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A Multicenter, Open Label, Cross-Over Study to Assess the Pharmacokinetics and Safety of Diazepam Buccal Soluble Film (DBSF) in Adult Subjects with Epilepsy

STATISTICAL ANALYSIS PLAN FINAL VERSION 1.1 DATED 14 SEPTEMBER 2018

STATISTICAL ANALYSIS PLAN

Sponsor:
MonoSol Rx, LLC
30 Technology Drive
Warren, NJ 07059
USA

A Multicenter, Open Label, Cross-Over Study to Assess the Pharmacokinetics and Safety of Diazepam Buccal Soluble Film (DBSF) in Adult Subjects with Epilepsy

Protocol No: 160326

Final Version: 1.1

Date: 14-Sep-2018

Prepared by:

Yogesh Pokharkar / Priya Diana D'silva

Syneos Health

Approval

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Protocol No: 160326, Amendment I

Frances Ekweonu, Clinical Operations Manager **Aquestive Therapeutics**	**Approval Date**
Allen H Heller MD MPH, **Principal, Pharma Study Design** **Consultant to Aquestive Therapeutics**	**Approval Date**
Priya Diana D'silva, Senior Statistician **Syneos Health**	**Approval Date**
Yogesh Sable, Principal Statistician **Syneos Health**	**Approval Date**

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14 SEP 2018

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15-SEP-2018

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Approval Date

14 SEP 2018

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AUC	Area under the concentration-time curve
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity (extrapolated)
AUC_{0-t}	Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first.
AUC_{0-4h}	Area under the concentration-time curve from time zero to 4 hour
AUC_{0-2h}	Area under the concentration-time curve from time zero to 2 hour
BLQ	Below the lower limit of quantitation
BMI	Body mass index
CI	Confidence interval
Cl	Clearance
Cl/kg	Clearance normalized for the subject body weight in kg
C_t	The last measurable concentration
C_{max}	Maximal observed plasma concentration
Corr	Correlation coefficient
CSR	Clinical study report
C-SSRS	Columbia Suicidal Severity Rating Scale
CV	Coefficient of variation (equivalent to C.V.)
Df	Degree of freedom
DIFF	Difference
DBSF	Diazepam Buccal Soluble Film
E	Base for natural logarithm
ECG	Electrocardiogram
EEG	Electroencephalogram
EMU	Epilepsy Monitoring Units
Err	Error
F	F statistic for F test
G	Gram
GCRC	General Clinical Research Centers
Geom	Geometric
GTC	Generalized Tonic-Clonic
Hr	Hour (equivalent to h)
H	Above normal range
H0	Null hypothesis
ICF	Informed consent form

Inc.	Incorporated
IWRS	Interactive Web Response System
K_{el}	Terminal elimination rate constant (equivalent to λ)
$K_{el\ Lower}$	The actual sampling time where K_{el} calculation begins
$K_{el\ Upper}$	The actual sampling time of the last measurable concentration used to estimate the K_{el}
Kg	Kilogram
/L	Per liter
L	Below normal range (conflicting with Liter)
Ln	Natural logarithm (equivalent to ln)
LS	Least-squares
Max	Maximum (equivalent to max.)
MedDRA®	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minimum (equivalent to min.)
mL	Milliliter
MS	Mean squares
MSE	Mean squares error
N	Number of observations
Ng	Nanogram
Pg	Picogram
PK	Pharmacokinetic
PR	Probability (equivalent to Pr and p)
PT	MedDRA® Preferred Term
QI	Qualified Investigator
QRS	The QRS complex is a structure on the ECG that corresponds to the depolarization of the ventricles
QT	Time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole
QTcF	QT corrected with Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical analysis system
SD	Standard deviation
SE	Standard error
SEQ	Sequence
SOC	MedDRA® System Organ Class

SOP	Standard Operating Procedure
SQRT	Square root
SS	Sum of squares
STD	Standard
T	t statistic for t-test (equivalent to T)
TEAE	Treatment-emergent adverse event
$T_{½\ el}$	Terminal elimination half-life
T_{max}	Time of maximal observed plasma concentration
TRT	Treatment
Vs	Versus
V_d	Volume of distribution
V_d/kg	Volume of distribution normalized for the subject body weight in kg
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) is intended to give a detailed description of the summaries and the analyses that will be generated for the present study by inVentiv Health Clinical. Analyses specified in this plan are based on Protocol 160326 Version 2.7, Amendment I, dated 06 June 2017. Safety, tolerability, and pharmacokinetic (PK) analyses will all be described.

The plan may change due to unforeseen circumstances and any changes made after the plan has been finalized will be documented. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the clinical study report (CSR). No change will be made without prior approval of the study sponsor. No revision to the SAP is required for changes which do not affect the statistical analysis methods, definitions, or rules defined in this document.

When applicable, all methodology and related processes will be conducted according to Standard Operating Procedures (SOPs) of InVentiv Health Clinical.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the comparative pharmacokinetics (PK) of Diazepam Buccal Soluble Film (DBSF) in subjects with epilepsy (A) in the interictal state, and (B) in the ictal/peri-ictal state.

(A) Subjects are considered to be in an interictal state if an interval of at least 3 hours has elapsed since any clinical observable postictal signs or symptoms (from the last observed seizure) and the patient has been seizure free over this period. Patients on EEG monitoring can be considered to be in an interictal state if an interval of at least 3 hours has elapsed since any postictal electrical findings on EEG.

