PROTOCOL 180323
AMENDMENT III

IND Number: 129068

A RANDOMIZED, OPEN-LABEL, 2-SEQUENCE, 3-TREATMENT, CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS OF SINGLE DOSES OF DIAZEPAM BUCCAL FILM (DBF) (AQUESTIVE THERAPEUTICS) COMPARED WITH DIASTAT® RECTAL GEL (VALEANT PHARMACEUTICALS NORTH AMERICA) IN ADULT MALE AND FEMALE SUBJECTS ON A CONCOMITANT REGIMEN OF ANTIEPILEPTIC DRUGS (AED) FOR THE TREATMENT OF EPILEPSY

Contract Research Organization:
inVentiv Health Clinique inc.
(« inVentiv »), a Syneos Health company

2500, rue Einstein
Québec (Québec)
Canada, G1P 0A2
Tel.: 1-418-527-4000

Sponsor:
Aquestive Therapeutics

30 Technology Drive
Warren, NJ 07059
USA
Tel.: 908-941-1900

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Protocol Historical File

Version number	Brief description/summary of changes	Date
Final	Version submitted to the IEC.	16-JAN-2019
Amendment I	Changes included in Amendment I: The following changes were brought to the study protocol as required by the Advarra institutional review board (IRB): 1. Female contraception duration was extended to 51 days and male contraception to 111 days following the last study drug administration, due to the half-life of the study drug. In addition, the sperm donation restriction was revised from 105 days to 111 days after the last study drug administration. 2. The exclusion criteria were revised to exclude subjects with any clinically significant rectal abnormality or any condition for which administration of rectal gel would cause a potential risk. 3. Baseline levels assessment of the concomitant antiepileptic drug(s) (AED) was added at screening. The AED level(s) must be within an acceptable therapeutic range. 4. The use of any AED of the benzodiazepine class (other than diazepam administered as study drug) is prohibited during the study. For all the pharmacokinetic (PK) blood samples to be collected as return visits, it is clarified that subjects may have the blood sample collected at home by a home care nurse. Information was added to section 9.13 Adverse Events in order to clarify the adverse events recording, follow up, and reporting process. Contact information was added for the Sponsor's safety representative.	19-FEB-2019
Amendment II	Changes included in Amendment II: Subjects who complete study periods 1 and 2 may volunteer to participate in a third period where they would receive a second dose of DBF administered following a high-fat meal. Details on clinical sites and biomedical laboratories names and locations have been removed from the protocol. Any flexibility in the washout duration was excluded since a	07-MAR-2019

	washout period of no more than 28 days must be used in this study. The smoking restriction period of at least 2 hours prior to until 4 hours after study drug administration has been removed from the protocol. Smoking is allowed on study and the restriction period around the dosing procedures will be managed by each clinical site. In case of a positive result to the urine benzodiazepine (drug) screen in periods 2 and 3, continuous subject participation in the study will be evaluated by the Principal Investigator. In addition, some minor editorial changes and clarifications have been made throughout the document, such as sentence clarifications, corrections of typographical or punctuation errors.	
Amendment III	See below for a description of changes.	24-MAY-2019

Changes included in Amendment III:

The following changes were brought to the study protocol Amendment II dated 07-MAR-2019:

The sample size has been increased to a maximum of 32 subjects. Moreover, since only exploratory pharmacokinetic data will be gathered from treatment period 3 (DBF administration following a high-fat-meal), no more than 50% of the subjects should receive this treatment. This involves changes to the following sections:

- page 9, section 2 Synopsis of Protocol - Study Design and Subjects;
- page 30, section 7 Study Design;
- page 31, section 8.1 Sample Size.

A discrepancy has been corrected on page 43, under section 9.9.4 DBF Application Site Inspection.

The urobilinogen has been removed from the urinalysis routine tests to be performed at screening and at study exit. The change was made on page 43, section 9.9.7.4 Urinalysis.

Sponsor's Signature Page

Aquestive Therapeutics

30 Technology Drive
Warren, NJ 07059
USA
Tel.: 908-941-1900

Sponsor's representatives:

Allen H. Heller

5/24/2019

Allen H Heller, MD, MPH
Founder and CEO, Pharma Study Design LLC
(Consultant to Aquestive Therapeutics)

Date

for Dan Barber

5/24/2019

Dan Barber, Vice-President Value Creation
Aquestive Therapeutics

Date

Investigator's Signature Page

I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with ICH Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and all other applicable regulations.

_____ _____
Investigator signature Date

_____
Investigator printed name

_____
Name of clinical facility

_____
Location of facility
(City, state, country)

1. Facilities and Responsible Staff

1.1 Clinical Research Organization (CRO)

inVentiv Health Clinique inc. (« inVentiv »), a Syneos Health company
2500, rue Einstein
Québec (Québec)
Canada, G1P 0A2
Tel.: 1-418-527-4000

1.2 Clinical Research Sites

This study will be conducted at multiple clinical facilities. Any clinical research sites involved in this study will be documented and communicated to the Ethic committee.

1.3 Biomedical Laboratory Facilities

Biomedical laboratories involved in clinical laboratory testing will be documented by the clinical research sites.

