# Statistical Analysis Plan

**Sponsor Name:** Aquestive Therapeutics

**Protocol Number:** 160325 (Crossover)
**Protocol Title:** A Multicenter, Open Label Crossover Study to Assess the Pharmacokinetics and Safety of Diazepam Buccal Soluble Film (DBF) in Pediatric Subjects with Epilepsy

**Protocol Version and Date:** Protocol Amendment 4 Date: March 6, 2020

**Syneos Health Project Code:** 16MO1R-0025

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## Revision History

| Version # | Date (DD-Mmm-YYYY) | Document Owner | Revision Summary |
|---|---|---|---|
| 01 | 21-Nov-2017 | Yogesh Pokharkar / Priya D'silva | Release Version 1.0,<br>Based on Protocol Amendment 1 Dated: August 4, 2017 |
| 02 | 21-Feb-2020 | Jit Mitra | Based on protocol Amendment 3 Dated: September 6, 2018 |
| 03 | 11-Jun-2020 | Jit Mitra | • Added new weight category in footnote of table 1 and added as a note in inclusion criteria 3.<br>• Added definition of Phase of study in section 6.2.3.<br>• Added definition for several baselines in section 6.2.1.<br>• Added strategy for PK analysis for new weight category in section 5.3.1.<br>• Added individual plots for PK parameters without dose normalization and some term changes in section 9.4.<br>• Used the term Nordiazepam instead of desmethyldiazepam everywhere and added sectionwise presentation of data for it. |

I confirm that I have reviewed this document and agree with the content.

## Approvals

### Syneos Health Approval

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## Table of Contents

# 1. Glossary of Abbreviations

| Abbreviation | Description |
|---|---|
| AE | Adverse event |
| AED | Antiepileptic drug |
| ANCOVA | Analysis of covariance |
| ATC | Anatomical Therapeutic Chemical |
| $AUC_{0\text{-}xh}$ | Area under the concentration-time curve from time zero until x hours estimated using the trapezoidal method |
| β-hCG | Beta-human chorionic gonadotropin |
| BLQ | Below the lower limit of quantitation |
| BMI | Body mass index |
| BP | Blood pressure |
| CI | Confidence interval |
| $C_{max}$ | Maximal observed plasma concentration |
| CNS | Central nervous system |
| CSR | Clinical study report |
| C-SSRS | Columbia Suicidal Severity Rating Scale |
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| DBF | Diazepam Buccal Film |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EEG | Electroencephalogram |
| EMU | Epilepsy Monitoring Units |
| FDA | Food and Drug Administration |
| GCRC | General Clinical Research Centers |
| GLM | General linear model |
| GTC | Generalized tonic-clonic |
| H | Above normal range |
| HR | Heart rate |
| ICF | Informed consent form |
| IRB | Institutional review board |
| IWRS | Interactive Web Response System |
| L | Below normal range |
| ln | Natural logarithm |
| LS | Least squares |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minimum |
| N | Number of observations |
| PK | Pharmacokinetic |

| Abbreviation | Description |
|---|---|
| PT | Preferred Term |
| QRS | 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 |
| QTcB | QT corrected with Bazett's formula |
| QTcF | QT corrected with Fridericia's formula |
| RR | Respiratory rate |
| SAE | Serious adverse event |
| $SaO_2$ | Oxygen saturation |
| SAP | Statistical analysis plan |
| SAS | Statistical analysis system |
| SD | Standard deviation |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TEAE | Treatment-emergent adverse event |
| THC | Tetrahydrocannabinol |
| $T_{max}$ | Time of maximal observed plasma concentration |
| vs | Versus |
| WHO DDE | World Health Organization Drug Dictionary Enhanced |

# 2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

## 2.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings.

## 2.2. Timings of Analyses

The primary analysis of safety and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study.

# 3. Study Objectives

## 3.1. Primary Objective

The primary objective is to assess the pharmacokinetics of Diazepam Buccal Soluble Film (currently referred to as Diazepam Buccal Film [DBF]) in pediatric subjects with epilepsy in (A) the interictal state and (B) the ictal/peri-ictal state, defined as follows:

(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 subject has been seizure free over this period. Subjects on electroencephalogram (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 following 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 as verified via EEG.

## 3.2. Secondary Objective(s)

Secondary objectives are as follows:

- Evaluate the safety/tolerability of DBF in pediatric subjects with epilepsy
- Evaluate the usability of DBF

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

## 3.3. Brief Description

Diazepam Buccal Film (DBF) is being developed as an alternative dosage form to Diastat® AcuDial™ rectal gel, a gel formulation of diazepam. The proposed indication is identical to that of Diastat AcuDial rectal gel: the treatment and management of selected, refractory patients with epilepsy who are on stable regimens of antiepileptic drugs (AEDs) and who require intermittent use of diazepam to control bouts of increased seizure activity (Diastat AcuDial package insert, 2016). Diastat AcuDial rectal gel has been marketed in the United States since 1997 and currently is the only Food and Drug Administration (FDA) approved drug in the US for this indication.

This study uses a multicenter, open-label, crossover design with the following periods: Screening Visit, Treatment Period A (interictal DBF dosing and pharmacokinetic (PK) evaluation, subjects aged 6-16 years), minimum washout period of 14 days between DBF treatment periods, Treatment Period B (ictal/peri-ictal DBF dosing and PK evaluation, all subjects), and Follow-up visit 14 (±2) days after treatment. If the subject must remain in the Epilepsy Monitoring Unit (EMU) or General Clinical Research Center (GCRC) for medical reasons after the end of Treatment Period A or B, this time will be designated as Post-treatment. The treatment periods may occur in either order depending on the occurrence of seizures.

Male or female pediatric subjects (aged 2-16 years) who are scheduled to enter the EMU or GCRC for evaluation and treatment of their epilepsy and who meet the inclusion and exclusion criteria are eligible to participate in this study. Subjects aged 2 to 5 years will enter Treatment Period B only. Subjects aged 6 to 16 years will enter both Treatment Period A and Treatment Period B.

Screening Period : The Screening Period will occur 0 to 28 days prior to the first treatment period. The subject or subject's legally authorized representative must provide written informed consent prior to the initiation of any screening procedures, and subjects must provide oral and/or written assent as required by the Institutional Review Board (IRB).

Check-in Procedures : Subjects will undergo standard admission procedures, including the placement of an indwelling cannula for intravenous access and assessment of medical history, medications, vital signs (oxygen saturation [$SaO_2$] via pulse oximetry, respiratory rate [RR], heart rate [HR], blood pressure [BP], temperature), 12-lead electrocardiogram (ECG), oral mucosa, and the Columbia Suicide Severity Rating scale (C-SSRS) as age-appropriate. At the Investigator's discretion, urine drug tests and a breath alcohol test will be performed. Urine pregnancy tests will also be performed for women of child bearing potential. Subjects who meet inclusion and exclusion criteria will be enrolled. If enrolled subjects who have completed a previous treatment visit no longer meet inclusion and exclusion criteria, they will be discontinued from the study.