(B) For the purposes of this study, the ictal state is defined as an ongoing clinically observable seizure or seizure activity as verified via EEG. The peri-ictal state is defined clinically as the subject's immediate postictal state following a generalized tonic-clonic (GTC) seizure or focal seizure with impaired awareness, and within 5 minutes after the last clonic jerk. For subjects on EEG monitoring, the peri-ictal state may be defined as less than 5 minutes after cessation of seizure activity (GTC or focal seizure with impaired awareness) as verified via EEG.

2.2 Secondary Objectives

Secondary objectives include:

- Evaluate the safety/tolerability of DBSF following single-dose administration in subjects with epilepsy
- Evaluate the usability of DBSF in Period A and Period B

Data from this study is intended to support a 505(b)(2) New Drug Application for the test product.

3. STUDY DESIGN

3.1 General Design

This is a multicenter, open label, single-dose, cross-over study in adult epilepsy subjects to assess the bioavailability of DBSF during the interictal and ictal/peri-ictal periods. It consists of following periods: Screening Period, Treatment Period A (interictal pharmacokinetic evaluation), Treatment Period B (ictal/peri-ictal DBSF dosing and pharmacokinetic evaluation), and Follow-up visit (14 ± 2 days after last treatment). Definitions of the interictal and ictal/peri-ictal states are given in Section 2.1. Approximately 40 adult (male or female) subjects with a clinical diagnosis of epilepsy being admitted to an Epilepsy Monitoring Units setting (EMUs), General Clinical Research Centers (GCRCs), or similar facility for evaluation of seizures will be enrolled for this study. A minimum of 30 subjects are expected to complete the study. All subjects will receive a 12.5 mg DBSF dose in both periods. There will be a washout period of at least 2 weeks between DBSF doses of Treatment Period A and Treatment Period B.

3.2 Study Period Definitions

Study periods will be conducted as follows:

Screening Period: The screening period will be from day of informed consent signed to one day prior to first visit (admission) in Treatment Period A or Treatment Period B, whichever occurs first. The screening period will occur minimum of 7 and maximum of 28 days prior to admission in GCRC or EMU facility.

Treatment Period A : Upon admission and until 8 hours (approximately) in GCRC or EMU facility + 6 additional visits for vital signs, adverse events (AEs), and blood samples (either at EMU, GCRC or similar facility, or Home Visits).

Washout Period: Minimum of 14 days between Treatment Period A and Treatment Period B doses.

Treatment Period B: Upon admission in Treatment Period B and until 4 hours (approximately) following DBSF administration. Duration of Treatment Period B will vary depending on seizure occurrence.

Period A and Period B may occur in either order as determined by seizure occurrence, e.g. if a subject experiences a seizure before dosing during first visit to EMU, GCRC or similar facility and if it has been determined that the subject meets inclusion/exclusion criteria, the investigator may regard that visit as Treatment Period B.

Post-Treatment Period: If the subject remains in the EMU, GCRC, or similar facility following the end of a treatment period, that time will be regarded as post-treatment period.

3.3 Treatment description

A subject will be administered a single dose of 12.5 mg DBSF, under fasting or fed conditions. The treatments administered in this study are presented in Table 3-1

Table 3-1 Treatment Description

Treatment	Description
A	1 x 12.5 mg Diazepam Buccal Soluble Film under fed or fasting conditions

The same treatment and dose will be used within-subject for Treatment Period A and Treatment Period B. This is an open-label study and subjects as well as clinic staff will not be blinded. Treatment assignment will not be randomized.

4. SCHEDULE OF ASSESSMENTS

Procedure/Activity	Screening (-28 days to -7 days to Period A/B, Day1)	Period A/B[a] Check-in (Predose)	Period A/B[a] Dosing / Postdose	Follow-up (14 ±2 d postdose)
ICF	X			
Register subject status in IWRS/ update status	X	X		X
Medical history/ demographics	X	X		
Concomitant medication review	X	X	X	X
Review of restrictions	X	X[b]	X[b]	
Columbia-Suicide Severity Rating Scale	X	X		X
Height and body weight	X[c]	X		
Blood pressure	X	X[d]	X[d]	X
Heart rate	X	X[d]	X[d]	X
Respiration rate	X	X[d]	X[d]	X
Temperature	X	X[d]	X[d]	X
Physical exam	X			X
Neurological exam	X			X
ECG	X	X	X[e]	
Pregnancy test	X[f]	X[f]		X[f]
Clinical laboratory tests	X			X
Drug screen (urine)	X[g]	X[g]		
Breath alcohol test	X	X		
Oral mucosal inspection	X[h]	X[h]	X[h]	X[h]
Inclusion/exclusion assessment	X	X		
Dispense/collect seizure diaries	X	X		
Continuous video EEG		X[i]	X[i]	
Study drug dosing			X	
PK sampling		X[j]	X[j]	
Assessment of usability			X[k]	
Adverse event reporting		X[l]	X[l]	X[l]

a. Treatment Periods A and B may occur in either order, depending on seizure occurrence, e.g., if a subject experiences a seizure during the first visit to the EMU or GCRC. In such cases, if feasible after IWRS registration, dose determination, and review of inclusion/exclusion criteria, the Investigator may regard that period as Treatment Period B and schedule another visit for Treatment Period A.
b. Confirmed at each follow-up visit blood draw, if applicable.
c. Height collected at screen only.
d. Vital signs (BP, HR, RR, and temperature) will be recorded predose and post dose at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes), and 4 hours (240 minutes). In Treatment Period A, vital signs will also be measured at 8 hours (480 minutes) in the EMU, GCRC or similar facility, and additional vital sign measurements will be made at 24, 48, 96, 144, 192, and 240 hours (± 2 hours) after DBSF administration in an outpatient setting (either at EMU, GCRC or similar facility, or via home visits). The subject's position may be seated or supine, but should be consistent throughout.

