NCT 03428360
Statistical Analysis Plan (SAP)
SAP Date: 11 August 2020

For

Protocol Title: An Open-Label, Safety and Tolerability Study of Chronic Intermittent Use of Diazepam Buccal Soluble Film (DBSF) in Pediatric, Adolescent and Adult Subjects with Epilepsy
Amendment 2 Protocol Date: 02 March 2020

Statistical Analysis Plan

Sponsor Name: Aquestive Therapeutics (Formerly known as MonoSol Rx)

Protocol Number: 42-1703
Protocol Title: An Open-Label, Safety and Tolerability Study of Chronic Intermittent Use of Diazepam Buccal Soluble Film (DBSF) in Pediatric, Adolescent and Adult Subjects with Epilepsy

Protocol Version and Date: Amendment 2 (dated 02 March 2020)
Amendment 1 (dated 11 September 2018)
Original Protocol Date: 31 July 2017

Syneos Health Project Code: 17MO1R0003

Authors: Priya D'Silva, Senior Biostatistician
Jit Mitra, Biostatistician

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	03-Jan-2019	Priya D'Silva	Initial Release Version
2.0	11-Aug-2020	Jit Mitra	Updates made on Sponsor's request

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

Approvals

Syneos Health Approval

Jit Mitra, Biostatistitian		13-Aug-2020
Name, Title Developing Biostatistician	Signature	Date (DD-Mmm-YYYY)
Priya Diana D'Silva, Senior Biostatistitian	*PriyaDiana*	14-Aug-20
Name, Title Lead Biostatistician	Signature	Date (DD-Mmm-YYYY)

Aquestive Therapeutics Approval

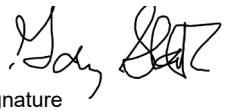
Frances Ekweonu	*Frances Ekweonu*	Aug 13th 2020
Name, Title Clinical Operations Manager Aquestive Therapeutics	Signature	Date (DD-Mmm-YYYY)
Gary Slatko MD, Chief Medical Officer		August 13, 2020
Name, Title Aquestive Therapeutics	Signature	Date (DD-Mmm-YYYY)
N/A		
Name, Title Aquestive Therapeutics	Signature	Date (DD-Mmm-YYYY)
N/A		
Name, Title Aquestive Therapeutics	Signature	Date (DD-Mmm-YYYY)

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
ARS	Acute Repetitive seizures
BMI	Body Mass index
BP	Blood pressure
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
C-SSRS	Columbia Suicidal Severity Rating Scale
DBSF	Diazepam Buccal Soluble Film
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
HR	Heart rate
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
NA	Not Applicable
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
QOL	Quality of Life
RR	Respiratory rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
WHO	World Health Organization

2. Purpose

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

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

This SAP is amended after three interim analysis, which are already completed based on the SAP version 1.0 dated 03-Jan-2019.

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

3. Study Objectives

3.1. Primary Objective

The primary objective of this study is:

- To assess the safety and tolerability of DBSF (study drug) administered a minimum of 3 times to subjects with epilepsy for the treatment of seizures over a minimum 6-month period.

3.2. Secondary Objective(s)

The secondary objectives of this study are:

- To evaluate the usability of study drug as assessed by the ability of caregivers/subjects to administer study drug based on the Instructions for Use (IFU).

- To evaluate the Quality of Life (QoL) of the subjects during the treatment period as assessed by use of age-appropriate epilepsy scales over a minimum 6-month period.

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

3.3. Subject Selection

Male and female subjects with a clinical diagnosis of epilepsy with bouts of increase seizure activity (e.g., ARS, frequent breakthrough seizures, seizure clusters or cluster seizures) will be screened. Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor. Approximately 120 subjects are expected to be screened in order to have a minimum of 100 enrolled subjects (50 adult and 50 pediatric/adolescent subjects). The enrollment should include at least 20 subjects in the 6 to 11-year-old group and 20 subjects in the 12 to 16-year-old group.

In addition to direct enrollment from screening, subjects who have completed the Phase 2 clinical trials (Study 160325 [Pediatric] and Study 160326 [Adult]) may screen and enroll (i.e., rollover subjects) into this Phase 3 long-term safety study when they come for their follow-up visit in the Phase 2 study. Seizure diary used during the Phase 2 studies will be reviewed at screening for this rollover subjects. Rollover subjects will be assessed using Protocol 42-1703 inclusion/exclusion criteria. The Phase 3 study Screening visit can be done on the same day as the Phase 2 study follow-up visit.

3.3.1. Inclusion Criteria

Subjects must meet all the following criteria in order to be included in the study:

I-01. Female or male between the ages of 2 and 65 years, inclusive

I-02. Written informed consent to participate in the study from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the Institutional Review Board (IRB) prior to the performance of any study-related procedure

I-03. Caregiver, if needed for subject, provides written informed consent and is able to administer study drug in the event of a seizure

I-04. Subject has an established diagnosis of epilepsy with motor seizures with clear alteration of awareness, and while on a regimen of anti-epileptic medication(s), still experiences bouts of seizures

(frequent break through seizures, e.g., ARS or seizure clusters) and who, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control at least 1 time a month on average. Subject must be on at least 1 concomitant anti-epileptic drug (AED) at screening.