Treatment Periods : The treatment periods will begin at a time of day consistent with usual EMU/GCRC protocol. Subjects will arrive at the EMU, GCRC, or similar facility on their scheduled day and time. Subjects are to continue taking their regular AEDs prior to and throughout each Treatment Period (in accordance with EMU or GCRC protocol). Dosing is described in Section 3.7.

*Treatment Period A (Subjects aged 6-16 years)* : Subjects will enter Treatment Period A as scheduled if at least a 3-hour interval has elapsed since any clinical postictal signs or symptoms (from the last observed seizure) have been observed and the subject has been seizure free over this period. If clinical assessment (and EEG monitoring, if applicable) show no seizure activity, the subject will receive a single dose of 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, or 17.5 mg DBF, based on the subject's weight and age (Table 1).

*Treatment Period B (All Subjects)* : Monitoring for the occurrence of seizures as per EMU or GCRC protocol will continue until the subject experiences a qualifying seizure (GTC seizure or focal seizure with impaired awareness). If the subject's AEDs are to be tapered (e.g., if tapering should be done per EMU or GCRC protocol), the Investigator will determine and record the time to begin tapering the AEDs, including the doses administered or prescribed, percent dose reduction, and tapering rate.

Seizure management and the required intervention will be determined by the Investigator. Subjects with a GTC seizure or focal seizure with impaired awareness who are determined to be medically appropriate to receive study drug (DBF) will receive a single dose of 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, or 17.5 mg DBF, based on the subject's weight and age (Table 1) (a) during the seizure, OR (b) within 5 minutes after the last clonic jerk, AND/OR (c) within 5 minutes after cessation of the seizure as verified via EEG.

Post-treatment : If the subject remains in the EMU, GCRC, or similar facility following the end of the treatment period, that time will be regarded as a post-treatment period. While the subject remains in the EMU, GCRC, or similar facility, general seizure activity, administration of additional AEDs, surgical

treatment of their epilepsy, and AEs will be recorded. The subject will be discharged when medically stable.

Follow-up Visit : Safety data (including concomitant medications, vital signs including SaO2 via pulse oximetry, clinical laboratory tests including urine pregnancy test in females of childbearing potential, AEs, physical and neurological examinations, C-SSRS, and inspection of oral mucosa) will be obtained at a 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).

### 3.4. Subject Selection

Screening procedures will be conducted 0 to 28 days prior to the first treatment period. The following screening procedures will be conducted for each potential subject:

- Obtain written informed consent as evidenced by potential subject's parent(s) or legally authorized representative signing an Informed Consent Form (ICF). Obtain verbal and/or written assent from the subject as required by the IRB. Subjects, parents, and legally authorized representatives will be given an opportunity to ask questions about the study before giving consent/assent.
- Register subject in the Interactive Web Response System (IWRS).
- Record medical/medication history (including diazepam or benzodiazepines, smoking history, etc), and demographic information based on existing medical records and an interview with the potential subject.
- Administer age-appropriate versions of the Columbia-Suicide Severity Rating Scale (subjects age 7 and older – see Section 10.8). For nonverbal subjects, the C-SSRS assessments should be personally completed by the subject using nonverbal methods with assistance of site staff trained for these assessments. If the scales cannot be completed, the site must document this.
- Collect urine samples for urinalysis and drug screening (see Section 10.3).
- Receiving any dosage form of diazepam or other benzodiazepines with the 2 weeks prior to the screening is not a reason to postpone screening procedures. However, if the subject or subjects' parent(s) or legally authorized representative reports that the subject has received any dosage form of diazepam (all other benzodiazepines are allowed) within the 2 weeks prior to the day of admission to clinic, then the clinic admission for treatment should be deferred for a minimum of 2 weeks and a maximum of 4 weeks. If the subject or parent(s) or legally authorized representative reports that the subject has taken no diazepam and the urine test is positive for benzodiazepines, then the Investigator should review the medication history to determine whether it is consistent with the positive urine test for benzodiazepines.
- To allow a subject who tests positive for tetrahydrocannabinol (THC) at screening to continue in the study, verify and affirm in writing that the use of a medicalmarijuana product is part of the subject's treatment plan as recommended by a physician for treatment of a medical condition.
- Obtain height and body weight.
- Obtain vital signs ($SaO_2$, temperature, RR, HR, BP) and 12-lead ECG.
- Collect blood samples for hematology, chemistry, and pregnancy testing (for females of childbearing potential). For a complete listing of all tests to be performed, see Section 10.3.
- Perform breath alcohol test in subjects.
- Perform a physical and neurological examination.
- Dispense seizure diaries, with instructions to subjects or parent(s) or legally authorized representatives to record the number of seizures, AED dosing, use of rescue, and any AEs.

- Investigator reviews inclusion/exclusion criteria and all screening results/data to assess eligibility of each potential subject.

### 3.4.1. Inclusion Criteria

Potential subjects meeting all of the following criteria may be included in the study:

I-1. Subjects have a clinical diagnosis of epilepsy (GTC seizures or focal seizures with impaired awareness) and are scheduled for admission to an EMU, GCRC, or similar facility for evaluation.
I-2. Male and female subjects between 2 and 16 years of age, inclusive.
I-3. Subjects have a body weight of ≥6 kg and ≤111 kg. (Note: Subjects with body weight in range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the investigator).
I-4. Subjects have an average frequency of >1 clinically apparent seizure every 3 days or >10 clinically apparent seizures per month, with alteration of consciousness as documented by reliable subject report, personal seizure diary records, and/or by seizure diaries dispensed at screening and verified prior to Treatment Period A or Treatment Period B.
I-5. Female subjects of childbearing potential (i.e., are having periods, are not surgically sterile) must have a negative serum pregnancy test (beta human chorionic gonadotropin; β-hCG) at screening and a negative urine pregnancy test on Day 1 prior to drug dosing. Female subjects of childbearing potential must agree to abstinence, have a partner who is sterile, or be practicing double barrier contraception or have been using an FDA-approved contraceptive (e.g., licensed hormonal or barrier methods) for greater than 2 months prior to screening visit, and must commit to an acceptable form of birth control for the duration of the study and for 30 days after participation in the study.
I-6. Male subjects with a female sexual partner of childbearing potential must agree to abstinence or practice adequate birth control during the study, including at least 1 barrier method such as a condom, diaphragm, or spermicide for greater than 2 months prior to screening visit, and must commit to an acceptable form of birth control for the duration of the study and for 30 days after participation in the study. Also, male subjects must agree to not donate sperm during the study and for 90 days after the follow-up visit.
I-7. Subjects are currently receiving at least 1 AED.
I-8. Subject's parent or legally authorized representative must be willing and able to complete informed consent and HIPAA authorization. Subjects must be willing to give assent as required by the IRB.
I-9. Subject must agree to be available or subject's parent(s) or legally authorized representative must agree to have the subject be available for both treatment periods and the follow-up visit and must be willing to comply with all required study procedures and adhere to all protocol requirements.
I-10. Subject or subject's parent(s) or legally authorized representative must be able to comprehend and be informed of the nature of the study, as assessed by the Investigator.