1.4 Clinical Pharmacology

inVentiv
2500, rue Einstein
Québec (Québec), Canada, G1P 0A2
Tel.: 1-418-527-4000

Pierre-Olivier Tremblay, M.Sc.
Vice-President, Clinical Pharmacology & Data Services

France Nadeau, B.Sc.
Senior Clinical Research Scientist (Protocol Editing)

1.5 Bioanalytical Facility

inVentiv
2500, rue Einstein
Québec (Québec), Canada, G1P 0A2
Tel.: 1-418-527-4000

Clark V. Williard, B.S.
Executive Director, Mass Spectrometry Operations

1.6 Medical Monitor

Dr. Heidi Mitchell, MD
Syneos Health

Table of Contents

2. Synopsis of Protocol

Project No.:	180323
Objectives:	Primary objective: • Evaluate the pharmacokinetics (PK) of single doses of Diazepam Buccal Film (DBF) at the recommended dose regimen (range 10 mg to 17.5 mg according to body weight) compared with Diastat® (DRG) at the labeled dose regimen (range 10 mg to 20 mg according to body weight) in adult male and female subjects on a stable concomitant regimen of antiepileptic drugs (AED) for the treatment of epilepsy, following a moderate-fat meal. Secondary objectives: • Evaluate the PK of single doses of DBF following a high-fat meal compared with DRG following a moderate-fat meal at the recommended dose regimen in adult male and female subjects on a stable concomitant regimen of AED for the treatment of epilepsy. • Assess the safety-tolerability of single doses of DBF and DRG administered to adult male and female subjects on a stable concomitant regimen of AEDs under fed conditions.
Study Design:	Randomized, multiple centers, single-dose, open-label, three-period, three-treatment, two-sequence crossover study under fed conditions. Periods 1 and 2: Each subject will receive both DBF and DRG in a randomized sequence following a moderate-fat meal administered according to weight category. DBF will be administered according to the currently recommended dose regimen (derived by Aquestive from population PK modeling in healthy volunteers). DRG will be administered depending on weight category according to the current product labeling for Diastat®. Period 3: **Subjects may be asked to participate in period 3.** Subjects who volunteer to participate in Period 3 will receive a second dose of DBF administered in exactly the same manner as the earlier dose of DBF with the exception that DBF in Period 3 will be administered following a high-fat meal.
Subjects:	**No more than 32** male and female volunteers, ≥ 18 and ≤ 65 years of age, smoker and/or non-smoker, with body weight between 38 and 134 kg (83 -294 lbs.) on a concomitant stable regimen including one or more AED. A stable regimen of AED is defined as no change in the prescribed AED regimen during the 30-day period prior to the first study drug administration and no change anticipated in the prescribed AED regimen over the course of study participation until the last PK blood sample collection. Eligible subjects will be enrolled in an effort to complete Period 2 with at least 16 subjects with representation of both genders, representation across the five weight categories of subjects taking one or more AED known to induce diazepam metabolism, and representation of subjects taking sodium divalproex/valproic acid. Subjects who are eligible may be enrolled without regard to weight category. **Since only exploratory PK data will be gathered from treatment period 3, no more than** 50% of the subjects who complete Period 1 and Period 2 will participate in Period 3.
Screening Procedures:	Demographic data, medical and medication histories, physical examination, brief neurologic examination, body measurements, oral cavity examination, electrocardiogram (ECG), vital signs (blood pressure [BP], heart rate [HR], and respiratory rate [RR]), oral temperature, digital oxygen monitoring, hematology,

<table>
<tr><td></td><td>biochemistry, HIV, hepatitis B and C tests, urinalysis, baseline AED levels*, alcohol breath test, urine pregnancy test, and urine drug screen.

*Unless baseline levels of concomitant AED were obtained within one year prior to the first dosing and show levels within an acceptable therapeutic range.</td></tr>
<tr><td>Confinements, Visits, and Washout:</td><td>For each period, subjects will be confined from approximately 14 hours before dosing until after the 24-hour post-dose blood draw. For subsequent blood draw, subjects may come back to the clinical site or have the blood sample collected at home by a home care nurse.