The study is open to subjects who, in the opinion of the Investigator, would benefit from use of study drug. Concomitant prescription for a benzodiazepine for rescue (including diazepam) at screening or ongoing, or concomitant use of a benzodiazepine ongoing as a part of the subject's daily antiepileptic drug regimen does not exclude a subject from eligibility. Subjects are to be encouraged to use study drug when a benzodiazepine rescue treatment is needed. However, treatment decisions are to be guided in all cases according to the Investigator's judgment as to the optimal treatment in the interest of the subject's care and welfare. Participation in this study is never a basis for the withholding of any treatment considered to be indicated in the interest of the subject.

I-05. Female subjects have negative serum and urine pregnancy test at screening (If the subject is unable to provide a urine sample, the option to use only serum pregnancy test will be according to Investigator judgment). Female subjects of childbearing potential (not surgically sterile or less than 2 years postmenopausal) must have a partner who is sterile, must have a partner who is sterile, agrees to abstinence, be practicing double barrier contraception or using an FDA-approved contraceptive (e.g., licensed hormonal or barrier methods) for greater than 2 months prior to screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days after the final study visit.

I-06. No clinically significant abnormal findings on the ECG (QTcF [Fridericia's Correction Formula] ≤ 450 msec for males and QTcF ≤ 470 msec for females)

I-07. Subject and caregiver (if applicable) must be willing to comply with all study visits and all required study procedures (including the use of electronic diary).

NOTE: Non-verbal and cognitively impaired subjects are eligible to participate in the study.

3.3.2. Exclusion Criteria

Subjects meeting any of the following criteria are ineligible to participate in this study:

E-01. A history of clinically significant gastrointestinal, renal/genitourinary, hepatic, hematologic, dermatologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other clinically significant abnormalities, such as physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the Investigator require further investigation or treatment or which may interfere with study procedures or safety or other medical conditions (e.g., cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the Investigator could affect the subject's safety or interfere with the study assessments or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject.

E-02. Subject has had a significant traumatic injury, major surgery, or open biopsy within 30 days prior to screening

E-03. Subject has a recent history of suicide attempt (defined as an active, interrupted, or aborted attempt with the past five years) or reports suicidal ideation in the past six months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS performed at the Screening Visit.

NOTE: If a subject cannot complete the assessment, the site must document this.

E-04. A history of allergic or adverse responses to diazepam or any other benzodiazepine.

E-05. Participation in another clinical trial other than Aquestive Therapeutics Phase 2 studies 160325 and 160326 within 30 days prior to screening. Participation in an observational (non-interventional) study is not an exclusion provided there are no scheduling conflicts with this study.

E-06. Received any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before assignment to study drug treatment.

E-07. Lactating female or positive urine and serum pregnancy test (β-hCG) at screening for female subjects ≥ 12 years of age (If the subject is unable to provide a urine sample, the option to use only serum pregnancy test will be according to Investigator judgment).

E-08. In subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion), positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C, or a positive test result for drugs of abuse or alcohol, except marijuana use for medicinal indications. When marijuana is or was used for medicinal indications in the opinion of the Investigator, it is not considered as drug abuse and the subject can be enrolled in states where marijuana is legal, even if the marijuana metabolites are positive in the urine.

NOTE: In such a case, the marijuana product will be recorded as a concomitant medication.

3.4. Determination of Sample Size

A maximum of 120 subjects with epilepsy will be screened, with about 50 pediatric and adolescent and about 50 adult subjects planned. A minimum of 100 subjects is expected to be enrolled. This sample size is based on practical reason instead of statistical consideration. The enrollment should include at least 20 subjects in the 6 to 11-year-old group and 20 subjects in the 12 to 16-year-old group.

3.5. Treatment Assignment

This is an open label study. Subjects will be assigned to treatment with study drug with the use of IWRS. There will be no subject randomization; however, each study drug kit will have a kit number which will be documented. The Investigator may adjust the study drug dose as medically appropriate, in accordance with guidelines.

3.6. Administration of Study Medication

Study drug dosing is determined according to age group and body weight within age group during each study site visit where subjects are dispensed 5, 7.5, 10, 12.5, 15, or 17.5 mg study drug. Dosing occurs away from the study site by the subject or caregiver.

Investigators can make dosing adjustments after the first administration and at subsequent visits. The Investigator may choose to adjust the dose upward or downward by 1 dose level depending on clinical response to study drug. For all age groups, the height and weight will be measured and recorded at all study visits. Subjects with body weights in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the investigator.

Dosing will occur away from the study site and administered by the subject or caregiver, if applicable. The dosing time will be triggered by occurrence of a qualifying event that for the individual subject is characteristic and is deemed by the prescriber to be of a kind for which a benzodiazepine would ordinarily be administered acutely. The subject and/or caregiver will administer the study drug as described in the IFU. The actual date and time of film placement will be documented in the electronic diary by the subject or caregiver and in the eCRF by the study site staff during study visits.

A second dose, when required, may be given within 4 to 12 hours after the first dose, as previously discussed between the investigator and subject/caregiver. No more than one episode every 5 days and no more than 5 episodes per month should be treated with study drug or with any other product containing diazepam (e.g., Diastat® AcuDial™) except as instructed by a physician.

