effects. The physiological effects such as pulse rate, blood pressure and respiratory rate will be monitored over the

course of the study session and correlated to both the drug dose administered and the PK of the drug.

6.2.3. Pharmacokinetic Analysis

Blood samples will be collected throughout a study session in order to assess drug PK. Samples from gabapentin treatment will be analyzed using a validated analytical method in compliance with Viatris standard operating procedures. The samples of placebo and diazepam (including its major active metabolite: N-desmethyldiazepam) will be analyzed. This will be done to primarily confirm that plasma levels of the drug are equivalent between participants and to evaluate whether subjective measures and AEs can be correlated with drug levels over time. Typically, blood will be drawn immediately after the collection of subjective measures are completed at each time point. If an analysis shows that a participant had low plasma levels of a drug, it may account for a lack of subjective responses in a drug session.

The PK parameter values for gabapentin and if deemed necessary, for diazepam (including its major active metabolite as data permit: N-desmethyldiazepam) will be calculated for each non-placebo treatment and each participant using noncompartmental analysis of concentration-time data. PK parameter values that will be evaluated are listed in Table 3.

PK parameters (Table 3) will be calculated for each participant/period/analyte using noncompartmental analysis of concentration-time data. Concentration values below the LLOQ were set to 0 before any summary, analyses and date presentations. Actual sample collection times will be used for the PK analysis.

A subject/period which lacks of any measurable concentrations or only has very low plasma concentrations on a supposed non-placebo period(s) will be defined as a major protocol deviation. A subject/period is considered to have very low plasma concentrations if its AUC is less than 5% of the corresponding analyte/treatment geometric mean AUC (which should be calculated without inclusion of data from the outlying subject).

A subject/period, with significant measurable concentrations on the placebo period or a specific treatment period in which the drug was not administered, will be defined as a major protocol deviation. A subject/period is considered to have significant plasma concentrations if its AUC is more than 5% of corresponding analyte and treatment geometric mean AUC. In the case of Gabapentin concentration, the 600 mg dose period will be used as the reference geometric mean.

A subject/period with significant measurable concentrations of the active metabolite of diazepam, N-desmethyldiazepam, that is not consistent with diazepam dosing in that period or the following period (carryover due to long half-life of the metabolite or possible poor metabolizers) will be defined as a major protocol deviation. A subject/period is considered to have significant plasma concentrations if its AUC is more than 5% of corresponding analyte and treatment geometric mean AUC.

Any period with the pre-dose concentration over 5% of the Cmax of the same period will be defined as major protocol deviation for that period.

A subject at any period classified as a major protocol deviation will be further excluded from the Evaluable Population for that period.The PK parameters (AUC_{inf}, AUC_{last}, C_{max}, t_{max}, $t_{½}$, partial AUCs [AUC_1, AUC_2, AUC_3, AUC_4, AUC_8]) will be derived for each participant/period/analyte and will be summarized by treatment and analyte. PK parameters for individual participant, as well as summary statistics (eg, group averages, SD, geometric means, coefficient of variation [CV], and geometric CV%) by treatment will be reported for PK parameters, as appropriate. Plasma concentration-time profiles of gabapentin, diazepam and its metabolite (N-desmethyldiazepam) will be presented. Concentrations will be listed and summarized by PK sampling time and treatment for each analyte.

6.2.4. Electrocardiogram Analyses

Electrocardiogram results collected at Screening will be listed.

6.2.5. Exploratory Analysis

Exploratory analysis may be conducted to evaluate the correlation between drug (gabapentin or diazepam) concentrations and selected PD endpoints (Bipolar VAS for "Drug Liking" and Unipolar VAS for "High"), as data permit.

6.2.6. Safety Summaries and Analyses

All safety analyses will be performed on the safety population.

The safety data will be described and summarized in accordance with the sponsor's Data Standards.

AEs, ECGs, BP, RR, PR, SpO2, continuous cardiac monitoring, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study.