There will be a washout period of 28 days between doses.</td></tr>
<tr><td>Drug Administration:</td><td>In Period 1 and Period 2, subjects will receive Treatment A and Treatment B following a moderate-fat meal, in a randomized sequence. Subjects who volunteer to participate in Period 3 will receive DBF following a high-fat meal. In each period, subjects will receive a single dose according to body weight, as described in the following table:
<table>
<tr><th>Product</th><th>Meal Condition</th><th>Weight Category</th><th>Weight (kg)</th><th>Dose</th></tr>
<tr><td rowspan="5">Test (Treatment A):
Diazepam Buccal Film (Aquestive Therapeutics, USA)</td><td rowspan="5">Moderate-Fat Meal</td><td>A1</td><td>38-50</td><td>1 x 10 mg</td></tr>
<tr><td>A2</td><td>51-62</td><td>1 x 12.5 mg</td></tr>
<tr><td>A3</td><td>63-75</td><td>1 x 15 mg</td></tr>
<tr><td>A4</td><td>76-87</td><td>1 x 15 mg</td></tr>
<tr><td>A5</td><td>88-111*</td><td>1 x 17.5 mg</td></tr>
<tr><td rowspan="5">Reference (Treatment B):
Diastat® AcuDial™ rectal gel (Valeant Pharmaceuticals</td><td rowspan="5">Moderate-Fat Meal</td><td>B1</td><td>38-50</td><td>2 mL (10 mg)</td></tr>
<tr><td>B2</td><td>51-62</td><td>2.5 mL (12.5</td></tr>
<tr><td>B3</td><td>63-75</td><td>3 mL (15 mg)</td></tr>
<tr><td>B4</td><td>76-87</td><td>3.5 mL (17.5</td></tr>
<tr><td>B5</td><td>88-111*</td><td>4 mL (20 mg)</td></tr>
<tr><td rowspan="5">Test (Treatment C):
Diazepam Buccal Film (Aquestive Therapeutics, USA)</td><td rowspan="5">High-Fat Meal</td><td>A1</td><td>38-50</td><td>1 x 10 mg</td></tr>
<tr><td>A2</td><td>51-62</td><td>1 x 12.5 mg</td></tr>
<tr><td>A3</td><td>63-75</td><td>1 x 15 mg</td></tr>
<tr><td>A4</td><td>76-87</td><td>1 x 15 mg</td></tr>
<tr><td>A5</td><td>88-111*</td><td>1 x 17.5 mg</td></tr>
</table>
*Subjects eligible for study with weights in the range of 112 to 134 kg will be dosed at the 88-111 kg weight range as shown above.

After a supervised fast of at least 10 hours, subjects will be served a standardized moderate-fat meal (in Periods 1 and 2) or a high-fat high-calorie meal (in Period 3). Drug administration will occur approximately 30 minutes after the meal has been started.

No water will be allowed during the DBF administration and for at least 15 minutes following DBF administration. Water will be allowed ad libitum at all other times.

DBF ease of use will be evaluated by the clinical staff and the subjects following the first film administration in Period 1 or Period 2. Questions regarding past experience in using DRG or other rescue medication for the treatment of epilepsy</td></tr>
</table>

	will also be asked to subjects, prior to DRG administration. Questions are listed in Appendix I – Diazepam PK Study Participant Questions.
Study Restrictions:	Subjects will be asked to refrain from using products that may potentially affect their safety and/or the pharmacokinetic profile of the study drug. For the complete list of restrictions refer to Appendix II – Study Restrictions. Main study restrictions include: • Any benzodiazepines (other than study drug), phenothiazines, or strong inhibitors of cytochrome P450 (CYP) enzymes (e.g. cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, itraconazole, diltiazem, and HIV antivirals), from 30 days prior to the first dosing until after the last PK blood sample collection of the study. Strong inducers of CYP enzymes (e.g. barbiturates, carbamazepine, glucocorticoids, phenytoin, phenobarbital, St. John´s Wort, rifampicin) and AEDs known to induce CYP enzymes are permitted provided that the regimen of such drugs is stable (taken at least once a day [q.d]. on a regular basis) within 30 days prior to first study drug administration and until at least 10 days after last study drug administration; • Any prescription medication (other than non-systemic topical products) within 30 days prior to first study drug administration. Prescription drugs (other than any benzodiazepines, phenothiazines, and strong inhibitors of CYP enzymes) that is part of a stable drug regimen (taken at least q.d. on a regular basis) are allowed if taken from at least 30 days prior to the first study drug administration and if there is no expected change in dosage throughout the study. • Over-the-counter (OTC) medications (other than spermicidal/barrier contraceptive products and non-systemic topical products), within 30 days prior to first study drug administration. OTC drugs that is part of a stable drug regimen (taken at least q.d. on a regular basis) is allowed if taken from at least 30 days prior to the first study drug administration and if there is no expected change in dosage throughout the study. • Natural health products (including oral multivitamins, herbal and/or dietary supplements and/or teas) from 30 days pre-dose until after the last PK blood sample collection of each period. • For females, oral or transdermal hormonal contraceptives within 30 days prior to first study drug administration until after the last PK blood sample collection of each period. Oral or transdermal hormonal contraceptives with a 28-days treatment cycle taken daily from at least 30 days prior to the first study drug administration will be allowed if there is no expected change in dosage throughout the study; • For females, implanted, injected, or intravaginal contraceptive within 6 months prior to first study drug administration until after the last PK blood sample collection of each period; • Monoamine oxidase (MAO) inhibitors from 30 days prior to the first dosing until 14 days after the last study drug administration; • Use of marijuana and THC containing products within 3 months prior to screening unless such products are a part of the subject's stable antiepileptic regimen; • Food containing poppy seeds from 48 hours pre-dose; • Food or beverages containing caffeine/methylxanthines derivatives or energy drinks from 48 hours prior to dosing until after the last PK blood