Based on subject diagnosis and history (Inclusion Criteria), it is expected that subjects will have a minimum of 3 uses of the study drug within the 6 months treatment period.

If a subject has experienced 3 uses of study drug, study participation will be complete at Month 6. For those subjects who have not experienced 3 uses of study drug, the Investigator and the Medical Monitor will assess on a case-by-case basis the likelihood of achieving 3 uses of study drug by continuing the subject on study for an additional 3 months. If the assessment concludes use of the study drug is not likely, the study will be considered complete for the subject. The sponsor may elect to end study participation for non-users prior to end of study.

3.7. Study Procedures and Flowchart

Study Period	Screening[a]	Baseline[b]	Study Drug Treatment[c] (Study drug dosing administered away from the study site)				Follow-up
Visit	Visit 1	Visit 2	Visit 3	Telephone Contact	Visit 4	Visit 5 (Final)	Telephone Contact
Study Day	Day -1 to -28	Day 1	within 14 days post first study drug dose	Day 30, Day 60	Day 90	Day 180	Month 7 (Day 210 – Day 217)
Informed Consent/Assent [d]	x						
Demography [e]	x						
Inclusion/Exclusion Criteria	x	x					
Training Subject/Caregiver on Study Drug Administration and Use of Electronic Diary [f]		x	x	x	x	x	
Medical/Disease History [g]	x	x					
Concomitant Medication Review	x	x	x		x	x	x
Vital Signs (blood pressure, heart rate, respiration rate, oral temperature)[h]	x	x	x		x	x	
Body Height and Weight [i]	x	x	x		x	x	
Complete Physical and Neurological Examination [j]	x						
Symptom Driven Physical and Neurological Examination[k]		x	x		x	x	
C-SSRS [l]	x	x	x		x	x	
Oral Mucosa Examination [m]	x	x	x		x	x	
12-lead ECG [n]	x	x	x		x	x	
Urine and Serum Pregnancy Tests [o]	x	x	x		x	x	
Collect Samples for Complete Blood Count,	x	x	x		x	x	

Blood Chemistry, Urinalysis, Urine Drug Screen, Breath Alcohol Tests[p]							
Gustatory Sense Assessment[q]		x	x		x	x	
Review Study Drug Administration (IFU) [r]		x	x		x	x	
Quality of Life by age appropriate epilepsy scales [s]	x	x	x		x	x	
Collect/Review Caregiver/Subject Diary [t]			x		x	x	
Supply Study Drug		x	x		x		
Collect/Count Study Drug		x	x		x	x	
Adverse Events Evaluation [u]	x	x	x	x	x	x	x
Study Site will telephone subjects [v]				x			x

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale: ECG = electrocardiogram; IFU = Instructions for Use; NIH = National Institutes of Health;
SAE=serious adverse event; WOCBP=women of childbearing potential.
a Screening evaluations are to be conducted for all direct enrolling subjects within 28 days before the baseline visit. Rollover subjects may consent and undergo screening during their final visit of their Phase 2 trial, thus eliminating an additional screening visit. Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor.
b The Baseline visit includes a battery of assessments, as well as training in study drug administration and documentation and supply of study drug and study logs. For rollover subjects, the assessments and training and supply can be completed during the final visit of their Phase 2 trial.
c Study site visits will be conducted at Baseline, within 14 days after the first study drug dose, and approximately every 3 months until completion 6 months or Discontinuation. The study site staff will telephone the subjects at approximately 1 and 2 months +- 7 days after baseline to check on status, reinforce training on study drug administration and diary documentation, and address any concerns. d Before the performance of any study-related procedure, written informed consent will be obtained from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the Institutional Review Board (IRB).
eAge, weight, height, gender, ethnicity and race at screening; Body weight and height will be measured at every site visit. Study drug dosage based on age and body weight. Duration of epilepsy history is documented.
f Training of subject/caregiver (as applicable) on the use of the electronic diary; use of the diary will be reviewed at each visit/contact to ensure subjects/caregivers understand and are comfortable with using the electronic diary.
h Vital signs include body temperature, respiration rate, heart rate, systolic and diastolic blood pressure measurements. All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm (if possible) for the duration of the study.
i Body height and weight is obtained for all subjects at screening to document body mass index (kg/m2). Body weight (without shoes and with empty pockets) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at all study site visits to calculate weight-based study drug dosage.
j Complete physical examination: head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological and musculoskeletal systems.
k Symptom-driven Physical and Neurological examinations will be conducted at the First/Day 1 visit, at the Final/Completion or Early Withdrawal visit, and as clinically indicated during the study.
l C-SSRS; If a subject cannot complete the assessment, the site must document this.
m Oral mucosal health assessment will be performed by the Investigator or trained Study nurse at all study site visits. In addition, any mucosal or tonguelacerations encountered during the study are recorded in the diary.
n 12-lead ECG testing is performed at Screening, Baseline, and at approximately 6 months or Final Visit. When performed on days of blood draws, ECG should be completed prior to blood collection.
O Serum and/or urine pregnancy test for females > 12 years of age. If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be according to Investigator judgment. Females with positive pregnancy tests cannot be dosed.
p Hematology testing includes Full and differential blood count, hematocrit, hemoglobin, RBC morphology, mean corpuscular volume, platelet count, RBC count and WBC with differential. Albumin, ALT, AST ALP, BUN, creatinine, Creatine kinase, Na, K Cl, Ca, Glucose, Protein, Total Protein, Total bilirubin Uric Acid will be performed. For urinalysis, dipstick is acceptable. Microscopic analyses if clinically indicated.
q Gustatory sense assessment will be administered to cognitively-appropriate subjects 12 years and older at all site visits. The general Labeled Magnitude Scale (gLMS) will remain as the evaluation scale for gustation (taste) testing; however, commercially available test strips from Burghart Messtechnik will replace the liquid taste solutions described as part of the NIH Toolbox Regional Taste Intensity Test.
r Study drug will be self-administered or with the assistance of a caregiver, as applicable. The dosing is administered remote from the study site, usually in the home setting, according to the IFU
s Quality of life will be assessed at all study site visits by age appropriate epilepsy scales. If a subject cannot complete the assessment, the site must document this.
t Use of an electronic diary will be reviewed with the subject/caregiver (as applicable) to determine their ability/willingness to use the electronic diary during treatment.