8. REFERENCES

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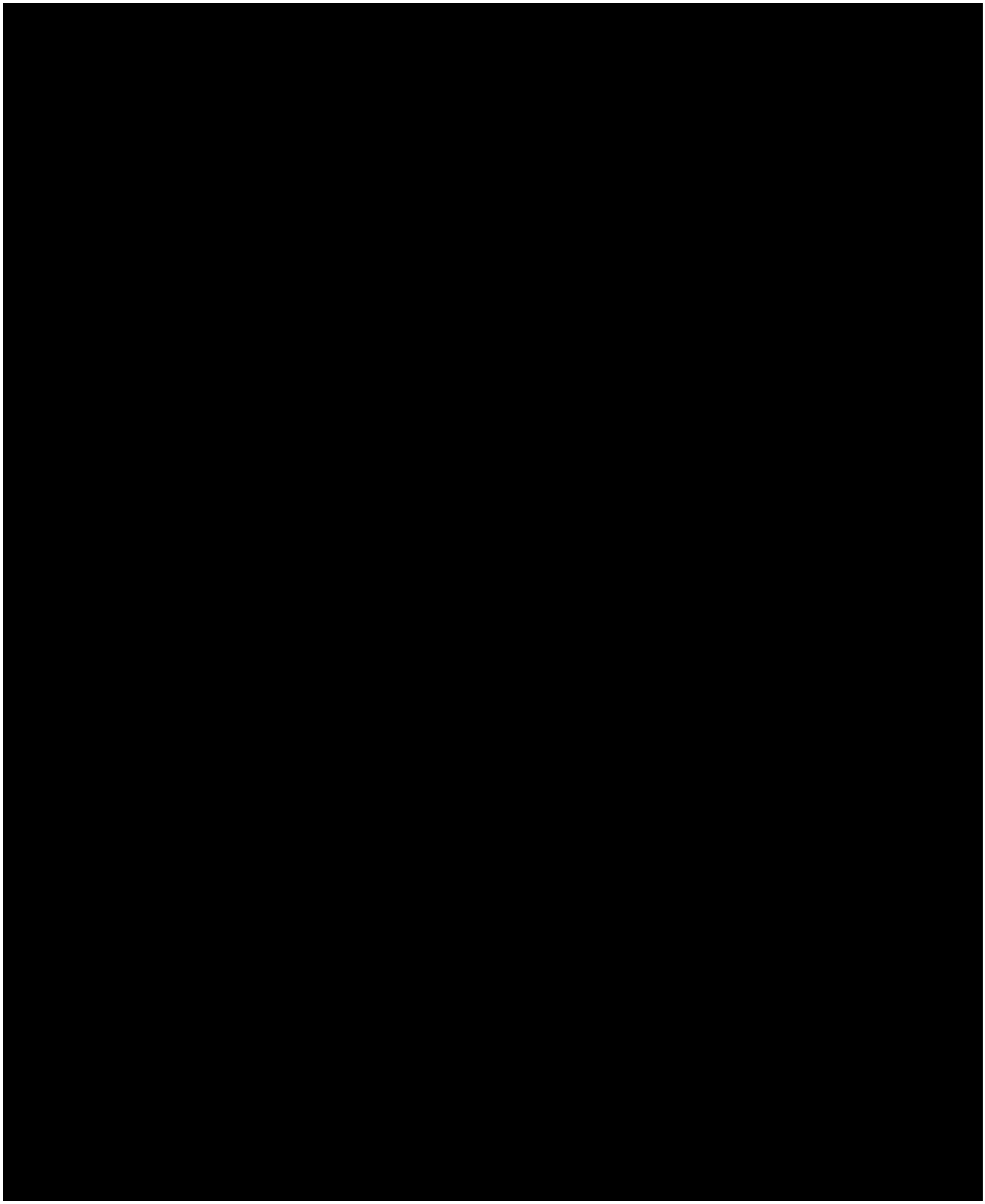
9. APPENDICES