	sample collection of each period; • Food or beverages containing grapefruit, star fruit, and/or pomelo from 30 days pre-dose until after the last PK blood sample collection of the study; • Alcohol-based products from 48 hours pre-dose until after the last PK blood sample collection of each period. Diazepam may cause sedation. Consistent with intended use of DBF and the use of DRG subjects should be in a safe comfortable position (sitting or reclining in bed) for at least one hour after dosing to allow for an assessment of drug effect including sedation. After one hour and depending on the assessment of the investigator/clinical staff, the subject may be permitted to ambulate provided that ambulation does not interfere with study procedures. Vital signs should be taken in a consistent position (sitting or reclining). Subject visits to the bathroom or washroom will be monitored by clinic staff for 4 hours after each study drug administration, and the following information will be recorded: whether the subject urinated, defecated, or vomited. Subjects will be instructed not to flush if they vomit. Vomitus will be verified and noted in the subject's file for further evaluation if needed. Subjects will be advised to avoid performing vigorous physical activities (e.g., intense or long-distance running or biking, etc.) at all times during the study duration (from at least 5 days prior to admission), including the washout period.
Sample Collection:	A total of 19 blood samples will be collected in each period: at pre-dose and (± 1 minute) 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, (± 3 minutes) 9, 12, 24, (± 60 minutes) 48, 72, 96, 120, 144, 192, and 240 hours post-dose.
Subject Safety:	Continuous cardiac ECG monitoring: from approximately 1 hour prior to dosing until 8 hours post-dose (and beyond if clinically indicated). Vital signs and digital oxygen monitoring before dosing and approximately 0.5, 1, 1.5, 2, 4, and 8 hours post-dose (and beyond if clinically indicated). Vital signs will also be recorded at approximately 12 and 24 hours post-dose. Serum pregnancy test (for women): before dosing Alcohol breath test and urine drug screen: before dosing. Medical surveillance: Subjects will be monitored throughout the study by the clinical staff for adverse events. In each period, the investigator will be on site for drug administration and until 8 hours post-dose, and available on call for the remainder of the study.
DBF Application Site Inspection:	DBF application site will be inspected at screening, prior to DBF administration, and approximately 6 and 24 hours after DBF administration to evaluate the oral mucosa (normal/abnormal). Assessments will be conducted by the Principal Investigator/Sub-Investigator or a trained nurse.
Study Exit Procedures:	Physical examination, brief neurologic examination, hematology, biochemistry, urinalysis, vital signs (BP, HR, and RR), oral temperature, digital oxygen monitoring, ECG, oral temperature, urine pregnancy test, and adverse events monitoring.
Analytical Method:	The Bioanalytical Division of inVentiv will analyze diazepam and nordiazepam in plasma samples using a validated method.
Pharmacokinetics:	Parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, Residual area, T_{max}, $T_{½\ el}$, K_{el}, Cl/F, V_d/F, Cl/F/kg, and V_d/F/kg.

	Data from nordiazepam will be reported and presented as supportive data.
Statistical Analyses:	Pharmacokinetics: For diazepam and nordiazepam, using GLM procedures in SAS, ANOVA will be performed on untransformed T_{max}, K_{el}, and $T_{½\ el}$ and on ln-transformed AUC_{0-t}, AUC_{0-inf}, C_{max}, Cl/F, Cl/F/kg, V_d/F, and V_d/F/kg at the alpha level of 0.05. Factors incorporated in the model will include: Sequence, Subject(Sequence), Period, and Treatment. T_{max} will be analyzed using an additional non parametric test (Wilcoxon signed-rank test). **Treatment Comparison Following a Moderate-Fat Meal:** The ratio of geometric means will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max} for the Test product versus the Reference product (A/B) irrespective of weight category. The 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln transformed data will also be calculated. Intra and inter-subject coefficient of variation will be estimated. **Treatment Comparison Following Different Meal Conditions:** An exploratory pair-wise analysis comparing DBF following a high-fat meal (Treatment C) with DRG following a moderate-fat meal (Treatment B) will also be conducted and reported. Additional analyses may be performed. Details of the pharmacokinetic and statistical analyses will be provided in the statistical analysis plan (SAP). Safety and tolerability: Treatment-emergent AEs will be tabulated by treatment. Changes from baseline values in vital signs, ECG, and clinical laboratory parameters will be evaluated. Safety and tolerability data will be reported using descriptive statistics. Details of the safety and tolerability analyses will be provided in the SAP.