u Adverse events should be recorded. Subjects must be followed for AEs for 30 days after the last study drug treatment administration or until all drug related toxicities have resolved, whichever is later.
v The study site staff will telephone the subjects at approximately 1 and 2 months □ 7 days after the baseline visit to check on the subject's health and seizure status, reinforce training on study drug administration and diary documentation, and to address concerns. The investigator or designee will conduct a follow-up phone call with the subject at 30-37 days after the Final Visit to check on subject status and collect reporting information, should any SAE have occurred.

4. Endpoints

4.1. Primary Endpoint

The primary endpoints of this study are obtained during study visits by a trained Principal Investigator, sub-investigator, or study nurse.

- TEAE assessment, including relationship to treatment with study drug and severity.
- Columbia Suicide Severity Rating Scale (C-SSRS) assessment: If a subject cannot complete the assessment, the site must document this.
- Vital signs (blood pressure, heart rate, respiration rate, oral temperature)
- Laboratory analyses (hematology, serum chemistry, and urinalysis)
- Pathological change in oral mucosa as measured by an oral examination
- Gustatory sense changes as measured by the general Labeled Magnitude Scale (gLMS) using commercially available Burghart Messtechnik test strips in cognitively appropriate subjects 12 years of age and older

4.2. Secondary Endpoints

Secondary endpoints are:

- Quality of Life (QoL) assessments by use of age-appropriate epilepsy scales; if a subject cannot complete the assessment, the site must document this.
- Assessment of usability by subject and/or caregiver
    - Handling and administration of study drug, based on the Instructions for Use (IFU)
    - Successful buccal insertion of study drug
        - Successful placement and adherence of the study drug against the buccal mucosa (inner cheek)
    - Oral cavity placement and retention
        - Study drug swallowed prior to sticking to inner cheek
        - Study drug spit out or blown out by subject after administration
- 12-lead electrocardiograms (ECGs)
- Use of concomitant medications
- Physical and neurological examinations
- Body height and weight; BMI (kg/m^2)

5. Analysis Sets

5.1. All Enrolled Subjects

This set represents all subjects that are passed screening and entered into the database. All Enrolled Subjects will be used for all subject disposition presentation.

5.2. Safety Analysis Set

This set will include all subjects administered at least 1 dose of study drug which is captured in the eCRF. The Safety Analysis Set will be used for all data summaries and listings other than subject disposition.

Additionally dose information will be captured in the eDiaries but that information will not be used to determine Safety Analysis Set.

6. General Aspects for Statistical Analysis

6.1. General Methods

- Statistical methodology and analyses are in accordance with the principles outlined by the International Conference on Harmonization (ICH) E9 guidelines. All statistical analyses will be done using SAS statistical software version 9.4 or higher.

- Subject listings of all data represented in the electronic CRF (eCRF) will be provided. Measurements from subjects excluded from the pre-defined analysis populations or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the subject listings. In general, the subject listings will be sorted by age-group, subject number, visit and assessment date and time (if applicable). Data captured in electronic Diaries (eDiaries) will not be listed unless and otherwise directed in the corresponding section.

- Unless otherwise specified, continuous/quantitative variables will be summarized using descriptive statistics which will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum and maximum. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.

- All categorical/qualitative data will be presented using frequency counts and percentage. The total number of subjects in the relevant population with non-missing data (N) will be used as the denominator for percentage calculations, unless stated otherwise in the table shell. All percentage will be presented as 1 decimal point, unless otherwise specified. Percentage equals to 100 will be presented as 100% and percentage will not be presented for 0 frequencies.

- In the case of multiple or repeat assessments at a scheduled visit, the record closest to the planned assessment day will be selected for the summary. If 2 records are equidistant from the target day, then the later record will be selected. All assessments will be listed.

- Unless otherwise specified, all tables will be produced by age-group and overall as column headers. Adverse event tables will be repeated for by onset dose and overall as column headers.