### 3.4.2. Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded:

E-1. Subjects with a progressive neurological disorder such as a brain tumor, demyelinating disease, or degenerative central nervous system (CNS) disease that is likely to progress in the next 12 months.

E-2. Subject has respiratory failure (or is at risk for respiratory failure) or other severe cardiorespiratory disease with New York Heart Association Class III or IV functional status or requires supplemental oxygen.

E-3. Female subjects who are lactating, have a positive serum pregnancy test (β-hCG) at screening, or have a positive urine pregnancy test at check-in for treatment periods.

E-4. Subjects with psychiatric disease that in the Investigator's judgment would prevent the subject's successful completion of the study.

E-5. Subject has a recent history of suicide attempt (defined as an active, interrupted, or aborted attempt with the past 5 years) or reports suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS performed at screening.

E-6. Subjects with known history or presence of any clinically significant hepatic (e.g., hepatic impairment), renal/genitourinary (renal impairment, kidney stones), psychiatric, dermatological, or hematological disease or condition, unless determined as not clinically significant by the Investigator or designee and confirmed by the sponsor via written communication prior to subject enrollment. Abnormal laboratory results considered clinically significant by the Investigator or designee will be evaluated by the Investigator in consultation with the Medical Monitor.

E-7. Subjects with any clinically significant illness other than epilepsy within 30 days prior to study drug administration, as determined by the Investigator.

E-8. Subjects with any significant physical or organ abnormality or other condition that would interfere with study participation or constitute a safety risk in the judgment of the Investigator.

E-9. Subjects with any significant lesion of the oral cavity or having oral prophylactic or dental procedures within 30 days prior to study drug administration.

E-10. Subjects with a QTcF (QT with Fredericia's correction) interval ≥450 msec for males or QTcF ≥470 msec for females on screening ECG, unless determined to be not clinically significant by the Investigator.

E-11. Subjects with a positive test result for any of the following drugs of abuse: amphetamines, cocaine, opiates, phencyclidine, or a positive breath alcohol test. Subjects who test positive for THC at screening will be excluded unless the Principal Investigator is able to affirm in writing that the use of a medical marijuana product is part of the subject's treatment plan as recommended by a physician for treatment of a medical condition. In such case, the subject will be allowed to continue with screening, and the medical marijuana product will be recorded as a concomitant medication.

E-12. Subjects with a known history or presence of:

- A. Substance abuse or dependence (including alcohol) within 1 year prior to first study drug administration
- B. Hypersensitivity or idiosyncratic reaction to diazepam, its excipients, sodium phosphates, and/or related substances, e.g., benzodiazepines
- C. Glaucoma (open or acute narrow angle)
- D. Severe allergic reactions (e.g., anaphylactic reactions, angioedema) to investigational product and excipients

E-13. Subjects who have participated in another clinical trial or who received an investigational drug within 30 days prior to study drug administration or 5 half-lives of the investigational drug—whichever is the longer period.

E-14. Subjects with presence of mouth jewelry, dentures, oral implants, braces, or piercings in the mouth or tongue that, in the opinion of the Principal Investigator, would be likely to interfere with successful completion of the dosing procedure.

E-15. Subjects with a blood or plasma donation within 30 days prior to screening.
E-16. Subjects not willing or unable to tolerate blood draws.
E-17. Consumption of alcohol within 48 hours before dosing; or food or beverages containing grapefruit, star fruit, Seville oranges, and/or pomelo, or their derived products (e.g., fruit juice) within 10 days prior to study drug administration.
E-18. Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (e.g., cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem, or human immunodeficiency virus antivirals) and strong inducers of CYP enzymes (e.g., glucocorticoids, St. John's Wort, or rifampicin), in the previous 30 days prior to study drug administration. (Barbiturates, carbamazepine, phenytoin, and other enzyme-modifying AEDs that are medically needed are permitted.)
E-19. Use of any monoamine oxidase inhibitors (e.g., phenelzine, tranylcypromine), phenothiazines (chlorpromazine) within 30 days prior to first study drug administration.
E-20. Employee or immediate relative of an employee of Aquestive Therapeutics, any of its affiliates or partners, or Syneos Health.

## 3.5. Determination of Sample Size

To provide adequate PK, safety, and usability assessments of DBF in the pediatric population, 16 to 18 subjects should complete the study, distributed across 3 age ranges as follows: 6 subjects aged 2 to 5 years, 6 subjects aged 6 to 11 years, and 4 to 6 subjects aged 12 to 16 years. To ensure adequate numbers of completed subjects, efforts will be made to enroll 8 subjects in each age group, for a total of 24 enrolled subjects.

## 3.6. Treatment Assignment and Blinding

This is an open-label study. Neither subjects nor clinic staff will be blinded. The treatment order (order of Treatment Period A and Treatment Period B) will not be randomized.

## 3.7. Administration of Study Medication

### 3.7.1. Check-in Procedures

For each treatment period, subjects will undergo standard admission procedures. A study drug kit will be assigned by the IWRS. Appropriately delegated clinical staff at each clinical site will use the IWRS to assign a kit of the appropriate dose (from the available 5, 7.5, 10, 12.5, 15, and 17.5 mg DBF doses) based on the subject's weight and age.

### 3.7.2. Treatment Period A (Subjects aged 6-16 Years)

Subjects will enter Treatment Period A as scheduled if at least a 3-hour interval has elapsed since any clinical postictal signs or symptoms (from the last observed seizure) have been observed and the subject has been seizure-free over this period. If clinical and/or EEG monitoring show no seizure activity, the subject will receive a single dose of DBF as assigned by the IWRS.

If the subject experiences a seizure before dosing during Treatment Period A, and if feasible after IWRS registration, dose determination, and review of inclusion/exclusion criteria, the Investigator may regard this visit as Treatment Period B, and Treatment A will be rescheduled. If no seizure occurs and Treatment Period A is completed, the subject will be scheduled for Treatment Period B.

### 3.7.3. Treatment Period B (All Subjects)

During Treatment Period B, the subject will be monitored until a GTC or focal seizure with impaired awareness is detected or the Investigator terminates the monitoring period. Seizure management and the required intervention will be determined by the Investigator.

The physician in charge will be encouraged but not required to use intravenous lorazepam for rescue and to avoid using intravenous diazepam. The Investigator will be allowed to discontinue the subject from the study protocol at any time throughout the study.

### 3.7.4. Dosing

DBF is provided in a range of doses from 5 to 17.5 mg to facilitate optimal dosing. The recommended dose of DBF is dependent on the subject's age and weight. The Investigator or attending EMU or GCRC medical staff will use the IWRS (based on Table 1) to choose appropriate doses for pediatric subjects.