e. A 12-lead ECG will be obtained at Screening, at the beginning of each Treatment Period, and at 4 hours after dose administration.
f. Serum pregnancy test will be performed for females of childbearing potential at screening; urine pregnancy test will be performed at Check-in for both treatment periods and at the follow-up visit.
g. If the subject reports taking any dosage form of diazepam or other benzodiazepines within the past 2 weeks, the visit will be rescheduled for 2 weeks later at the Investigator's discretion. If the subject reports taking no diazepam or other benzodiazepines, but the urine test is positive for benzodiazepines, then the Investigator will make a judgment as to whether to reschedule the visit.
h. The Investigator will make an illumination-assisted visual inspection of the oral mucosa during Screening and on Day 1 prior to study drug administration. After the study staff assesses the timing of disintegration/dissolution of the buccal film, the Investigator will again make an illumination-assisted visual inspection of the oral mucosa, including the DBSF application site, at approximately 10 minutes, 30 minutes, and 60 minutes after complete disintegration/dissolution of the film. A further inspection of oral mucosa will be made at the Follow-up Visit.
i. If indicated by EMU or GCRC protocol, continuous video EEG monitoring for seizure detection will be performed throughout each Treatment Period. Sites will maintain the EEG recordings with the study documents, but data from the EEG recordings will not be collected for the study dataset.
j. For both treatment periods, plasma samples for diazepam and desmethyldiazepam PK will be obtained predose and post dose administration at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), and 4 hours (240 minutes). In Treatment Period A, a plasma sample will also be taken at 8 hours (480 minutes) in the EMU, GCRC or similar facility, and additional plasma samples will be collected post DBSF administration at 24, 48, 96, 144, 192, and 240 hours (±2 hours) in an outpatient setting (either at EMU, GCRC or similar facility, or via home visits).
k. To assess usability of DBSF, oral cavity insertion, retention, and placement will be evaluated for each study drug administration.
l. Adverse events are to be collected from time of consent throughout study. Seizures that occur after dosing during Treatment Period A or B, including after DBSF administration in Period A at 24, 48, 96, 144, 192, and 240 hours (±2 hours) in an outpatient setting, should be captured as adverse events unrelated to study drug.
m. Follow-up visit in an outpatient setting (to be determined by Investigator or Staff) at 14 ± 2 days after the last treatment period (A or B).

5. ANALYSIS POPULATIONS

The analysis of safety or usability parameters will be based on the safety population detailed in Section 5.1 below. The analysis of PK parameters will be based on the PK population detailed in Section 5.2 below. Treatment assignment will be according to the actual treatment received.

5.1 Safety Population

The safety population is defined as the group of subjects who receive at least one dose of the study medication.

5.2 Pharmacokinetic Population and Pharmacokinetic Analysis Data Set

The pharmacokinetic population will include all subjects who:

- Do not have a major protocol deviation that would impact the reliability of PK parameter estimation,
- Have completed at least one treatment period (Period A or Period B), and
- Have no missed samples, or have missed samples but for whom it has been predicted prior to the start of bioanalytical analysis that reliable estimates of the PK parameters should be possible.

Data from subjects who were dismissed/withdrawn (for any reason other than non-compliance) or who withdrew will be evaluated by Medical Monitor and/or the Sponsor for inclusion in the PK and statistical analysis. If reliable estimation of PK parameters will be judged possible, the data will be included in the analysis. If removed from the analysis, the data will be presented in the tables but excluded from descriptive statistics.

For a given analyte, any subject with pre-dose concentrations will be excluded from the pharmacokinetic and statistical analysis for the concerned analyte and period combination if the pre-dose concentration is greater than 5% of the C_{max} value of that period and analyte for that subject.

Data (concentrations and PK parameters) from subjects who are not included in the PK population (due to major protocol violation, reliable estimation was predicted to be impossible or excluded due to a pre-dose concentration greater than 5% of their Cmax) will be presented but excluded from all statistical analyses.

Here are some aspects to be considered (but not to be limited to) when determining data availability for PK population: inclusion and exclusion criteria, acceptable times for visit dates and measurements, compliance with treatment, the nature and quality of the data, withdrawal and any protocol deviation. The final responsibility of deciding which subjects are to be included or excluded lies with the principal investigator and/or the sponsor. The data from the subject included in the PK population will be included in the final PK analysis data set. All PK summaries and analyses will be performed using the final PK analysis data set. The final data set will be defined prior to bio-analysis.

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

Percentages and Decimal Places

If not otherwise specified, the following rules are applied, with the exception of PK tables and listings:

- Percentages will be presented to 1 decimal point.
- Percentages equal to 0 or 100 will be presented as such without a decimal point.
- Minimum and maximum will be presented with the same precision as the original values and, mean, standard deviation, and median will be presented with one more decimal place than the original values.

All digits will be used for pharmacokinetic and statistical PK calculations. For PK tables and listing, the final reportable results or data will be presented by rounding off to two decimal digits, except for the following situations (this applies to individual data and descriptive statistics):

- K_{el} and correlation (Corr) data: rounded off to four decimal digits.
- Pharmacokinetic parameters related to time such as T_{max}, $K_{el\ Lower}$, $K_{el\ Upper}$, T_{lag}, T_{last}, and T_{min} must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits.
- Concentration versus time data: reported as they appear in the final summary concentration table provided by the bioanalytical laboratory.
- Ratios and 90% confidence intervals are presented to 2 decimal places.