6.2. Key Definitions

Baseline: Unless otherwise specified, the baseline value is the last non-missing measurement or assessment prior to Study Day 1 study drug administration. It can be taken as the measurement on the Baseline Visit (i.e. Visit 2) and if missing taken as the measurement on the Screening Visit (i.e. Visit 1).

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 as Date of Assessment - Date of First Dosing + (1, if Date of Assessment is on or after first dosing; 0, otherwise).

Onset Dose and Onset Day: Onset Dose and Onset Day is the dose and day of dose immediately prior to the event or assessment (since dose may change over time). Onset Dose and Onset Day (calculated as Date of Event or Assessment - Date of dose immediately prior to the event or assessment + 1) will be blank if it is prior to first study drug administration.

6.3. Missing Data

No imputation will be done for the missing data.

6.4. Visit Windows

In general, all safety data will be summarized by scheduled visits based on the scheduled events indicated in section 3.7. The visits indicated on the eCRF (i.e. eCRF visit) will be used as the analysis visits for analysis of most parameters.

6.5. Pooling of Centres

Pooling of investigative sites is not applicable for this study.

6.6. Subgroups

No subgroup analysis will be done for this study.

7. Subject Characteristics

7.1. Subject Disposition and Withdrawals

A listing of disposition, by age-group and subject identification number, presenting the Screen Result/Baseline Date, Protocol Version, whether apart of Enrolled Set and Safety Set, Status as completed or withdrawn, Days in Study as date of last available visit - date of baseline visit + 1, Number of doses as captured in eCRF and eDiary, and if withdrawn, the Reason and the Date.

The following frequencies (number and percent) will be displayed in the subject disposition table, by age-group and overall: Subjects Screened, Subjects failed Screening, Subjects passed Screening, Subjects in the Enrolled Set, Subjects passed Screening but not Enrolled, Subjects in the Safety Analysis Set. Also the same will be calculated for Completed and Withdrawn categorized by <180 and ≥180 days in the study and hence number of doses taken (as captured in eCRF) categorized by 0, 1-2 and ≥3 doses. For withdrawn subjects reason for non completion will be summarized.

The analyses of disposition will be based on the All Enrolled Subjects.

7.2. Demographic and Other Baseline Characteristics

Subject demographic and baseline characteristics will be summarized descriptively by age group and overall. Subject demographic baseline disease characteristics will include age, race, gender, weight (kg), height (cm), BMI (kg/m^2), and duration of epilepsy (in years). BMI will be calculated as: BMI (kg/m^2) = Weight(kg)/[Height(cm)/100]^2.

All of the above will be listed. The summary and listing will use Safety Analysis Set.

7.3. Protocol Deviation

All protocol deviations will be listed by age-group, subject identification number and start date. All protocol deviations will be classified into a number of general categories and further into Major and Minor type of deviations.

7.4. Medical History

All medical histories will be listed by age-group, subject identification number and start date. Medical Histories will be coded into system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or later and will be listed along with verbatim terms. Medical histories related to epilepsy will be flagged using MedDRA High Level Group Terms as Seizures (incl subtypes) and System organ class as Nervous system disorders.

7.5. Medication

Prior Medication: Prior Medication is categorized as any medication which started before first study dose.

Concomitant Medication: Concomitant Medication is categorized as any medication which started after first study dose or (started before the study drug but continued during study drug).

The following table can be utilized to determine prior and concomitant medications.

Medication start (↓) /end (→) date	< first drug intake	≥ first drug intake	All cases where year is missing or ongoing is ticked	Month and Day is missing		Only Day is missing	
				Year of Medication < Year of first drug intake	Year of Medication ≥ Year of first drug intake	Month-Year of Medication < Month-Year of first drug intake	Month-Year of Medication ≥ Month-Year of first drug intake
< first drug intake	**P**	**PC**	**PC**	**P**	**PC**	**P**	**PC**
≥ first drug intake		**C**	**C**		**C**		**C**

All cases where year is missing		**P**	**PC**		**PC**	**P**	**PC**	**P**	**PC**
Month and Day is missing	Year of Medication < Year of first drug intake	**P**	**PC**		**PC**	**P**	**PC**	**P**	**PC**
	Year of Medication ≥ Year of first drug intake		**C**		**C**		**C**		**PC**
Only Day is missing	Month-Year of Medication < Month-Year of first drug intake	**P**	**PC**		**PC**	**P**	**PC**	**P**	**C**
	Month-Year of Medication ≥ Month-Year of first drug intake		**C**		**C**		**C**		**C**

P=Prior medication, C=Concomitant medication

All Prior and concomitant medications will be coded into Anatomical Therapeutic Chemical (ATC) Classification and preferred term using World Health Organization Drug Dictionary Enhanced (WHO DDE) Version June 2016 , format B2 or later.