*Table 1 : Dosage of Diazepam Buccal Film*

| **Dose (mg)** | **Weight (kg)** | | | | | |
|---|---|---|---|---|---|---|
| | Age 2–5 Years | | Age 6–11 Years | | Age 12–16 Years | |
| | Original | Amended | Original | Amended | Original | Amended |
| 5 | 6 to 10 | 6 to 10 | 10 to 15 | 10 to 16 | 14 to 25 | 14 to 25 |
| 7.5 | 11 to 20 | 11 to 15 | 16 to 33 | 17 to 25 | 26 to 50 | 26 to 37 |
| 10 | 21 to 25 | 16 to 20 | 34 to 41 | 26 to 33 | 51 to 62 | 38 to 50 |
| 12.5 | 26 to 44 | 21 to 25 | 42 to 74 | 34 to 41 | 63 to 111 | 51 to 62 |
| 15 | | 26 to 35 | | 42 to 58 | | 63 to 87 |
| 17.5 | | 36 to 44 | | 59 to 74 | | 88 to 111 |

Original: From the Original Protocol dated June 5, 2017. Amended: From the Protocol Amendment 3 Dated September 6, 2018.

Note: Subjects with body weight in range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the investigator.

## 3.8. Study Procedures and Flowchart

The schedule of study events is given in Table 2.

*Table 2 : Schedule of Assessments*

| | | Treatment A[a] | | Treatment B[a] | | Follow-upU |
|---|---|---|---|---|---|---|
| **Procedure/Activity** | **Screening (Day -28 to Day -7)** | **Check-in predose** | **Dosing/ postdose** | **Check-in predose** | **Dosing/ postdose** | **(14±2d postdose** |
| ICF and assent[b] | x | | | | | |
| Inclusion/Exclusion assessment | x | x | | x | | |
| IWRS: Register subject, determine DBF dose, update status | x | x | | x | | x |
| Medical history/demographics | x | x | | x | | |
| Concomitant medication review | x | x | | x | | x |
| Date/time of the subject's last meal before DBF dose | | x | | x | | |
| Review of restrictions | x | x[c] | x[c] | x[c] | x[c] | |
| C-SSRS (age-appropriate versions) | x | x | | x | | x |
| Height and body weight | x[d] | x | | x | | |
| Oxygen saturation | x | x[e] | x[e] | x[e] | x[e] | x |
| Blood pressure | x | x[f] | x[f] | x[f] | x[f] | x |
| Heart rate | x | x[f] | x[f] | x[f] | x[f] | x |
| Respiratory rate | x | x[f] | x[f] | x[f] | x[f] | x |
| Temperature | x | x[f] | x[f] | x[f] | x[f] | x |
| Physical/neurological exam | x[g] | | | | | x |
| ECG | x[h] | x[h] | x[h] | x[h] | x[h] | |
| Pregnancy test | x[i] | x[i] | | x[i] | | x[i] |
| Clinical laboratory tests | x | | | | | x |
| Drug screen (urine) | x[j] | x[j] | | x[j] | | |
| Breath alcohol test | x | x | | x | | x |
| Oral mucosal inspection | x[k] | x[k] | x[k] | x[k] | x[k] | x[k] |
| Dispense/collect seizure diaries | x | x | | x | | x |
| Continuous video EEG | | x[l] | x[l] | x[l] | x[l] | |
| Study drug dosing | | | x | | x | |
| PK sampling | | x | x[m] | x | x[m] | |
| Assessment of usability | | | x[n] | | x[n] | |
| Adverse event reporting | | x[o] | x[o] | x[o] | x[o] | x[o] |

AE = Adverse event; BP = Blood Pressure; C-SSRS = Columbia-Suicide Severity Rating Scale; DBF = Diazepam Buccal Film; ECG = electrocardiogram; EEG = electroencephalogram; EMU = Epilepsy Monitoring Unit; GCRC = General Clinical Research Center; HR = Heart rate; ICF = informed consent form; IRB = Institutional review board; IWRS = Interactive Web Response System; PK = pharmacokinetic; RR = Respiratory rate; $SaO_2$ = Oxygen saturation; THC = tetrahydrocannabinol;

a. Only subjects aged 6-16 will undergo Treatment Period 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. Obtain written informed consent from parent(s) or legally authorized representative. Obtain verbal and/or written assent from subjects as required by IRB.
c. Confirmed at each ambulatory blood draw, if applicable.
d. Height measured at Screening only.
e. At both treatment visits, SaO2 via pulse oximetry will be recorded predose and at 5, 10, 20, 30, 40, 50 minutes postdose and thereafter at each time vital signs are recorded: 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes), and 4 hours (240 minutes).
f. At both treatment visits, vital signs (BP, HR, RR, and temperature) are to be recorded predose. BP, HR, and RR are to be recorded postdose 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, even though no blood will be drawn at this time point), and 4 hours (240 minutes) after dosing. The subject's position may be seated or supine but should be consistent throughout.
g. Physical/neurological examination will be performed at screening and at follow-up or at an early discontinuation visit.
h. A 12-lead ECG will be obtained at screening, at the beginning of each treatment period, and at 4 hours after dose administration.
i. A serum pregnancy test will be performed for females of childbearing potential at screening; a urine pregnancy test will be performed at each treatment period check-in and at follow-up.
j. Screening: Receiving any dosage form of diazepam or other benzodiazepines within the 2 weeks before screening is not a reason to postpone screening. Treatment periods: If the subject or parent(s) or legally authorized representative reports that the subject received any dosage form of diazepam (all other benzodiazepines are acceptable) within 2 weeks prior to the day of admission to the clinic when Treatment Period A or B may be conducted, then the admission should be deferred for a minimum of 2 weeks and a maximum of 4 weeks. If the subject or parent(s) or legally authorized representative reports that the subject has taken no diazepam in the previous 2 weeks but the urine test is positive for benzodiazepines at check-in the Investigator should consider the subject's drug history and evaluate whether the drug history is consistent with the positive urine result. Considering both the drug history and the urine test positive for benzodiazepines, the Investigator may choose to reschedule the clinical admission, but the protocol does not require the Investigator to reschedule. Subjects who test positive for THC at screening may participate if the Principal Investigator is able to affirm in writing that the use of a medical marijuana product is part of the subject's treatment plan as recommended by a physician for treatment of a medical condition. In such case, the medical marijuana product will be recorded as a concomitant medication.
k. The Investigator will make an illumination-assisted visual inspection of the oral mucosa during screening and during each treatment period prior to study drug administration and at approximately 15 minutes, 30 minutes, and 60 minutes after film placement. A further inspection of oral mucosa will be made at follow-up.
l. If indicated by EMU or GCRC protocol, continuous video EEG monitoring for seizure detection will be performed throughout each treatment period (4 hours). Sites will maintain the EEG recordings with the study documents, but data from the EEG recordings will not be collected for the study dataset.
m. For both treatment periods, plasma samples for determination of diazepam and Nordiazepam PK samples are to be obtained at predose and postdose 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) after dosing. Collection of plasma samples will continue even if the administration of another AED is needed for rescue.
n. The study staff will evaluate the insertion process to determine usability of the film.
o. AEs are to be collected from time of consent throughout the study.