Analysis

Unless specified, all the analyses will be performed overall or by associated current or more recent treatment period, as appropriate. Subjects who discontinue during the washout period or during the baseline assessment will be included under the last or most recent treatment period in which subject received treatment prior to discontinuation.

Software to be used for Analysis

PK analysis will be performed using Phoenix WinNonlin® version 6.4, which is validated for bioequivalence/bioavailability studies by inVentiv Health Clinical. The inferential statistical analyses, the safety data tables and listings, as well as PK tables and listings will be created using SAS®, software version 9.2 or a higher version. PK figures will be created using R version 3.2.2 (or higher). The PK report text will be created using Microsoft® Office Word 2010, or a higher version.

6.1.2 Handling of Dropouts and Missing Data

Unless otherwise specified in the SAP, missing values will not be imputed. If missing values are imputed, the result of all imputation strategies and newly derived information must be stored in the ADaM (Analysis Data Model) dataset. The shifts required for the shift tables should already be included in the ADaM dataset.

Concentration values below the lower limit of quantitation (BLQ) and samples with no reportable value occurring prior to dosing will be handled as described in Section 6.6.1.

6.1.3 Pooling of Investigative Sites

Pooling of investigative sites is not applicable for this study.

6.2 Determination of Sample Size

Approximately forty (40) subjects with epilepsy will be recruited to attain a sample size of at least 30 completed.

6.3 Subject Characteristics

6.3.1 Subject Disposition

Subject disposition will be summarized by treatment period and overall as indicated below. The following categories will be summarized by number and percentage.

- Screened and screen failures subjects (only overall)
- Enrolled and not enrolled subjects (only overall)
- Subject who are dosed in Treatment Period A, Treatment Period B, and overall
- Subject who are not dosed in Treatment Period A, Treatment Period B, and overall
- Subject who are included in PK population for each treatment period and overall
- Subject who have completed treatment Period A, Treatment Period B and overall
- Subjects who were dismissed or did not complete the treatment period.
- Reason for absence/early termination

Subject disposition information will be listed. In addition, subjects who were dismissed from a treatment period or who did not complete a treatment period will also be presented in this listing, including absence/early termination reason and date and time of discontinuation.

For subjects enrolled, not enrolled and screen failures, the percentage denominator will be the number of screened subjects. For all other calculations, the percentage denominator will be the number of subjects dosed in each treatment period. For overall, percentages based on the overall number of subjects dosed (safety population).

6.3.2 Protocol Deviations

All protocol deviations will be collected on CRF and will be listed by subject including start date, end date and impact of deviation. Study day will be presented along with start and end date of deviation.

6.3.3 Background and Demographic Characteristics

Descriptive statistics (sample size, mean, median, standard deviation [SD], minimum [Min] and maximum [Max]) will be presented for continuous variables: age, body mass index [BMI], height, and weight. Frequency counts and percentages will be tabulated for categorical variables: age group (<18, 18-40, 41-65, and > 65 years), gender, ethnicity, and race.

Results will be presented overall for the safety population and by treatment period for PK population. No statistical tests for comparison of demographic and baseline data between treatment periods will be performed

All demographic characteristics will be listed by subject.

6.3.4 Study Drug Administration

The study drug administration details (including treatment received, start/end date, start/end time, route and frequency of administration) will be listed by subject. The dosing time will be set to the time the film is placed on the buccal mucosa. The total time taken for complete dissolution of film will be recorded in seconds and listed by subject.

Treated seizure information collected during Treatment Period B will be listed by subject. Treated seizure start/stop date including seizure type will be included in the listing.

6.3.5 Prior and Concomitant Medications and Therapies

The World Health Organization Drug Enhanced (WHO DDE) Version Jun2016, format B2 will be used to classify all medications reported during the study to an Anatomical Therapeutic Chemical (ATC) Level 1 term and a standardized medication name.

Prior is all medication/therapy stopped prior to the first drug administration, regardless of medication start date. Concomitant is any medication started and not stopped before the first drug administration in Treatment Period A or Treatment Period B, whichever occurs first.

Medications will be summarized overall and separately for prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) category Level 1 and by standardized medication name. ATC Level 1 categories and standardized medication names will appear in an alphabetical order on the summary table. For each medication, the number of subjects and percentages will be displayed.

The use of prior and/or concomitant medication will be listed by subject.

6.3.6 Medical Histories

Medical history will be collected at screening and reviewed at the check-in visit for each treatment period. The Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.0 will be used to classify all medical history findings to a System Organ Class (SOC) and Preferred Term (PT).

All medical history data will be listed and sorted by subject and alphabetically according to SOC and PT

6.4 Efficacy Analysis

No efficacy analysis is planned as per the protocol.

6.5 Safety Analysis

Safety data will be evaluated through the assessment of adverse events (AEs), laboratory parameters (serum chemistry, hematology, and urinalysis), 12-lead electrocardiogram (ECG), clinical signs and symptoms from physical and neurological examination, Columbia-Suicide Severity Rating Scale (C-SSRS) and vital signs assessments. Treatment-Emergent Adverse Events (TEAEs), laboratory values, and vital signs, will be summarized overall or according to the associated treatment period in which they were collected, as appropriate. Safety data will be summarized but not subjected to inferential analysis.

Shells for all tables and listing referred to in this section are displayed in separate document.