Summary (number and percent) tables will be provided for each prior and concomitant medications by ATC class and preferred term and further classified into age group and overall. Additionally, Summary of Concomitant Medications with Benzodiazepine and Summary of Concomitant Medications: Anti-epileptic Drugs will be produced. Antiepileptic drug to be identified by ATC code N03 for ANTIEPILEPTICS and further branched into chemical classes and preferred terms. Concomitant Medications with Benzodiazepine will be identified by ATC code as N03AE for Benzodiazepine derivatives and further to be branched as Scheduled use (medications that are prescribed chronically or they are given on a known schedule such as a daily basis (once/day or twice/day etc), weekly, monthly) and Rescue use (medications that are used for rescue and the terms could be “prn”, “as needed”, or “rescue”).

8. Analysis of Safety

The safety set will be based on all subjects who received at least one study treatment. Safety parameters will be presented by age-group and overall. Additionally Adverse event tables will be repeated by onset doses and overall. All listings will be provided by age group, Subject identification number, and if applicable, Visit, Onset Dose (mg) and Collection Date (day).

Safety will be assessed through descriptive summaries and/or listings of adverse events, laboratory test results, ECGs, body weight, physical examination findings and vital signs.

8.1. Extent of Exposure

A summary table will be utilized to show descriptive statistics (sample size, mean, median, SD, Min and Max) of Duration (Days) on Study, Doses (Number Received) on Study as captured in eCRF, Doses (Number Received) on Study as Captured in eDiary.

Subjects' treatment exposure will be listed with the drug administration per visit. If not administered then the reason for not administration of the drug will be presented in listing. The number of doses and study duration will already be listed in subject dispostion listing and will not be repeated here.

Type of Seizures treated will be listed as captured in eCRF.

Drug Accountibility in terms of Amount of Drug (in Pouch) Dispensed, Taken and Returned along with dates and reason for the Drug not Returned will be listed.

8.2. Adverse Events

8.2.1. Definitions

Treatment-Emergent Adverse Event: An AE will be considered a treatment-emergent adverse event (TEAE) if the AE starts or worsens after first dose of study medication. The following table will be utilized to dermine a TEAE:

AE Start Date	AE End Date	Rule on AE End Date	Rule on AE Start Date	TEAE
Not missing			AE Start Date < Treatment Start Date	N
			AE Start Date ≥ Treatment Start Date	Y
Partly missing	Not missing	AE End Date < Treatment Start Date		N
		AE End Date ≥ Treatment Start Date	non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
	Partly missing	non missing part of AE End Date < Treatment Start Date		N
		non missing part of AE End Date ≥ Treatment Start Date	non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
	Totally Missing or Ongoing		non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
Totally Missing	Not missing	AE End Date < Treatment Start Date		N
		AE End Date ≥ Treatment Start Date		Y

AE Start Date	AE End Date	Rule on AE End Date	Rule on AE Start Date	TEAE
	Partly missing	non missing part of AE End Date < Treatment Start Date		N
		non missing part of AE End Date ≥ Treatment Start Date		Y
	Totally Missing or Ongoing			Y

Serious Adverse Event: A serious adverse event is any AE that meets any of the following criteria:

- is fatal
- is life-threatening
- results in inpatient hospitalization or prolongation of existing hospitalization
- results in a persistent or significant incapacity or substantial disruption of the
- ability to conduct normal life functions
- is a congenital anomaly/birth defect

Adverse Event of special interest: An AE of special interest(AESI) will be categorized as:

a) Oral Irritation Safety related AESI – include the following (but not limited to):
Buccal Mucosal Swelling, Mouth Ulceration, Injuries to Oral Cavity (such as Tongue or Mucosa Laceration, Broken Tooth, Bleeding), Erythema, Stomatitis, Gingivitis, Xerostomia, Staining, Dysphagia, Dysgeusia, Burning, Stinging, Tingling

b) Abuse related AESI – include the following:
Euphoria, Euphoric Mood, Feeling of Relaxation, Anger, Dissociative Effects, Hallucinations, Psychosis, Changes in Mood, Impaired Cognition, Attention, Psychomotor Effects, Inappropriate Affect, Overdose and Misuse

Relationship of an Adverse Event with DBF: An AE will be categorized as Possible, Probable, Unlikely and Unrelated in terms of relationship with DBF. Further an AE will be termed as related to DBF if it is categorized as Possible, Probable or the relationship is missing.

Intensity of an Adverse Event: An AE will be categorized as Mild, Moderate and Severe in terms of it's intensity. Further an AE will be termed as severe if it is categorized as Severe or the intensity is missing.

8.2.2. Reporting

Adverse event terms recorded on the eCRF will be mapped to preferred terms and system organ classes using the MedDRA dictionary. MedDRA version 19.1 or above should be used for coding.

All AE summary tables will be will be presented by age-group and overall and will be repeated by onset doses and overall. All listings will be provided by age group, Subject identification number, Onset Dose (mg) and Event Date (day).