# 4. Endpoints

## 4.1. Pharmacokinetic Endpoints

The following PK parameters for diazepam will be determined:

- Observed peak drug concentration ($C_{max}$)
- Observed time to reach maximum drug concentration ($T_{max}$)
- $AUC_{0-4h}$, $AUC_{0-2h}$

## 4.2. Safety Endpoints

Frequency of the following safety endpoints will be reported:

- Type, incidence, and severity of AEs
- Treatment emergent adverse events (TEAEs) related to study drug
- TEAEs leading to discontinuation
- SAEs
- CSSRS (age-appropriate versions)
- Vital signs ($SaO_2$, BP, HR, RR, and temperature)
- Physical/neurological examination at screening and at the follow-up visit.
- 12-lead ECG at screening, and for each treatment period before DBF administration and 4 hours after dose administration.
- Clinical laboratory tests (hematology, serum chemistry, and urinalysis) at screening and at follow-up or at early termination.
- Oral mucosa inspection to assess for any local irritation

Other tests used to ensure study eligibility and safety are as follows: serum pregnancy test in females of childbearing potential, urine drug screen, and breath alcohol test at screening;urine pregnancy test, urine drug screen, and breath alcohol test before dosing (Treatment Periods A and B), and at follow-up.

For purposes of the analysis, it is intended that seizures reported as AEs as described below will be handled as unrelated to the study drug :

- Seizures will be reported as AEs using the AE electronic Case Report Form (eCRF) pages if they occur during the period from clinic admission for Treatment A or Treatment B up to 24 hours after administration of the study drug.
- Seizures occurring more than 24 hours after administration of the study drug will be reported as AEs only if the seizure is more severe than normal or is a change from the subject's normal seizure activity.

## 4.3. Usability Endpoints

Frequency of the following usability endpoints will be reported for each treatment period:

- Oral cavity placement assessment
  - ✓ Whether placement was successfully achieved
  - ✓ Time of successful film placement.
  - ✓ Placement location (right or left side)

- Oral cavity insertion and retention assessment
  - ✓ Number of attempts needed to achieve successful placement
    - ➢ An attempt is defined as inserting the finger with the film into the subject's mouth. Placement is judged to be successful when the film adheres to the center of the buccal mucosa of either the right or the left cheek.
    - ➢ Categorical explanations will be captured for attempt failures
  - ✓ Whether any remnant of the film remained 15 minutes after placement.
  - ✓ Number of occurrences of DBF being spit out or blown out by the subject after adherence to the buccal mucosa
    - ➢ Categorical explanations will be provided for each occurrence
    - ➢ Whether film was reinserted
  - ✓ Number of occurrences of saliva exiting the subject's mouth
    - ➢ Recorded time and estimated amount of saliva (in mL)
    - ➢ Categorical explanations will be recorded for each occurrence
  - ✓ Whether subject had removed film or parts of film from the subject's mouth (as revealed by check of the subject's hands).

# 5. Analysis Sets

The following sections define the analysis sets to be used for analyzing the endpoints. Treatment assignment will be according to the actual treatment received.

## 5.1. Screened Set

All subjects who have been screened will be included in this set. The analysis of disposition and protocol deviations will include all screened subjects.

## 5.2. Safety Set

The safety population is defined as the group of subjects who receive at least 1 dose of the study medication. The analysis of safety or usability parameters will be based on the safety population.

## 5.3. Pharmacokinetic Set

The PK population will include subjects who meet all of the following criteria:

- Do not have a major protocol deviation that would impact the reliability of PK parameter estimation,
- Have completed at least 1 treatment period (Period A or Period B)
- 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.

The analysis of PK parameters will be based on the PK population.

### 5.3.1. Pharmacokinetic Analysis Data Set

Data from subjects who were dismissed/withdrawn (for any reason other than noncompliance) or who withdrew will be evaluated by Syneos Health PK scientist 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 PK 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 $C_{max}$) will be presented but excluded from the statistical analyses.

Here are some aspects to be considered (but not to be limited to) when determining data availability for the 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 investigator. The data from all subjects included in the PK population will be included in the final PK analysis data set. All PK summaries and the primary analyses will be performed using the final PK analysis data set.

**Note:** The evaluation of PK parameters will be performed by the Syneos Health PK Scientist prior to the database lock after all PK samples are tested. The sponsor will not be involved in this evaluation to avoid

any bias. The PK scientist will be blinded to the subject level information such as age, weight, dose and treatment period in order to derive the PK parameters.

Subjects with body weight in range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the investigator. But since the primary analysis in 160325 is the AB comparison, these subjects will not be excluded from paired analysis if the subject is otherwise valid for analysis. However, PK concentration and parameters for these subjects will not be included while calculating the summary statistics, with notification. These subjects will be included in the listings.

# 6. General Aspects for Statistical Analysis

## 6.1. General 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 place.
- Percentages equal to 0 or 100 will be presented as such without a decimal point.
- Minimum (Min) and maximum (Max) will be presented with the same precision as the original values; mean and median will be presented with 1 more decimal place than the original values; and standard deviation (SD) will be presented with 2 more decimal places than the original values.

All digits will be used for PK and statistical PK calculations. For PK tables and listings, the final reportable results or data will be presented by rounding off to 2 decimal digits, except for the following situations (this applies to individual data and descriptive statistics):

- $K_{el}$ and correlation data: rounded off to 4 decimal places.
- $T_{max}$ will be reported with the same precision as the actual sampling time: rounded off to 3 decimal places.
- Concentration versus time data will be reported as they appear in the final summary concentration table provided by the bioanalytical laboratory.
- Ratios and 90% confidence intervals (Cis) will be presented to 2 decimal places.

*Analysis* : Unless specified, all analyses will be performed overall or by associated current treatment period or more recent treatment period and age group, 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 the subject received treatment prior to discontinuation.

The following age categories will be used for analysis: ages 2 to 5 years, ages 6 to 11 years, and ages 12 to 16 years.

*Coding* : Adverse events will be graded by the Investigator based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 or later, and will be coded for summarization using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.0 or later). Concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO DDE version March 2017, Format B or later.

## 6.2. Key Definitions

### 6.2.1. Baseline Value

Baseline for all period will be defined as the last available nonmissing observation/assessment prior to the first dose of study drug administration.

Baseline for Period 1 will be defined as the last available nonmissing observation/assessment prior to the first dose of study drug administration.

Baseline for Period 2 will be defined as the last available nonmissing observation/assessment prior to the second dose of study drug administration. If missing at check-in procedures for period 2, it may include information from period 1 baseline or screening, with appropriate notification.

Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations.

### 6.2.2. Study Day

Study day is the number of days since the first study drug administration, which is counted as Study Day 1. Study day is calculated using the formula below:

Study day = date of assessment - date of first study drug administration + 1, if date of assessment is after the date of first drug administration; or:

Study day = date of assessment - date of first study drug administration, if date of assessment is prior to the date of first drug administration.