6.5.1 Adverse Events

Treatment-emergent AEs (TEAEs) and non-TEAEs (those occurring prior to administration of study medication or that first occurred prior to study drug administration and did not worsen in frequency or severity) will be listed. TEAEs will be defined as AEs that occur on or after the date and time of first study drug administration, or those that first occur pre-dose but worsen in frequency or severity after study drug administration. TEAEs will be captured through the end of the study. TEAEs will be attributed to the most recent treatment period in which study drug is taken. A TEAE with a start date and time during the wash-out period (ending at the time of study drug administration) will be attributed to the study drug taken during the previous treatment period.

The incidence of TEAEs will be summarized using the safety population. The MedDRA® dictionary version 20.0 will be used to classify all AEs reported during the study by SOC and PT.

Incidence of subjects who experienced TEAEs will be presented by treatment period and overall, for each SOC and PT, and also by investigator-assessed relationship and severity. Each subject may only contribute once to each of the incidence rates, for a TEAE following a given treatment, regardless of the number of occurrences; the highest severity or highest relationship will be presented, as appropriate. In each table, SOC will be presented in descending order of overall incidence rate in terms of frequency of subjects and then in frequency of events (alphabetical order will be used in case of equal rates and frequency of events). For each SOC, PT will be presented the same way.

Incidence of TEAEs (number of events) will also be presented by treatment period, SOC, and PT, by investigator-assessed relationship and severity.

The relationship of TEAEs to study drug will be classified according to the study protocol as unrelated, unlikely, possible, or probable. The Severity of AEs will be rated as according to the study protocol as: mild, moderate, or severe.

A significant AE will be defined as any event (other than those reported as serious) that led to an intervention, including withdrawal of treatment, or significant additional concomitant therapy.

Serious and significant AEs will be listed separately.

6.5.2 Physical and Neurological Examination

A physical and neurological examination will be performed at screening and at the early termination or follow-up visit.

A physical examination includes assessments of head, eyes, ears, nose, throat (HEENT), respiratory, lymph nodes, spine, skin, abdomen, cardiovascular, extremities, general appearance and others, if any. A neurological examination includes assessments of cranial nerves, muscle tone & strength, sensory function, coordination, gait, cognitive function and others, if any.

Physical and neurological examination data will be listed separately by subject.

Any abnormal findings judged to be clinically significant will be documented as medical history or as an AE, depending upon whether noted at screening, prior to dosing or after dosing, as appropriate. Any physical examination or neurological examination findings documented as AEs will be included in the AE summaries.

6.5.3 Vital Signs

Vital sign measurements (blood pressure, heart rate, respiratory rate and temperature) will be performed at screening, several times during each treatment period and at early termination or follow-up visit in each period.

In Treatment Period A, vital sign measurements (blood pressure, heart rate, respiratory rate and temperature) will be measured at pre-dose (within 1 hour prior to drug administration) and at 0.25, 0.5, 1, 2, 3, 4 and 8 hours post-dose, +/- 5 minutes for all timepoints; in addition, vital signs are also to be collected at 24, 48, 96, 144, 192, and 240 hours (+/- 2 hours) post DBSF administration in an outpatient setting. In Treatment Period B, vital sign measurements (blood pressure and heart rate) will be measured at pre-dose (within 1 hour prior to drug administration) and at 0.25, 0.5 and 2 hours post-dose, +/- 5 minutes for all timepoints.

Descriptive statistics (sample size, mean, median, SD, Min and Max,) for each vital sign parameter will be presented overall for screening and follow-up visit and by the associated treatment period for on-study measurements. Descriptive statistics for change from screening to follow-up visit and changes from baseline for on-study measurements will also be presented. Baseline will be defined as the last non-missing result (scheduled or unscheduled) obtained prior to study drug administration in each treatment period. Results from post-dose repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A listing of all vital signs results will be provided.

6.5.4 Electrocardiogram

ECG measurements will be performed at the time of screening. During Treatment Periods A and B, ECG measurements will be obtained pre-dose and post dose administration at the end of the treatment period. The quantitative ECG measurements are heart rate (HR) or ventricular rate (VR), PR interval, QRS interval, QT interval, QTcB interval (Bazett formula correction), and QTcF interval (Fridericia's formula correction).

Descriptive statistics (sample size, mean, median, SD, Min and Max) for each ECG parameter will be presented overall for screening and by associated treatment period for on-study measurements. Descriptive statistics for change from baseline for on-study measurements will also be presented. Baseline will be defined as the last non-missing result (scheduled or unscheduled) obtained prior to study drug administration in each treatment period. Results from post-dose repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A listing of all ECG results including screening measurements will be presented.

6.5.5 Laboratory Parameters

Clinical laboratory (serum chemistry, hematology, and urinalysis) results will be obtained at screening and at early termination or follow-up visit. In addition, clinical laboratory results will be obtained post-dose administration at the end of each treatment period.

Serum chemistry parameters include the following: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, urea, calcium, chloride, creatinine, creatinine kinase, lactate dehydrogenase, glucose, potassium, sodium, bilirubin, protein, uric acid and serum pregnancy test.

Hematology parameters include the following: hematocrit, hemoglobin, platelet count, red blood cell count, red blood cell indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), and white blood cell count with differential.

Urinalysis parameters include the following: pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, leukocytes, and urine pregnancy test. Unless otherwise specified, microscopic examination will be performed on abnormal finding.

Listings of all clinical laboratory results will be provided with the abnormal values flagged with "L" for low and "H" for high for continuous parameters, and "A" for abnormal for categorical parameters.