An overall summary of AEs and TEAEs reporting the number of subjects with adverse events and the number of adverse events will be presented. The following categories will be included in this overall summary:

- Any AE
- Any TEAE

- Any Serious TEAE
- Any Related TEAE
- Any Severe TEAE
- Any Severe and Related TEAE
- Any Serious and Related TEAE
- Any AESI
- Any AE leading to Study Drug Discontinuation
- Any Related AE leading to Study Drug Discontinuation
- Any Serious AE leading to Study Drug Discontinuation
- Any Serious and Related AE leading to Study Drug Discontinuation
- Any AE leading to Death
- Any Related AE leading to Death

The number and percentage of subjects and events by system organ class and preferred term will be calculated (by age-group and overall and repeated by onset doses and overall) and sorted by descending frequency of subjects and then descending frequency of events for each system organ class and preferred term within the overall column. Each subject is counted once to each of the incidence rates, regardless of the number of occurrences. These are:

- Summary of TEAE
- Summary of Serious TEAE
- Summary of Related TEAE
- Summary of Severe TEAE
- Summary of Severe and Related TEAE
- Summary of Serious and Related TEAE
- Summary of AESI
- Summary of AE leading to Study Drug Discontinuation
- Summary of Related AE leading to Study Drug Discontinuation
- Summary of Serious AE leading to Study Drug Discontinuation
- Summary of Serious and Related AE leading to Study Drug Discontinuation
- Summary of AE leading to Death
- Summary of Related AE leading to Death
- Summary of TEAEs by Relationship with DBF
- Summary of TEAEs by Intensity

Listings of all Adverse Events, Serious Adverse Events, Adverse Events of Special Interest, Adverse Events leading to Study drug discontinuation and Adverse Events leading to death will be presented.

8.3. Laboratory Evaluations

Clinical laboratory data will be summarized using descriptive statistics (sample size, mean, median, SD, Min and Max) will be presented for the baseline and all post baseline visits for hematology and serum chemistry only. Descriptive statistics for change from baseline for on-study measurements will also be presented for each parameter.

For both hematology and serum chemistry laboratory tests, Low, normal, and high classifications will be applied to determine whether the laboratory test value was below (low), within (normal), or above (high) its

reference range. For both separate tables will be utilized to show frequencies (number and percent) at baseline and post-baseline visits as Low, Normal, High and Missing and for post baseline visits shifts from baseline will also be shown for each parameters.

For Urinalysis frequencies (number and percent) of subjects will be shown by visit and shifts from baseline for each parameter.

Separate listings will be produced for hematology, serum chemistry, Urinalysis and all other laboratory testing (including Serology, Pregnancy Tests, Breath Alcohol Test, Urine Tests for Drugs of Abuse and if any thing which is other than Hematology, Blood Chemistry, Urinalysis).

8.4. Vital Signs and ECG

Descriptive statistics (sample size, mean, median, SD, Min and Max) for each vital sign and ECG parameter will be presented by overall for the baseline and all post baseline visits in separate tables. Descriptive statistics for change from baseline for on-study measurements will also be presented for each parameter.

Corresponding listings of all vital signs and ECG results will be provided by age group, Subject identification number, Visit, Onset Dose (mg) and Collection Date (day).

8.5. Physical and Neurological Examination

Listings of all physical and neurological examination results will be provided by age group, Subject identification number, Visit, Onset Dose (mg) and Collection Date (day).

For both separate tables will be utilized to show frequencies (number and percent) at baseline as Normal, Abnormal and Not Done or Missing and for post baseline visits as Change Or Abnormality, No Change Or Abnormality and Not Done or Missing.

8.6. Other Safety

8.6.1. Oral Mucosa Examination

All Oral mucosa examination will be listed. No summary statistics will be provided.

8.6.2. Gustatory Labeled Magnitude Scale (gLMS) sense Assessments

All Gustatory Labeled Magnitude Scale (gLMS) sense Assessments will be listed. Also it will be tabulated as frequencies(number and percent) of subjects at each of baseline and post-baseline visits and shifts from baseline to post-baseline visits by categories No sensation/ Barely detectable/ Weak/ Moderate/ Strong/ Very strong/ Strongest imaginable sensation/ Missing.

8.6.3. Columbia Suicide Severity Rating Scale (C-SSRS)

All Columbia Suicide Severity Rating Scale (C-SSRS) will be listed. Also it will be tabulated as frequencies(number and percent) of subjects at each of baseline and post-baseline visits by categories.

8.6.4. Quality of Life in Epilepsy Inventory Assessments

Following listings for Quality of Life in Epilepsy Inventory Assessments will be produced:

- Quality of Life in Epilepsy Inventory Assessments questions
- Quality of Life in Epilepsy Inventory Assessments (Scores) for PedsQL: Epilepsy Module Adult Report for Toddlers (Age Category : Infants(2-4 years))

- Quality of Life in Epilepsy Inventory Assessments (Scores) for PedsQL: Epilepsy Module Parent Report for Young Child (Age Category : Younger Children(5-7 years))
- Quality of Life in Epilepsy Inventory Assessments (Scores) for PedsQL: Epilepsy Module Parent Report for Children (Age Category : Older Children(8-10 years))
- Quality of Life in Epilepsy Inventory Assessments (Scores) for QOLIE-AD-48 (Age Category : Adolescents(11-17 years))
- Quality of Life in Epilepsy Inventory Assessments (Scores) for QOLIE-31-P (Age Category : Adults(18 years or more))

A summary table by Type/Group (Maximum Score) with descriptive statistics (sample size, mean, median, SD, Min and Max) will be presented for the baseline and all post baseline visits. Same descriptive statistics will be calculated for change from baseline in the same table. This table will be done by Infant(as 2-4 years), Younger Child(as 5-7 years), Older Child(as 8-10 years), Adolescent(as 11-17 years) and Adult(as 18 years or more) as column headers and not by the usual columns proposed for safety tables.