### 6.2.3. Study Phases for occurences

For occurences, like adverse events and medications, three phases will be defined:

1) Prior Phase: This will include any occurences from screening till the first dose of the study drug.
2) Period 1 Phase: This will include any occurences from first dose of the study drug till
    a. if period 2 is administrated: prior to the second dose administrated.
    b. if period 2 not administrated: the last observed occurrence.
3) Period 2 Phase (when period 2 is administrated): This will include any occurences from second dose of the study drug till the last observed occurrence.

Note: Last observed occurrence can be beyond the end of study visit.

## 6.3. 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.

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 9.3.1.1.

## 6.4. Pooling of Centers

Pooling of investigative sites is not required in the statistical analysis for this study.

# 7. Demographic, Other Baseline Characteristics and Medication

## 7.1. Subject Disposition and Withdrawals

Subject disposition will be summarized by treatment period, age categories (2-5 years, 6-11 years, and 12-16 years) and overall as indicated below. The following categories will be summarized by number and percentage.

- Screened and screen failures subjects (by age group and overall)
- Enrolled and not enrolled subjects (by age group and overall)
- Subjects who are dosed in each treatment period by age group and overall
- Subjects who are not dosed in each treatment period by age group
- Subjects who are included in the PK population for each treatment period by age group and overall
- Subjects who have completed each treatment period by age group and overall
- Subjects who were discontinued or did not complete the treatment period
- Reasons for absence/early termination.

Subject disposition information will be listed. In addition, subjects who were discontinued 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 or age category. For overall, percentages based on the overall number of subjects dosed (safety population).

## 7.2. Demographic and Other Baseline Characteristics

Descriptive statistics (sample size, mean, median, SD, Min and 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 (2-5, 6-11, 12-16 years), gender, ethnicity, and race.

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

All demographic and baseline characteristics will be listed by subject.

## 7.3. Medical History

Medical history will be collected at screening and reviewed at the check-in visit for each treatment period. MedDRA Version 20.0 or later 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.

## 7.4. Medication

WHO DDE Version Mar2017, Format B or later 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 medication is defined as medication/therapy stopped prior to the first drug administration, regardless of medication start date. Concomitant medication is defined as any medication started at any time and not stopped before the first study drug administration in Treatment Period A or Treatment Period B, whichever occurs first.

Medications will be summarized by age group and overall, separately for prior and concomitant medications by 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.

### 7.5. Protocol Deviations

All protocol deviations will be collected and 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.

# 8. Efficacy

No efficacy analysis is planned as per the protocol.

# 9. Analysis of Pharmacokinetics

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in a 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.

## 9.1. PK Sampling Schedule

During both treatment periods, plasma samples for the determination of diazepam and nordiazepam (the active metabolite) pharmacokinetics will be obtained at predose (0 hours), and 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) after dosing. Collection of plasma samples will continue even if the administration of another AED is needed for rescue.

## 9.2. Plasma PK Endpoint

The following PK parameters for diazepam will be determined:

- $C_{max,\ 0\text{-}2h}$, $C_{max,\ 0\text{-}4h}$
- $T_{max,\ 0\text{-}2h}$, $T_{max,\ 0\text{-}4h}$
- $AUC_{0\text{-}2h}$, $AUC_{0\text{-}4h}$

## 9.3. Presentation of Concentration Data

### 9.3.1. Handling of Missing Data

*9.3.1.1. Handling of the BLQ and the No Reportable Concentration Values*

During PK and statistical analyses, drug concentration values that are BLQ of an assay will be considered as zero except when they occur between 2 non-BLQ concentrations when they will be considered as missing for PK 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.

*9.3.1.2. 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 postdose sampling times expressed in hours and rounded off to 3 decimal places will be used to calculate the PK parameters; predose samples occurring prior to dosing will be reported as zero (0.000), regardless of the time difference. Scheduled sampling times will be presented in concentration tables and mean graphs and actual times will be presented for the individual graphs. A by-subject listing of the actual times for PK collections will be provided for PK samples.

### 9.3.2. Listing and Presentation of Individual PK Data

Individual and mean plasma concentration versus time curves will be presented using linear and semi-log scales for diazepam and nordiazepam. Listings and descriptive statistics (number of observations, arithmetic mean, SD, coefficient of variation [CV], median, Min, Max, and geometric mean) of the concentrations for diazepam and nordiazepam over time will be provided.

## 9.4. PK Parameter Derivation

During both treatment periods, plasma samples for diazepam and the active metabolite nordiazepam will be obtained pre-dose (0 hours) and postdose 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).

Plasma samples from diazepam and nordiazepam will be used to calculate the following PK parameters by standard noncompartmental methods:

| | |
|---|---|
| $AUC_{0-2h}$ | Area under the concentration-time curve from time zero to 2 hours. $AUC_{0-2h}$ is calculated using the trapezoidal method. For a subject with missing concentration data at the sampling time 2 hours postdose, the calculation of $AUC_{0-2h}$ will not be done for the concerned treatment period. $AUC_{0-2h}$ dose-normalized to 1 mg will also be provided ($AUC_{0-2h}$ /D) where D is the dose in mg. |
| $AUC_{0-4h}$ | Area under the concentration-time curve from time zero to 4 hours. $AUC_{0-4h}$ is calculated using the trapezoidal method. For a subject with missing concentration data at the sampling time 4 hours postdose, the calculation of $AUC_{0-4h}$ will not be done for the concerned treatment period. $AUC_{0-4h}$ dose-normalized to 1 mg will also be provided ($AUC_{0-4h}$ /D) where D is the dose in mg. |
| $C_{max, 0-2h}$ | Maximal observed plasma concentration, taken from the plasma concentration-time profile from time zero to 2 hours. $C_{max, 0-2h}$ dose-normalized to 1 mg will also be provided ($C_{max, 0-2h}$/D) where D is the dose in mg. |
| $C_{max, 0-4h}$ | Maximal observed plasma concentration, taken from the plasma concentration-time profile from time zero to 4 hours. $C_{max, 0-4h}$ dose-normalized to 1 mg will also be provided ($C_{max, 0-4h}$/D) where D is the dose in mg. |
| $T_{max, 0-2h}$ | Time when the maximal plasma concentration is observed, taken from the concentration-time profile from time zero to 2 hours. |
| $T_{max, 0-4h}$ | Time when the maximal plasma concentration is observed, taken from the concentration-time profile from time zero to 4 hours. |

For subjects with missing or nonreportable diazepam/nordiazepam concentrations, the data will be reviewed both prior to knowledge of the bioanalysis (without the plasma concentrations) and with knowledge of the bioanalysis (e.g., for predose elevated concentrations or unreasonable concentrations) on a case-by-case basis by the PK scientist to determine if the data are reliable for PK parameter estimation. The reviewers will be blinded to the subject level information such as age, weight, dose and treatment period. The blinded adjudication will be recorded before statistical analysis of the PK data. If the data are not considered reliable, PK parameters will not be presented and included in the statistical analysis. Explanations for PK parameters that could not be estimated will be provided in the CSR.