Appendix 1. SAS Code



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run;
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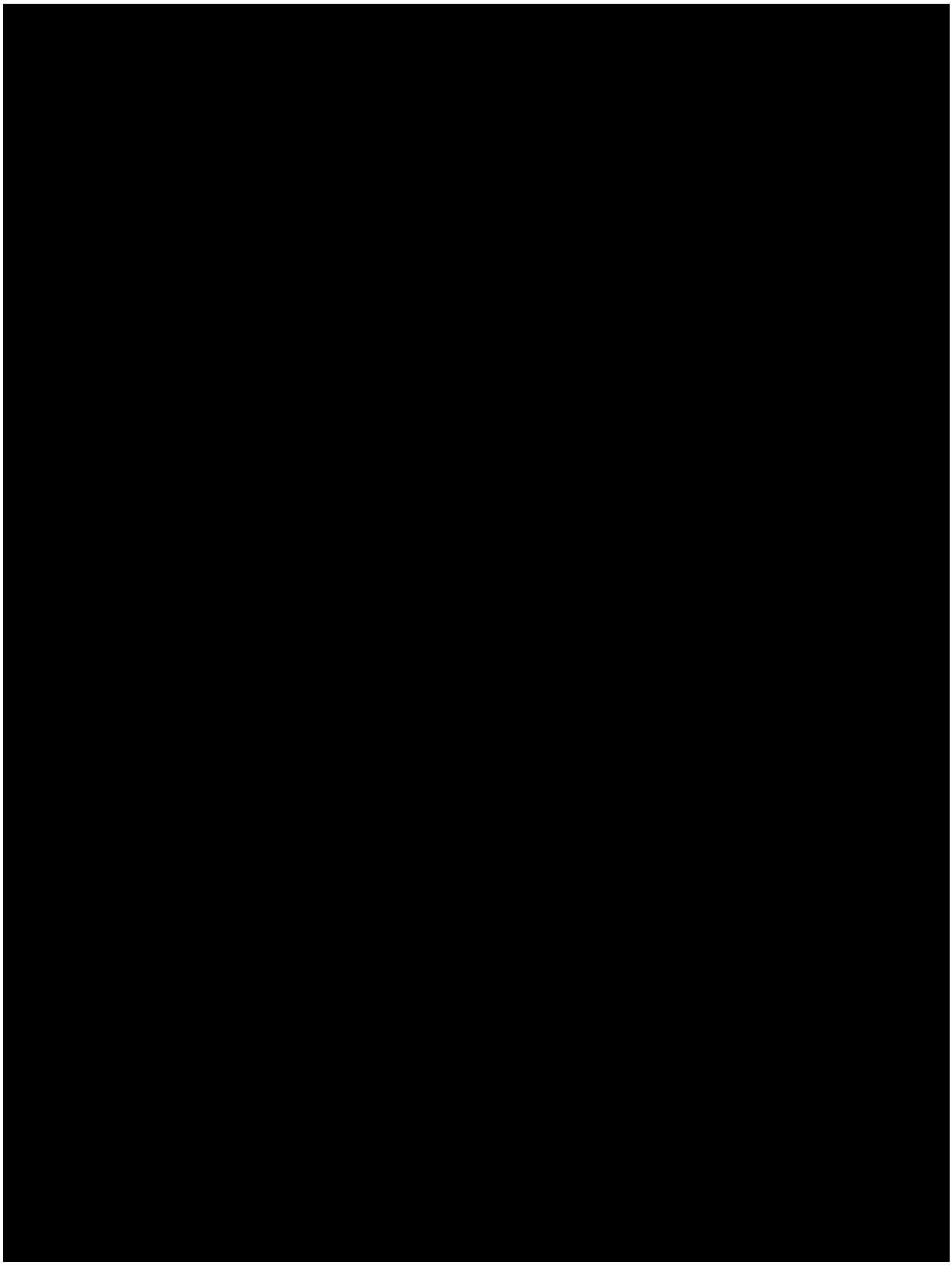
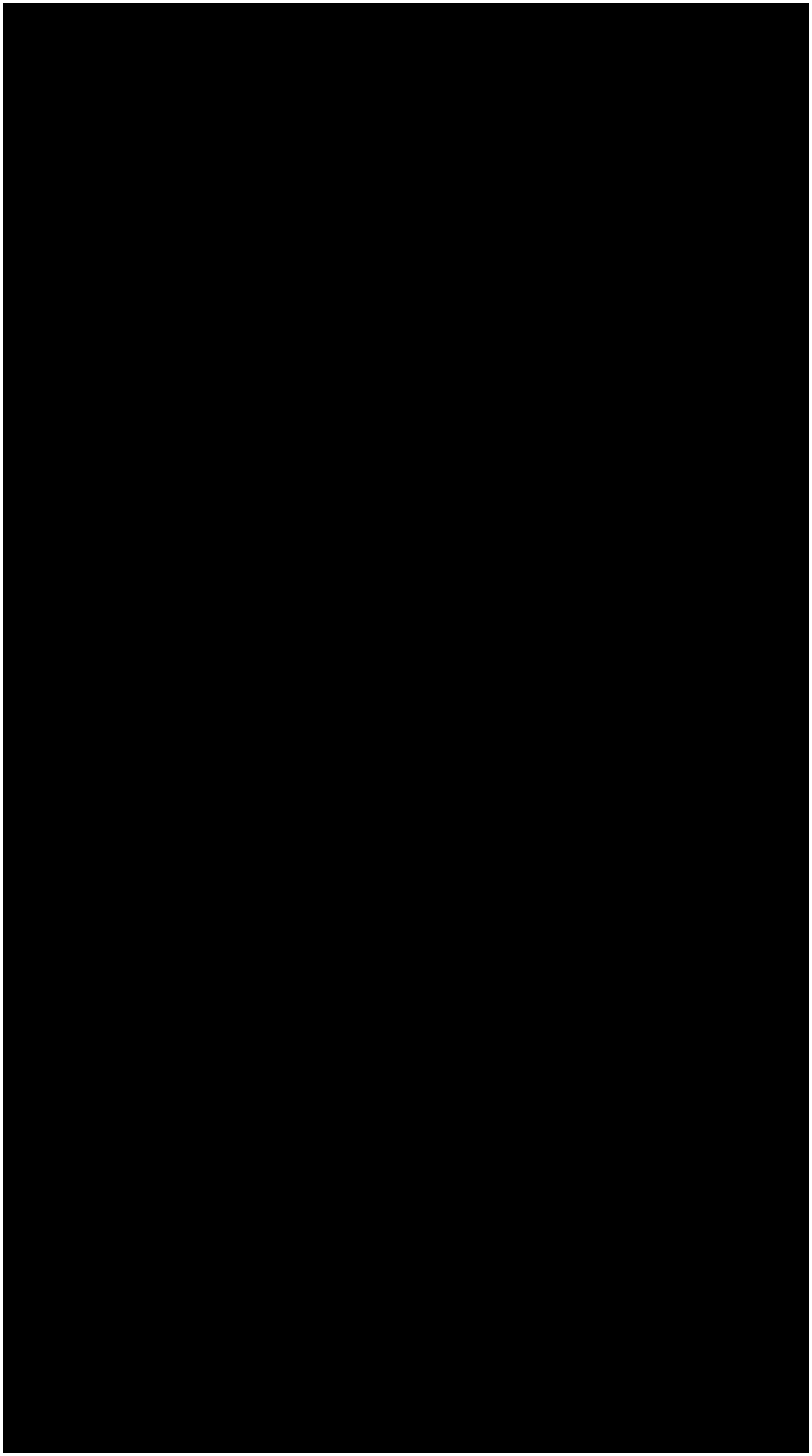
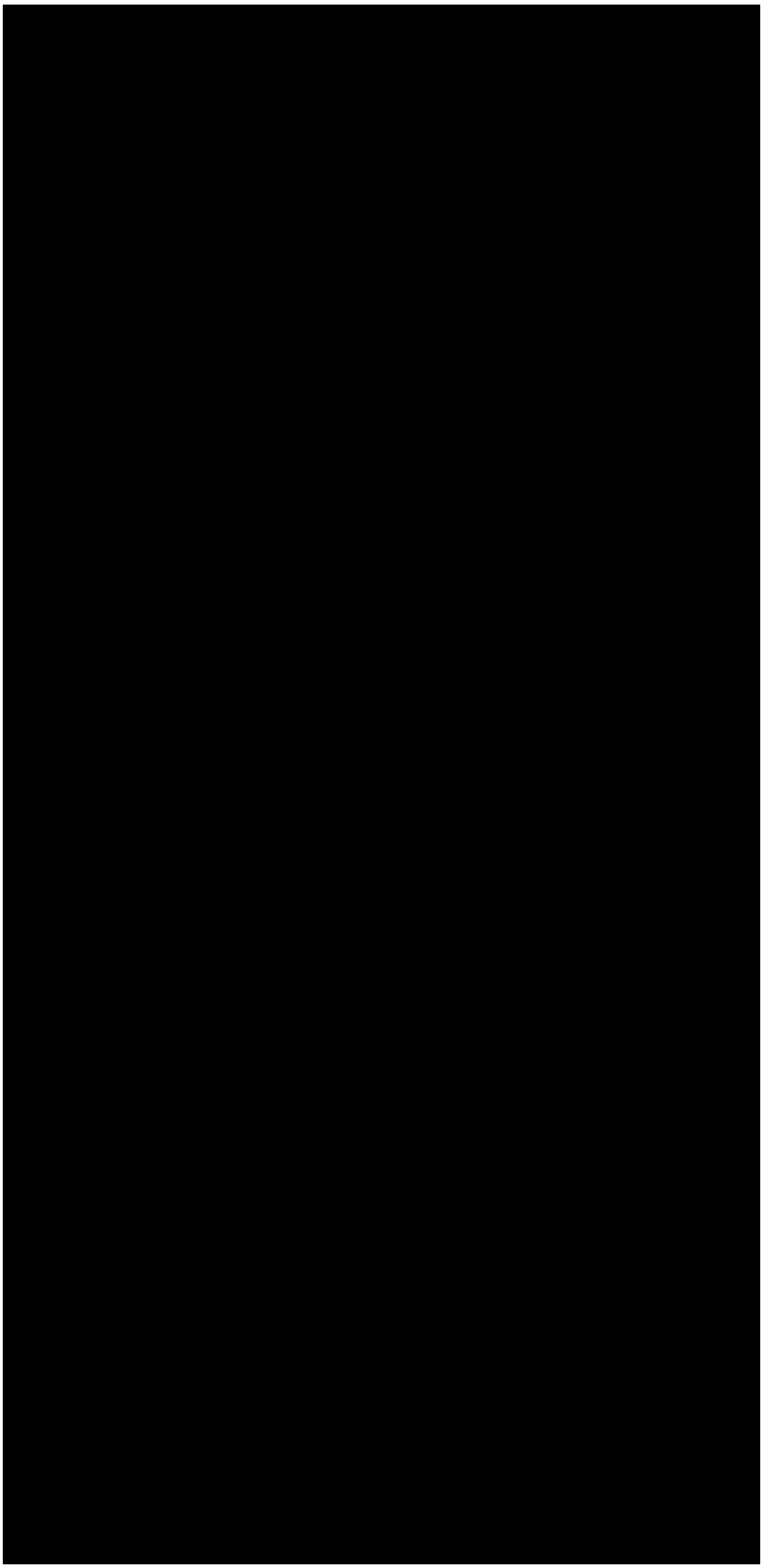
[redacted]







%**TRIPLETEST**(TEST,DIFF,TRIPLES TEST ON DIFFERENCES);

Appendix 2. List of Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
AUEC	area under the effect-time profile from time zero to the last quantifiable effect
BP	blood pressure
C_{max}	maximum observed concentration
CRU	Clinical Research Unit

Abbreviation	Term
CV	coefficient of variation
ECG	electrocardiogram
E_{max}	maximum effect
GABA	gamma-amino butyric acid
HCl	hydrochloride
IR	immediate release
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	pulse rate
Q_1	first quartile (25^{th} percentile)
Q_3	third quartile (75^{th} percentile)
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SoA	Schedule of Activities
T_{max}	time of maximum concentration
VAS	visual analog scale