9. Interim Analyses

This SAP amendment is based on the experience of the previous three interim analysis and in order to better representation the data. This SAP amendment will be applicable only for the final analysis and no other interim analysis.

10. Changes from Analysis Planned in Protocol

10.1. Analysis of Usability data

Analysis of Usability data which is captured in the eDiaries are removed from this SAP amendment.

10.2. Analysis of Adverse events of special interest

Some adverse events of special interest are defined in this SAP based on the experiences in the previous interim analyses and other studies with DBF.

10.3. Concomitant medications of interest

Concomitant Medications with Benzodiazepine (by Scheduled and Rescue use) and Concomitant Medications with Anti-epileptic Drugs are included in this SAP.

10.4. Epilepsy related Medical History

Rules have been difined to identify Epilepsy related Medical History which are of interest.

11. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

11.1. Format of Output

Unless otherwise specified, all computer-generated output should be produced in landscape mode. Required margins: at least 1.25 inches on top (the binding margin [or left for portrait output]), at least 1 inch on right, left, and bottom. All output should have the sponsor name, protocol number, the type of delivery, and page number. Tables/listings/figures should be internally paginated in relation to total length (i.e., page number should appear sequentially as page n of N, where N is the total number of pages in the table).

a) Output numeration will conform to International Conference on Harmonisation (ICH) recommendations. The study population should be identified immediately following the title.

b) Column headings should be in initial upper-case characters.

c) For numeric variables, include “unit” in column or row headings where appropriate.

d) Footnotes should be single spaced, but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table.

e) If the categories are not ordered (e.g., race), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

f) An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

g) Listings should be sorted by cohorts and subject numbers.

h) In a listing, display the subject number only once for the subject with multiple records. If a subject’s records run into multiple pages, display the subject number once for every page.

11.2. Format of Data

a) Unless otherwise specified for continuous variables, the estimated mean, standard deviation and median for a set of values should be printed out to 1 more significant digit than the individual units of measurement. The minimum and maximum should report the same significant digits as the original values.

b) Data in columns of a table should be formatted as follows:

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

c) Unless otherwise specified, percentage values should be printed with 1 digit to the right of the decimal point (e.g., 12.8%, 5.4%). Less-than signs “<0.1%” should be printed when values are >0 and <0.1% (not 0%).

d) Missing data should be represented on subject listings as either a hyphen (“-“) with a corresponding

footnote ("- = unknown or not evaluated"), or as "NA," with the footnote "NA = not applicable," whichever is appropriate.

e) Dates should be printed in SAS® date9.format ("DDMMMYYYY": 23MAR2020). Missing portions of dates should be represented on subject listings as dashes (--MAR2020). Dates that are missing because they are not applicable for the subject are output as"NA", unless otherwise specified.

f) Time should be printed in SAS® TOD5.format ("HH:MM": 17:30). Missing portions of time should be represented on subject listings as dashes (--:30). Times that are missing because they are not applicable for the subject are output as "NA", unless otherwise specified.

11.3. 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

11.4. Table, Listing, and Figure Format

11.4.1. General

- All TFLs will be produced in landscape format on A4 (ISO 216 standard), unless otherwise specified.
- All TFLs will be produced using the Times new Roman, size 10.
- 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 Times new Roman, size 10.
- 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 (see below).
- 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.

11.4.2. Headers

- All output should have the following header at the top left of each page:

- Aquestive Therapeutics; Protocol Number: 42-1703
- 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.

Aquestive Therapeutics	Confidential	Page n of N
Protocol Number: 42-1703		Final/Draft Output

11.4.3. 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.
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z: First Line of Title (Analysis Set)
Second Line of Title if Needed

11.4.4. 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).

11.4.5. Body of the Data Display

11.4.5.1. 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.

11.4.5.2. 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
Minimum	XXX
Maximum	XXX

- If there is only 1 data point i.e. n=1 then only n and mean (=data) will be shown. If unavoidable show “-“(hyphen) in all other places.

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every-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.

11.4.5.3. 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 "NA", with the footnote "NA = not applicable", whichever is appropriate.

- Dates should be printed in SAS® date9.format ("DDMMMYYYY": 23MAR2020). Missing portions of dates should be represented on subject listings as dashes (--MAR2020). Dates that are missing because they are not applicable for the subject are output as"NA", 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.

- Full page utilization in sense of line numbers are expected.

- If any of the selection within columns/subheaders are continuing into next page please mark (cont.) in the next page.

11.4.5.4. 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.

11.4.6. 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 source listing(if table or figure), the name of the program used to produce the data display, the name of the ADaM dataset used, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas ADaM: xxxxx Listing source: 16.x.y.z’) in following order:

For tables and Figures:
Data Source: Listing XXXX Program:XXXX.sas ADaM: ADxxx Table Generation: ddmmmyyyy/hh:mm
For Listings:
Program:XXXX.sas ADaM: ADxxx Listing Generation: ddmmmyyyy/hh:mm

12. 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."