### 9.4.1. PK Parameter Summarization

For diazepam and nordiazepam, plasma PK parameters will be listed for each treatment period (Period A and Period B) by age group (2-5, 6-11, 12-16 years) and dose levels and weight category. In order to

summarize, for each age group and by period, arithmetic mean, SD, Min, Max, median and CV will be calculated for PK parameters. Additionally, geometric means will be calculated for $AUC_{0-2h}$, $AUC_{0-2h}/D$, $AUC_{0-4h}$, $AUC_{0-4h}/D$, $C_{max,\ 0-2h}$, $C_{max,\ 0-2h}/D$, $C_{max,\ 0-4h}$ and $C_{max,\ 0-4h}/D$.

For Diazepam:

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

As an exploratory analysis period geometric mean ratios (B/A) and corresponding 90% CIs will be evaluated for $AUC_{0-2h}$, $AUC_{0-4h}$, $C_{max,\ 0-2h}$ and $C_{max,\ 0-4h}$. Using the generalized linear model (GLM) procedure in SAS, an analysis of covariance (ANCOVA) will be performed on ln-transformed $AUC_{0-2h}$, $AUC_{0-4h}$, $C_{max,\ 0-2h}$ and $C_{max,\ 0-4h}$ for diazepam only at the alpha level of 0.05. Factors incorporated in the statistical model will include Treatment (A and B) as a fixed factor and dose as a covariate. Also, Subject will be included as a random factor. The treatment effect will be tested against residual mean squares. The ANCOVA for each parameter, will include calculations of least-squares (LS) means for each treatment period, the LS-mean for treatment period differences using the ESTIMATE statement and the standard errors associated with these differences. Probability (p) values will be derived from Type III sums of squares. $T_{max,\ 0-2h}$ and $T_{max,\ 0-4h}$ will be analyzed using a nonparametric test (Wilcoxon signed-rank test).

The ratios of geometric means (B/A) and corresponding 90% CIs, based on LS means from the ANCOVA of the ln-transformed data, will be calculated for $AUC_{0-2h}$, $AUC_{0-4h}$, $C_{max,\ 0-2h}$ and $C_{max,\ 0-4h}$. Inter and intrasubject CVs will be estimated. Only subjects with valid PK data in both Treatment Period A and Treatment Period B will be included in ANCOVA analysis and statistical treatments comparison without considering the age-group.

Individual plots of the $C_{max,\ 0-2h}/D$, $C_{max,\ 0-4h}/D$, $AUC_{0-2h}/D$, $AUC_{0-4h}/D$, $C_{max,\ 0-2h}$, $C_{max,\ 0-4h}$, $AUC_{0-2h}$ and $AUC_{0-4h}$ vs age group and weight category will be presented, separate for each treatment period. Any patient with any valid profile for period A or B will be included in this plot.

For Nordiazepam:

PK parameters will not be compared or plotted for nordiazepam.

# 10. Safety

Safety data will be evaluated through the assessment of AEs, laboratory parameters (serum chemistry, hematology, and urinalysis), 12-lead ECG, clinical signs and symptoms from physical and neurological examination, C-SSRS and vital signs assessments. TEAEs, laboratory values, and vital signs, will be summarized by age group, dose levels within age groups and 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 listings referenced to in this section are displayed in a separate document.

## 10.1. Extent of Exposure

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.

## 10.2. Adverse Events / Adverse Drug Reactions

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. MedDRA version 20.0 or later 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 age group, dose level, treatment period and overall, by 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 age group, 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 study drug, or significant additional concomitant therapy.

Serious and significant AEs will be listed separately.

### 10.3. Laboratory Evaluations

Clinical laboratory (serum chemistry, hematology, and urinalysis) results will be obtained at screening and at early termination or follow-up visit. Table 3 provides the list of laboratory assessments.

*Table 3 : Laboratory Assessments*

| Type Of Test | Components | | |
|---|---|---|---|
| Hematology | Hemoglobin<br>Hematocrit | RBC count<br>Platelet count | WBC count and differential<br>Peripheral blood smear |
| Serum chemistry | Glucose<br>Calcium<br>Sodium chloride<br>Albumin<br>Protein<br>Bilirubin | Alkaline phosphatase<br>Lactate dehydrogenase<br>AST<br>ALT<br>Potassium | BUN<br>Uric acid<br>Creatinine<br>Creatine kinase<br>Pregnancy (β-hCG)[a] |
| Urinalysis | Bilirubin<br>Blood<br>Glucose<br>pH | Ketones<br>Leukocytes<br>Nitrites<br>Protein | Pregnancya<br>Specific gravity<br>UBG |
| Additional tests | Breath alcohol test as per EMU/GCRC protocol | | |
| Urine drug tests | Amphetamines, Phencyclidine, Cocaine, Opiates, Benzodiazepines, THC | | |
| Diazepam and Nordiazepam | Active drug and metabolite in DBF formulation | | |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = Beta-human chorionic gonadotropin; BUN = blood urea nitrogen; DBF = Diazepam Buccal Film; EMU = Epilepsy Monitoring Unit; GCRC = General Clinical Research Center; RBC = red blood cells; THC = tetrahydrocannabinol; UBG = urobilinogen; WBC = white blood cells.

[a]Serum and urine pregnancy tests for females of child-bearing potential only

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 by age group and overall for screening and follow-up visit. Change from screening to follow-up visit will also be presented. For categorical variables (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 1 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 2 formulae used are presented in the following paragraphs :

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):

$$s = \frac{xU_s}{U_x}$$

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

### 10.4. Vital Signs

Vital sign measurements (SaO2 measured via pulse oximetry, BP, HR, RR and temperature) will be performed at screening, several times during each treatment period and at early termination or follow-up visit in each period. During both treatment periods, vital sign measurements (blood pressure, heart rate, respiratory rate and temperature) will be measured at pre-dose (±5 minutes) and post-dose at 0.25 h (15 minutes), 0.5 h (30 minutes), 1 h (60 minutes), 1.5 h (90 minutes), 2 h (120 minutes), 3 h (180 minutes), and 4 h (240 minutes). SaO2 will be measured at predose and at 5, 10, 20, 30, 40, and 50 minutes postdose, and subsequently at the same times that the other vital signs are recorded. The subject's position may be seated or supine, but should be consistent throughout.

Descriptive statistics (sample size, mean, median, SD, Min and Max,) for each vital sign parameter will be presented by overall for the screening visit and the follow-up visit. Similar descriptive statistics will also be presented by age group, dose level and 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 nonmissing result (scheduled or unscheduled) obtained prior to study drug administration in each treatment period. Results from postdose 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.

### 10.5. ECG

ECG measurements will be performed at the time of screening, at the beginning of each treatment period, and at the end of each treatment period. The quantitative ECG measurements are HR or ventricular rate, PR interval, QRS interval, QT interval, QTcB interval (Bazett formula correction), and QTcF interval (Fridericia's formula correction).