3. List of Abbreviations

AE	Adverse Event
AED	Antiepileptic drug
ANOVA	Analysis of variance
AUC	Area Under the Concentration-time Curve
$AUC_{0\text{-}inf}$	Area Under the Concentration-time Curve From Time Zero to Infinity (extrapolated)
$AUC_{0\text{-}t}$	Area Under the Concentration-time Curve From Time Zero to the Last Non-zero Concentration
BA	Bioavailability
BP	Blood Pressure
CK	Creatine Kinase
Cl/F	Apparent Total Clearance (L/hr) estimated from dose/$AUC_{0\text{-}inf}$
Cl/F/kg	Apparent Total Clearance/kg (L/hr) estimated from dose/kg/$AUC_{0\text{-}inf}$
C_{max}	Maximum Observed Concentration
CRO	Contract Research Organization
CRF	Case Report Form
CYP	Cytochrome P450
DBF	Diazepam Buccal Film
DRG	Diastat® rectal gel
ECG	Electrocardiogram
EDC	Electronic data capture
FDA	Food and Drug Administration
g	Grams
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethic Committee
IND	Investigational new drug
IRB	Institutional Review Board
lbs.	pounds
K_{el}	Elimination Rate Constant
kg	Kilogram
kg/m^2	Kilogram/Meter Squared
MDMA	Methylene Di-Methamphetamine (Ecstasy)
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliters
msec	Millisecond

mmHg	Millimeter of Mercury
MAO	Monoamine oxidase
N/A or NA	Not applicable, Not Available
NDA	New drug application
PCP	Phencyclidine
PK	Pharmacokinetic
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
QTcF	Fridericia's Corrected QT Interval
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD or STD	Standard Deviation
SOC	System Organ Classification
SOP	Standard Operating Procedure
SARS	Severe Acute Respiratory Syndrome
$T_{½\ el}$	Terminal elimination half-life, estimated as $\ln(2)/K_{el}$
THC	Tetrahydrocannabinol
Temp	Temperature
T_{max}	Time when the maximal plasma concentration is observed
UBG	Urobilinogen
U.S.	United States
V_d/F	Apparent Volume of distribution (L) estimated from Cl/K_{el} (β)
$V_d/F/kg$	Apparent Volume of distribution/kg (L) estimated from Cl/K_{el} (β)/kg

4. Schedule of Events

PROCEDURE	Screening	Periods 1, 2 & 3				Study Exit
		D-1	D1	D2	D3-D11	
Demographic Data	X					
Medical and Medication Histories	X					
Review and Monitoring of AEs and Concomitant Medications		X	X	X	X	X
Physical Exam and Brief Neurologic Exam	X					X
Body Measurements	X					
Oral Temperature	X					X
Vital signs (BP, HR, RR)	X		X[1]	X[2]		X
Digital Oxygen Monitoring	X		X[1]			X
Continuous Cardiac ECG Monitoring			X[3]			
ECG	X					X
Hematology	X					X
Biochemistry	X					X
HIV and Hepatitis	X					
Urinalysis	X					X
Baseline AED Levels Assessment[4]	X					
Urine Drug Screen	X	X				
Alcohol Breath Test	X	X				
Serum Pregnancy Test		X				
Urine Pregnancy Test	X					X
Confinement		X	X			
Drug Administration[5]			X			
Visual Inspection of DBF Application Site	X		X[6]	X[6]		
PK Samples[7]			X	X	X	

1 Vital signs and digital oxygen monitoring before dosing and approximately 0.5, 1, 1.5, 2, 4, and 8 hours post-dose (and beyond if clinically indicated).

2 Vital signs approximately 12 and 24 hours post-dose.

3 Continuous cardiac ECG monitoring: from approximately 1 hour pre-dose until 8 h after dosing (and beyond if clinically indicated).

4 Unless baseline levels of concomitant AED was obtained within one year prior to the first dosing and show levels within an acceptable therapeutic range.

5 Questions regarding past experience in using DRG or other rescue medication for the treatment of epilepsy will be asked to subjects prior to DRG administration. DBF ease of use will be evaluated by the clinical staff and the subjects following the first film administration (in Period 1 or Period 2).

6 A visual inspection of the application site will be conducted prior to DBF administration and approximately 6 and 24 hours after DBF administration to evaluate the oral mucosa (normal/abnormal).

7 Blood samples: pre-dose and (± 1 minute) 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, (± 3 minutes) 9, 12, 24, (± 60 minutes) 48, 72, 96, 120, 144, 192, and 240 hours post-dose.

5. Introduction

5.1 Background on Treatment and Management of Individuals with Refractory Epilepsy

Acute repetitive seizures, including breakthrough seizures, repetitive seizures, and seizure clusters occur in a significant number of epilepsy patients who are on established antiepileptic drug treatment. These types of seizures have distinguishable characteristics that are usually recognized by patients, caregivers, and physicians.

Although patients typically recover between seizures, these seizures can last from minutes to hours. When these seizures occur outside a hospital, the patient is often transported to an acute care facility for treatment to prevent prolonged seizures. If treatment is not prompt and effective there is a risk that seizure activity will continue, and may become life threatening, including the risk of status epilepticus. In these cases, the primary goals of the treatment are seizure cessation and prevention of seizure recurrence. Usually, acute benzodiazepine treatment is effective for seizure control and often results in rapid seizure termination. Nevertheless, many treatment options rely on appropriate intervention by medical personnel, and treatment may be delayed while the patient is transported to a medical facility.[1]

Outpatient treatment for these types of seizures may reduce emergency medical intervention, decrease seizure duration, prevent general deterioration due to the repeated seizures and improve the quality of life of these patients.