Descriptive statistics (sample size, mean, median, SD, Min and Max) for each clinical laboratory test (continuous variables) will be presented overall for screening and follow-up visit. Change from screening to follow-up visit will also be presented. For categorical variable (urinalysis), the number of subjects (frequency and percentage) will be tabulated by result (e.g. negative,

positive, trace…). A summary table of shifts from screening to follow-up visit will be provided. Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

If more than one clinical laboratory is used for the study, a formula that takes into consideration the relative normal ranges of each test of laboratories used will be applied in order to normalize these data. The conversion formula used will depend on the typical distribution of the normal range for each laboratory test; the two formulae used are presented below:

Hemoglobin, hematocrit, and platelet count test results are considered to have a normal distribution (Chuang-Stein, 1992) and the following formula will be used (Karvanen J., 2003):

$$s = L_s + (x - L_x)\frac{U_s - L_s}{U_x - L_x}$$

Where U= Upper limit; L= Lower limit; s= Primary facility result; and x= Secondary facility results.

The remaining hematology, serum chemistry, and urinalysis test results are considered to have a non-normal distribution (Chuang-Stein, 1992) and the following formula will be used (Karvanen J., 2003):

$$s = \frac{x\,U_s}{U_x}$$

Prior to applying these formulae, if required, units will be adjusted.

6.5.6 Visual Oral Inspection

A visual inspection assisted by illumination of the DBSF application site will be performed at screening and on day 1 prior to study drug administration and approximately 0.167(10 minutes), 0.5 (30 minutes), and 1 hour (60 minutes) +/- 5 minutes for all timepoints, after complete disintegration/dissolution of the buccal soluble film in both treatment periods to check for any mucosal irritation.

Any abnormal findings judged to be clinically significant will be documented as medical history or as an AE, depending upon whether noted at screening, prior to dosing or after dosing, as appropriate. Any oral safety findings documented as AEs will be included in the AE summaries.

A listing of all visual oral inspection results will be provided.

6.5.7 Columbia Suicidal Severity Rating Scale

The Columbia Suicidal Severity Rating Scale (C-SSRS), which assesses suicidal behavior and ideation, will be administered at each study visit. Qualified, trained staff will administer the C-SSRS, Baseline-Screening version at screening, and the C-SSRS, Since Last Visit version at the Treatment Period A and Treatment period B check-in. Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with

specific plan and intent) suicidal ideation during the study will be discontinued from the study and referred to a mental health professional.

A listing of C-SSRS results will be provided.

6.6 Pharmacokinetics Analysis

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in separate document; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

6.6.1 Handling of the BLQ and the No Reportable Concentration Values

During pharmacokinetic and statistical analyses, drug concentration values below the lower limit of quantitation (BLQ) of an assay will be considered as zero except when they occur between two non-BLQ concentrations where they will be considered as missing for pharmacokinetic calculations and estimations in a given period. A sample with a no reportable value occurring prior to the dosing for a given period will be replaced by zero. For tabulation, graphical representation and calculation purposes, all samples with no reportable value observed after dosing will be set to missing.

6.6.2 Handling of the Difference Between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and the actual clock time for each collection time for the PK samples will be recorded using the electronic data capture. For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to dosing, which will always be reported as zero (0.000), regardless of the time difference. In the PK section of the report, scheduled sampling times will be presented in concentration tables and mean graphs while actual times are presented for the individual graphs. A listing of the actual times for PKs will be provided for PK samples.

6.6.3 Pharmacokinetic Parameters

Epilepsy Study

For both treatment periods, plasma samples for diazepam and the active metabolite desmethyldiazepam will be obtained pre-dose and post dose administration at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), and 4 hours (240 minutes).

To facilitate comparison between Treatment Period A and Treatment Period B, plasma concentrations from diazepam and desmethyldiazepam will be used to calculate the following PK parameters based on truncated PK profile (0 to 4 hours) by standard non-compartmental methods:

AUC_{0-4h} Area under the concentration-time curve from time zero to 4 hour. AUC_{0-4h} is

	calculated using the trapezoidal method. For a subject with a missing concentration data at the sampling time 4 hours post-dose, the calculation of AUC_{0-4h} must not be done for the concerned treatment period.
C_{max}	Maximal observed plasma concentration, taken from the plasma concentration-time profile.
T_{max}	Time when the maximal plasma concentration is observed, taken from the concentration-time profile.
AUC_{0-2h}	Area under the concentration-time curve from time zero to 2 hour. AUC_{0-2h} is calculated using the trapezoidal method. For a subject with a missing concentration data at the sampling time 2 hours post-dose, the calculation of AUC_{0-2h} must not be done for the concerned treatment period.

In addition, plasma samples in Treatment Period A will also be taken at 8 hours (480 minutes) in the EMU, GCRC or similar facility, and additional plasma samples will be collected post DBSF administration at 24, 48, 96, 144, 192, and 240 hours (±2 hours) in an outpatient setting (either at EMU, GCRC or similar facility, or via home visits).