Descriptive statistics (sample size, mean, and median, SD, Min and Max) for each ECG parameter will be presented by age group and overall for screening and by age group, dose level and 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 nonmissing result (scheduled or

unscheduled) obtained prior to study drug administration in each treatment period. Results from postdose 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.

### 10.6. 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, respiratory, lymph nodes, spine, skin, abdomen, cardiovascular, extremities, general appearance and others, if any. A neurological examination includes assessments of cranial nerves, muscle tone and strength, sensory function, coordination, gait, cognitive function and others, if any.

Physical and neurological examination data will be listed separately by age group, dose levels and treatment period for each 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.

### 10.7. Visual Oral Inspection

A visual inspection assisted by illumination of the DBF application site will be performed at screening and during Treatment Periods A and B prior to dosing and at approximately 0.25 h (15 minutes), 0.5 h (30 minutes), and 1 h (60 minutes) after application of the film (±5 minutes for all time points) to check for any mucosal irritation. A further inspection of oral mucosa will be made at follow-up.

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.

### 10.8. Columbia Suicidal Severity Rating Scale

The C-SSRS, which assesses suicidal behavior and ideation, will be administered at screening, at the check -in visit for each treatment period, and at the follow-up visit to subjects aged 7 or older. Qualified, trained staff will administer the age-appropriate versions of the C-SSRS: Subjects aged 7-11 will be administered the Children's Baseline-Screening and Children's Since Last Contact versions. Subjects aged 12-16 years will be administered the Baseline-Screening and Since Last Visit versions.

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.

## 10.9. Other Safety

The following usability endpoints will be reported and summarized for each treatment period by age group and overall.

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

The total number of unsuccessful attempts of DBF buccal insertion will be captured in the eCRF. Descriptive statistics (n, mean, SD, median, Min, Max) will be provided by treatment period, age group and overall for number of unsuccessful attempts to place the DBF. The number and percentage will be provided for categories 0, 1, 2, 3 and >3 unsuccessful attempts to place DBF for each treatment period. The categorical explanation for each unsuccessful attempt to place DBF will be listed.

Unsuccessful retention will have occurred if a subject allowed saliva to exit the mouth during DBF adherence to the buccal mucosa; if the DBF was swallowed by the subject; or if a subject spit or blew out the DBF after adherence to the buccal mucosa or subject chewed, talked, or moved the DBF prior to complete disintegration/dissolution. The occurrences of these 3 types of events are recorded in the eCRF for each treatment period. The number and percentage of safety subjects with any unsuccessful retention will be summarized by age group and treatment period. Also, the number and percentage of safety subjects experiencing each type of unsuccessful retention will be summarized by age group and treatment period.

After DBF administration, visual inspection of film will be conducted every 60 seconds until disintegration/dissolution is noted or for a maximum of 5 minutes. All data regarding DBF 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.

# 11. Interim Analyses

No interim analysis is planned.

## 12. Changes from Analysis Planned in Protocol

The PK profiles for 0 to 2 hours postdose were not initially planned in the protocol. However, as the US FDA requested the analysis of the 0 to 2 hours profile along with the 0 to 4 hours profile for the adult study (Protocol 160326), the analysis of PK profile for 0 to 2 hours postdose has been included in the SAP for this pediatric study to avoid later ad hoc analyses.

Although AUCs for 0 to 2 hours and 0 to 4 hours postdose were not included in the protocol as endpoints, they have been included as PK endpoints in the SAP.

## 13. Reference List

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.
3. Diastat® AcuDial™ (diazepam rectal gel) [package insert]. 16 December 2016. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=88e0f275-dd7b-447d-b9d3-316a06da934f Accessed 01 Oct 2019.

# 14. Programming Considerations

Computer-generated output will adhere to the following specifications. The standard operating procedures (SOPs) of Syneos Health Clinical will be followed in the creation and quality control of all tables, listings and figures.

PK analysis will be performed using Phoenix WinNonlin® version 8.0, which is validated for bioequivalence/bioavailability studies by Syneos Health. 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.

## 14.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output.
- One output file can contain several outputs.or each output will be stored in a separate file.
- Output files will be delivered in Word format or portable document format pdf.
- Numbering of TFLs will follow ICH E3 guidance.

## 14.2. Table, Listing, and Figure Format

### 14.2.1. General

- All TFLs will be produced in landscape format on American letter size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., $m^2$) will be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

### 14.2.2. Headers

- All output should have the following header at the top left of each page:
- Aquestive Therapeutics Protocol Number: 160325 (Crossover)
- Final Run and the system Date
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

```
Sponsor Name: Aquestive Therapeutics        Confidential                          Page n of N
Protocol: 160325 (Crossover)                                          Dry Run/Final Run Outputs
```

### 14.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

```
Table x.y.z
First Line of Title
Second Line of Title if Needed
(Safety Set)
```

### 14.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

### 14.2.5. Body of the Data Display

#### *14.2.5.1. General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

#### *14.2.5.2. Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

| Severity Rating | N |
|---|---|
| severe | 0 |
| moderate | 8 |
| mild | 3 |

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

| | |
|---|---|
| n | XX |
| Mean | XXX.X |
| SD | X.XX |
| Median | XXX.X |
| Min | XXX |
| Max | XXX |

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Everyp-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as “-”.

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

#### *14.2.5.3. Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.

- Dates are printed in SAS ISO8601DT.format (“yyyy-mm-dd”: 2000-06-01). Missing portions of dates are represented on subject listings as dashes (2000-06). Dates that are missing because they are not applicable for the subject are output as “N/A”, unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

#### *14.2.5.4. Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

### 14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas  Listing source: 16.x.y.z’).

# 15. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907) .

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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| * | 16.2.7.1 | Non-Treatment Emergent Adverse Events | Safety |
| * | 16.2.7.2 | Treatment Emergent Adverse Events | Safety |
| * | 16.2.7.3 | Serious Adverse Events | Safety |
| * | 16.2.7.4 | Significant Adverse Events | Safety |
| 16.2.8 | | Listing of Individual Laboratory Measurements by Subject | |
| 16.2.8.1 | | Clinical Laboratory Data | |
| * | 16.2.8.1.1 | Hematology | Safety |
| * | 16.2.8.1.2 | Serum Chemistry | Safety |
| * | 16.2.8.1.3 | Urinalysis | Safety |
| * | 16.2.8.1.4 | Breathe Alchohol Test | Safety |
| * | 16.2.8.1.5 | Drug Screen | Safety |
| 16.2.8.2 | | Other Safety Data | |
| * | 16.2.8.2.1 | Vital Signs | Safety |
| * | 16.2.8.2.2 | Pulse Oximetry | Safety |
| * | 16.2.8.2.3 | Electrocardiogram (ECG) | Safety |
| * | 16.2.8.2.4 | Physical Examinations | Safety |
| * | 16.2.8.2.5 | Neurological Examinations | Safety |
| * | 16.2.8.2.6 | Oral Cavity Visual Inspection | Safety |
| * | 16.2.8.2.7 | Columbia-Suicide Severity Rating Scale (C-SSRS) | Safety |

# 19. Shells

Shells are provided in a separate document.