5.2 Diazepam

Diazepam is a benzodiazepine that exerts anxiolytic, sedative, muscle-relaxant, anticonvulsant, and amnestic effects. Most of these effects are thought to result from a facilitation of the action of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.[2]

Diazepam is a Schedule IV controlled substance approved for the treatment of anxiety, acute alcohol withdrawal, skeletal muscle spasm, and convulsive disorders. Diazepam is used as adjunctive treatment of seizures other than status epilepticus in selected, refractory patients with partial seizures or generalized tonic-clonic seizures who require intermittent use of diazepam to control bouts of increased seizure activity.[2] It is used off-label for numerous other conditions including insomnia, restless leg syndrome, and pre-/post-operative sedation.

Diazepam can be taken by mouth, inserted into the rectum, injected into muscle, or injected intravenously. When given intravenously, effects begin in one to five minutes. When diazepam is taken orally, effects may be delayed as long as 40 minutes.[1]

Intravenous diazepam is a first-line treatment for status epilepticus. Diazepam gel has been demonstrated superior to placebo gel in reducing the risk of continuing seizures. Diazepam is rarely used for the long-term treatment of epilepsy because tolerance to its anticonvulsant effects develops over time with continuous treatment. However, diazepam is effective when used intermittently for the prevention of repeated seizures. Like other benzodiazepines, diazepam administration may cause sedation, anxiolysis, and amnesia.[1]

5.2.1 Mechanism of Action

Diazepam is a benzodiazepine derivative that exhibits anti-anxiety, sedative, hypnotic and anticonvulsant properties. Although the precise mechanism by which diazepam exerts its anti-seizure effects is unknown, animal and in vitro studies suggest that diazepam acts to suppress seizures through an interaction with γ-aminobutyric acid (GABA) receptors of the A-type ($GABA_A$).[3] $GABA_A$ receptors mediate the sedative, anterograde amnesic, anticonvulsive, anxiolytic, muscle relaxant, and temporal/spatial memory effects of benzodiazepines.[1] It is believed that diazepam enhances the actions of GABA by causing GABA to more tightly bind to the $GABA_A$ receptors located within the limbic system, including areas of the thalamus and hypothalamus.

GABA, the major inhibitory neurotransmitter in the central nervous system, acts at these receptors to open the membrane channel, and allows chloride ions to flow into neurons. Excessive neuronal depolarization is implicated in the generation and spread of seizures.[3] Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials, ultimately leading to membrane hyperpolarization and a decrease in neuronal excitability.

5.2.2 Metabolism and Elimination

Diazepam is extensively metabolized to one major active metabolite (N-desmethyldiazepam [nordiazepam]) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) in plasma. At therapeutic doses, under steady state conditions, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam, while oxazepam and temazepam are not usually detectable. Both diazepam and desmethyldiazepam bind extensively to plasma proteins (95-98%).[3]

The volume of distribution of Diastat rectal gel is calculated to be approximately 1 L/kg. Following rectal administration of a 15 mg dose of Diastat, the mean elimination half-life was reported to be about 46 hours (CV=43%) for diazepam and 71 hours (CV=37%) for desmethyldiazepam.[3] After oral administration, the initial distribution phase is followed by a prolonged terminal elimination phase, with a half-life up to 48 hours, and the terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours.[4]

The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no activity and are “poor metabolizers”) and CYP3A4. No inhibition was demonstrated in the presence of inhibitors selective for CYP2A6, CYP2C9, CYP2D6, CYP2E1, or CYP1A2, indicating that these enzymes are not significantly involved in metabolism of diazepam.[3]

Diazepam and its metabolites are excreted mainly in the urine, predominantly as their glucuronide conjugates.[4]

5.2.3 Pharmacokinetics

Following rectal administration, diazepam is well absorbed, reaching peak plasma concentrations in 1.5 hours,[3] and the absolute bioavailability of Diastat rectal gel relative to Valium injectable is 90%.

After Valium oral administration, the average time to achieve peak plasma concentrations is 1–1.5 hours, with a range of 0.25 to 2.5 hours, and more than 90% of diazepam is absorbed. Valium absorption is delayed and decreased when diazepam is administered with a moderate-fat meal. In the presence of food, mean lag times are approximately 45 minutes as compared with 15 minutes when fasting. There is also an increase in the average time to achieve peak concentrations to about 2.5 hours in the presence of food as compared with 1.25 hours when fasting. This results in an average decrease in C_{max} of 20% in addition to a 27% decrease in area under the plasma concentration-time curve (AUC; range 15% to 50%) when administered with food.[4]

5.3 Diastat® AcuDial™

Diazepam rectal gel administered after the onset of acute repetitive and prolonged seizures has been shown to significantly reduce seizure recurrence and emergency department admissions. Nonetheless, social objections to and legal concerns about rectal administration have limited its use.[1]