For diazepam and desmethyldiazepam, plasma samples based on full PK profile (0 to 240 hours) will be used to calculate the following PK parameters in Treatment Period A by standard non-compartmental methods:

AUC_{0-t}	Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first. AUC_{0-t} is calculated using the trapezoidal method.
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $AUC_{0-t} + C_{last} / K_{el}$, where C_{last} is the last observed non-zero concentration.
Residual Area	Residual area, calculated as $100*(1- AUC_{0-t} / AUC_{0-inf})$.
C_{max}	Maximal observed plasma concentration, taken from the plasma concentration-time profile
T_{max}	Time when the maximal plasma concentration is observed, taken from the concentration-time profile
K_{el} or λ	Terminal elimination rate constant. This parameter will be the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the elimination phase. Four non-zero observations during the elimination phase (excluding the C_{max}) will be used to calculate K_{el}, or a minimum of 3 concentration points will be used if fewer than four observations are available. The time point where ln-linear K_{el} calculation begins ($K_{el\ Lower}$), and the actual sampling time of the last quantifiable concentration used to estimate the K_{el} ($K_{el\ Upper}$) will be reported with the correlation coefficient from the linear regression to calculate K_{el} (Corr).

$T_{½\ el}$	Terminal elimination half-life, calculated as ln(2) / K_{el}.
Cl	Clearance, calculated as Dose / $AUC_{0\text{-}inf.}$
Cl/kg	Clearance normalized for the subject body weight in kg, calculated as (Dose / $AUC_{0\text{-}inf}$) / weight.
V_d	Volume of distribution, calculated as Cl/ K_{el}.
V_d/kg	Volume of distribution normalized for the subject body weight in kg, calculated as (Cl/ K_{el}) / weight.

The K_{el}, $T_{½\ el}$, $AUC_{0\text{-}inf}$, Cl, Cl/kg, V_d, and V_d/kg parameters will not be estimated for plasma concentration-time profiles where the terminal linear phase is not clearly defined.

For subjects with missing or non-reportable diazepam/desmethyldiazepam concentrations for three or more of the last samples (e.g. timepoints pass T_{max}), the data will be reviewed on a case-by-case basis by pharmacokinetic scientist and/or sponsor to determine if the data are reliable for C_{max} and T_{max}. If so, only the C_{max} and T_{max} will be presented and included in the statistical analysis. Other PK parameters will not be reported. Explanations for PK parameters that could not be estimated will be provided in the CSR.

Phase 1 Healthy Volunteers Data

For diazepam and desmethyldiazepam, the plasma concentration data for treatment Diazepam 15 mg buccal soluble film will be selected from ongoing pivotal study (MonoSol 162021).

In this pivotal study, a total of 20 blood samples will be collected from each subject (N=36) at pre-dose (0.000), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 192, and 240 hours post-dose in each study period. For the 48, 72, 96, 144, 192, and 240-hour post-dose timepoints, a window of ±60 minutes will be allowed for blood collection.

For diazepam and desmethyldiazepam, plasma samples based on full PK profile (0 to 240 hours) will be used to calculate PK parameters (as mentioned for epilepsy study) in healthy volunteer's data by standard non-compartmental methods. To facilitate comparison between epilepsy study with healthy volunteer study, PK parameters ($AUC_{0\text{-}4h}$, C_{max} and T_{max}) will also be calculated based on truncated PK profile (0 to 4 hours).

As PK profile in healthy volunteers is richer (more frequent timepoints) than the PK profile in EMU study. It might be possible that the PK parameter comparisons between epilepsy study and healthy volunteer data will be biased. Hence, to avoid this bias, PK parameter calculation for healthy volunteers mentioned above will be performed on both full data (with all available timepoints) and more sparse data (excluding timepoints which are not there in the epilepsy study).

6.6.4 Statistical Analyses

All inferential statistical analyses comparing Period A, Period B and healthy volunteers will be interpreted in an exploratory sense only at an alpha level of 5% for statistical significance.

For both epilepsy and healthy volunteer's studies, individual and mean plasma concentration versus time curves will be presented using linear and semi-log scales for diazepam and desmethyldiazepam. Listings and descriptive statistics (number of observations, arithmetic mean, SD, coefficient of variation [CV%], median, Min, Max, and geometric mean) of the concentrations versus time will be provided.

For diazepam and desmethyldiazepam, plasma PK parameters based on both full and truncated PK profiles in epilepsy and healthy volunteers (full and sparse data) studies will be listed and summarized descriptively for each treatment period (Period A and Period B) for subjects with epilepsy, and for the DBSF 15 mg treatment for healthy volunteers. Arithmetic means, standard deviations, minimum, maximum, median, and coefficients of variation will be calculated for PK parameters. Additionally, geometric means will be calculated for AUC_{0-t}, $AUC_{0-2h,}$ AUC_{0-4h}, AUC_{0-inf}, $C_{max,}$ Cl, Cl/kg, V_d, and V_d/kg.

Analysis for Epilepsy Study

For comparison (Period A vs. Period B), additional tables presenting the individual ratios for $AUC_{0-2h,}$ AUC_{0-4h} and C_{max} (based on truncated PK profile (0 to 2 hours and 0 to 4 hours)) as well as individual differences for T_{max} (based on truncated PK profile (0 to 4 hours)) will be provided.

Using GLM procedure in SAS®, analysis of variance (ANOVA) will be performed on ln-transformed $AUC_{0-2h,}$ AUC_{0-4h} and C_{max} (based on truncated PK profile (0 to 2 hours and 0 to 4 hours)) for diazepam only. Factors incorporated in the statistical model will include Period as a fixed factor and Subject as a random factor. The Period effect will be tested against residual mean square. ANOVA, for each parameter, will include calculations of least-squares (LS-) means for each period, the LS-mean for period differences using the ESTIMATE statement, and the standard error associated with this difference. T_{max} (based on truncated PK profile (0 to 2 hours and 0 to 4 hours)) will be analyzed using a non-parametric test (Wilcoxon signed-rank test).