The rectal route of administration of diazepam is not ideal. First, it entails the need to expose and appropriately position a patient in order to administer drug, both of which can be time consuming, with a potential delay of time to treatment. Successful use of a rectal product also is dependent upon the competence of the caregiver and requires training in the correct administration of the gel. Improper technique could lead to patient injury and leakage of gel from the rectum can result in incomplete dosing. Additionally, the attitude of many patients toward a rectal route of drug administration is unfavorable, which may impact compliance to treatment. Each of these factors has a potential impact on usability and morbidity. Persistent seizure activity is associated with worse outcomes across a spectrum of precipitating conditions. In addition, experimental models of status epilepticus have demonstrated that the effectiveness of anticonvulsant medication to terminate seizures rapidly decreases as the time between the start of convulsions and drug administration lengthens. Further, it has been demonstrated that if seizures are not terminated quickly, escalating doses of benzodiazepines are required to achieve seizure cessation and seizures may become refractory to anticonvulsant therapy.[1]

A need for better, more patient-friendly therapies for seizure emergencies such as prolonged seizures, acute repetitive seizures, or status epilepticus has resulted in development of innovative benzodiazepine formulations using non-rectal routes.[1]

5.4 Diazepam Buccal Film (DBF)

One new route of diazepam administration is via buccal soluble film. Buccal soluble diazepam (DBF) may be particularly well-suited for administration in outpatient settings. The study drug is administered by placing the film against the inner aspect of the cheek, where it adheres, and allows for transbuccal absorption of diazepam. There is no need to position or disrobe the subject. Additionally, there is less potential for delay in initial treatment and greater subject and caregiver acceptance with improved compliance may also be expected.

The development of DBF will meet the treatment need for a form of diazepam that is effective, safe, allows for reliable dose administration, and is easier to administer than the rectal gel in a subset of epileptic subjects. Subjects, caregivers, and physicians have indicated that this type of product would be desirable for acute, intermittent treatment of breakthrough, repetitive or cluster seizures. The clinical trials with DBF have focused on assessing its relative bioavailability to the reference therapy, Diastat® AcuDial™ rectal gel, dose proportionality, assessment of food effect, and the pharmacokinetics in subjects with epilepsy. Overall safety and tolerability have been assessed in clinical trials conducted with DBF.

Aquestive Therapeutics initiated development of DBF, specifically intended for buccal delivery for subjects who require control of intermittent bouts of seizure activity. DBF contains the Food and Drug Administration (FDA) approved active ingredient diazepam, a benzodiazepine, as a treatment for the management of selected, refractory subjects with epilepsy, on stable regimens of antiepileptic drugs who require intermittent use of diazepam to control bouts of increased seizure activity. The study drug, with a planned dose range of 5 mg to 17.5 mg, is expected to achieve peak plasma concentrations of diazepam equivalent to the reference therapy, Diastat® AcuDial™ rectal gel. The DBF product is intended for submission as a 505(b)(2) New Drug Application (NDA) using Diastat® AcuDial™ rectal gel as the reference therapy.

5.5 Background on Diazepam Buccal Film (DBF)

Diastat® AcuDial™ rectal gel is prescribed for increased seizure activity as defined by a marked increase in seizure activity, sometimes heralded by non-convulsive symptoms that are characteristic for each subject and deemed by the prescriber to be the kind of seizure for which a benzodiazepine would be administered.[3] Diastat® AcuDial™ rectal gel has been marketed in the US since 1997 and currently is the only FDA approved drug in the US for this indication.

Though the Diastat® AcuDial™ rectal gel formulation is considered safe and effective, the route of administration is less than ideal. The mechanics of administering a rectal gel can be a difficult, time-consuming, and embarrassing experience for both subject and care-givers alike. For example, the subject or caregiver must first remove articles of clothing and then place the subject in an appropriate position. The Diastat® AcuDial™ rectal gel syringe tip is inserted into the rectum to a specific depth and the gel expressed into the rectal vault. However, improper technique can lead to subject injury, and leakage of gel from the rectum can result in incomplete dosing. Additionally, some subjects have a negative view of the rectal route of administration, and this may reduce compliance to treatment. Each of these factors has a potential influence on subject morbidity. Persistent seizure activity is associated with less favorable outcomes across a spectrum of precipitating conditions. Further, it has been demonstrated that if seizures are not terminated quickly, escalating doses of benzodiazepines are required to achieve seizure cessation and seizures may become refractory to anticonvulsant therapy.

The DBF is intended for application to the inner aspect of the cheek where it adheres, dissolves, and releases the drug into the buccal mucosa. Though buccal absorption is expected as the primary route of absorption of the drug, some absorption through the gastrointestinal (GI) tract may be possible due to swallowing of some dissolved drug substance in the saliva. It is expected that that timing of use of the buccal film will be similar to the use of Diastat® AcuDial™ rectal gel, i.e., the film would be administered after a seizure with characteristics for which the Reference Listed Drug (RLD) would be indicated.

5.5.1 Nonclinical Studies

Mechanism of Action: Diazepam is a benzodiazepine derivative that exhibits anti-anxiety, sedative, hypnotic and anticonvulsant properties. Although the precise mechanism by which diazepam exerts its anti-seizure effects is unknown, animal and in vitro studies suggest that diazepam acts to suppress seizures through an interaction with γ-aminobutyric acid (GABA) receptors of the A-type ($GABA_A$).[3] $GABA_A$ receptors mediate the sedative, anterograde amnesic, anticonvulsive, anxiolytic, muscle relaxant, and temporal/spatial memory effects of benzodiazepines.[1] It is believed that diazepam enhances the actions of GABA by causing GABA to more tightly bind to the $GABA_A$ receptors located within the limbic system, including areas of the thalamus and hypothalamus.