The ratios of geometric means (Period A/ Period B) and corresponding 90% confidence interval, based on least-squares means from the ANOVA of the ln-transformed data, will be calculated for AUC_{0-2h}, AUC_{0-4h} and C_{max} (based on truncated PK profile (0 to 2 hours and 0 to 4 hours)). Inter and intra-subject coefficients of variation will be estimated.

Note: There were few subjects who were in Tretament B administered the film incorrectly for one of the site. Hence an ad-hoc analysis will be done for the B Vs A comparison tables, by excluding these subjects. The subjects are 104007, 104008, 104015, 104029 and 104030.

Comparison with Phase 1 Healthy Volunteers Data

For all comparisons with healthy volunteers, the PK parameters calculated from sparse data (considering only common timepoints with epilepsy study) of healthy volunteers will be used. PK parameters calculated based on full data (including all timepoints) of healthy volunteers will be summarized separately by descriptive statistics only.

For diazepam and desmethyldiazepam, PK parameters $AUC_{0\text{-}4h}$ and C_{max} (based on truncated PK profile (0 to 4 hours)), and $AUC_{0\text{-}t,}$ $AUC_{0\text{-}inf}$ and C_{max} (based on full PK profile (0 to 240 hours)) for the healthy volunteers will also be dose-normalized to 12.5 mg (the dose in epilepsy study) for comparison purpose. The descriptive statistics for the parameters dose-normalized to 12.5 mg will also be presented.

For each group comparison separately (i.e. Subject with Epilepsy (Period A) vs Healthy Volunteers, and Subject with Epilepsy (Period B) vs Healthy Volunteers), using GLM procedure in SAS®, ANOVA will be performed on ln-transformed dose normalized (to 12.5 mg) $AUC_{0\text{-}4h}$ and C_{max} (based on truncated PK profile (0 to 4 hours)) for diazepam only. Factors incorporated in the model will include Group as a fixed factor. The Group effect will be tested against residual mean square. ANOVA, for each parameter, will include calculations of least-squares (LS-) means for each period, the LS-mean for group difference using the ESTIMATE statement, and the standard error associated with this difference. T_{max} (based on truncated PK profile (0 to 4 hours)) will be analyzed using a non-parametric test (Wilcoxon rank-sum test).

The dose-normalized ratios of geometric means (Subject with Epilepsy (Period A)/Healthy Volunteers, and Subject with Epilepsy (Period B)/Healthy Volunteers) and corresponding 90% confidence intervals, based on least-squares means from these separate ANOVAs of the ln-transformed dose-normalized data, will be calculated for $AUC_{0\text{-}4h}$ and C_{max} (based on truncated PK profile (0 to 4 hours)).

In addition, similar ANOVA will also be performed on ln-transformed dose normalized (to 12.5 mg) PK parameters $AUC_{0\text{-}t,}$ $AUC_{0\text{-}inf,}$ and C_{max} for diazepam only. The Group (Subjects with Epilepsy (Period A) and Healthy Volunteers) will be considered as a fixed factor. T_{max} (based on full PK profile (0 to 240 hours)) will be analyzed using a non-parametric test (Wilcoxon rank-sum test). The dose-normalized ratio of geometric means (Subject with Epilepsy (Period A)/Healthy Volunteers) and corresponding 90% confidence interval, based on least-squares means from the ANOVA of the ln-transformed dose-normalized data, will be calculated for $AUC_{0\text{-}t,}$ $AUC_{0\text{-}inf}$ and $C_{max.}$

6.7 Analysis of Other Assessments

The following usability endpoints will be reported and summarized by treatment period

- Oral cavity insertion and retention assessment
- Oral cavity placement assessment

The total number of unsuccessful attempts of DBSF buccal insertion will be captured on CRF. Descriptive statistics (n, mean, SD, median, min, max) will be provided by treatment period for number of unsuccessful attempts to place DBSF. The number and percentage will be provided for categories 0, 1, 2, 3 and >3 unsuccessful attempts to place DBSF for each treatment period. The categorical explanation for each unsuccessful attempt to place DBSF will be listed.

Unsuccessful retention will have occurred if a subject allowed saliva to exit the mouth during DBSF adherence to the buccal mucosa; if the DBSF was swallowed by the subject; or if a subject spit or blew out the DBSF after adherence to the buccal mucosa or subject chewed, talked, or moved the DBSF prior to complete disintegration/dissolution. The occurrences of these three types of events are recorded on the CRF for each treatment period. The number and percentage of safety subjects with any unsuccessful retention will be summarized by treatment period, and the number and percentage of safety subjects experiencing each type of unsuccessful retention will be summarized by treatment period.

After DBSF administration, visual inspection of film will be conducted every 60 second until disintegration/dissolution is noted or for a maximum of 5 minutes. All data regarding DBSF placement, retention and visualization for each treatment period will be listed. Categorical explanation for each type of unsuccessful retention will also be included in the listing.

6.8 Interim Analysis

No interim analysis is planned.

6.9 Changes to Methods Planned in the Protocol

- In protocol Section 14.2.2. it is written:
  "Summary statistics for desmethyldiazepam shall be limited to C_{max} and AUC_t (Period A) and to C_{max} and $AUC_{(0-4h)}$ (Period B)".

  However, summary statistics will be calculated for each PK parameter.

7. REFERENCES

1. Chuang-Stein C. Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal. 1992; 26:77-84.
2. Karvanen J. The statistical basis of laboratory data normalization. Drug Information Journal. 2003; 37:101-107.