GABA, the major inhibitory neurotransmitter in the central nervous system, acts at these receptors to open the membrane channel, and allows chloride ions to flow into neurons. Excessive neuronal depolarization is implicated in the generation and spread of seizures.[3] Entry of chloride ions causes an inhibitory potential that reduces the ability of neurons to depolarize to the threshold potential necessary to produce action potentials, ultimately leading to membrane hyperpolarization and a decrease in neuronal excitability.

Metabolism and Elimination: It has been reported in the literature that diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam). With steady state dosing, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in the literature is probably attributable to variability of CYP2C19 (which is known to exhibit genetic polymorphism; about 3-5% of Caucasians have little or no CYP2C19 activity and are "poor metabolizers") and CYP3A4. No inhibition was demonstrated in the presence of inhibitors selective for CYP2A6, CYP2C9, CYP2D6, CYP2E1, or CYP1A2, indicating that these enzymes are not significantly involved in metabolism of diazepam.[3]

5.5.2 Clinical Studies

As of December, 2018, six clinical studies in healthy adult volunteers have been completed with the DBF product. These comprise two bioavailability pilot studies in comparison with Diastat gel® (1899 and 1900), a dose-proportionality study (162013), a bioavailability study in comparison with Diastat® gel (162021), and two food effect studies. A two-arm food effect study investigated the effect of a high fat meal (Study 162022). A four-arm food effect study compared the pharmacokinetics of diazepam (A) fasting in an upright position after dosing (B) fasting in a reclining position after dosing (C) Following a high fat meal in a reclining position after dosing (D) Following a moderate fat meal in a reclining position after dosing (Study172018).[1]

5.5.2.1 Safety in Clinical Studies

It is anticipated that the adverse event (AE) profile from systemic exposure observed with study drug will resemble the already well-known profile for diazepam in general and the reference therapy, Diastat® AcuDial™ rectal gel, in particular. Diazepam rectal gel AE data were collected

from double-blind, placebo-controlled studies and open label studies with 573 subjects exposed to diazepam rectal gel. The majority of AEs were mild to moderate in severity and transient. The most frequent AE reported with diazepam rectal gel in the two double-blind, placebo-controlled studies was somnolence (23%). Less frequent AEs were headache (≤5%), diarrhea (≤4%), ataxia (≤3%), dizziness (≤3%), euphoria (≤3%), incoordination (≤3%), rash (≤3%), vasodilatation (≤2%), and asthma (≤2%).[3]

In the 6 completed DBF studies, there have been a total of 154 subjects enrolled, with 132 subjects (65.9% male, 34.1% female; age range 19-64) having received at least one dose of study drug. A total of 268 doses of DBF and 119 doses of Diastat® AcuDial™ were administered.[1]

Sixty-five percent of all administrations of DBF (n = 175) and 63.9% (n=78) of Diastat administrations were followed by one or more Treatment Emergent Adverse Events (TEAE). A total of 252 TEAEs were reported following administrations of DBSF; the majority were mild (90.9%) or moderate (8.3%) in severity. 80.1% were deemed to be possibly or probably related to study drug. Of 103 TEAEs reported following Diastat doses, 98%were mild and 2% were moderate. 75.7% were possibly or probably related.[1]

There was 1 serious adverse event (SAE) reported and 2 TEAEs leading to discontinuation. There were no adverse events resulting in persistent impairment and there were no deaths reported.[1]

In all studies to date, somnolence followed by dizziness was the most frequently reported TEAE, consistent with the known pharmacologic action of diazepam. Somnolence has also been the most frequent AE reported for Diastat.[1]

The frequency of AEs increased in a dose-related manner with DBSF. An analysis of 138 administrations of 15 or 20 mg in a fasted state showed no particular pattern of TEAEs according to C_{max} or increase in frequency with an increase in C_{max}.[1]

A decreased frequency of AEs following dosing in a fed state was observed in the two food effect studies.[1]

Overall, the administration of DBF was safe and well tolerated in healthy subjects following a single oral dose of 5 mg through 20 mg under both fast and fed conditions. Adverse events were primarily mild to moderate in severity, short-lasting and consistent with the known pharmacologic effects of diazepam. There were few SAEs reported and no events associated with death or lasting impairment were observed.[1]

5.5.2.2 Pharmacokinetics in Clinical Studies

Pharmacokinetics: A 15 mg dose of Diastat® AcuDial™ rectal gel following rectal administration produces peak plasma concentrations in 1.5 hours, with absolute bioavailability of 90% relative to Valium® injectable. The volume of distribution of diazepam rectal gel is calculated to be approximately 1 L/kg. The mean elimination half-life of diazepam and desmethyldiazepam following administration of a 15 mg dose of diazepam rectal gel was found to be about 46 hours (CV=43%) and 71 hours (CV=37%), respectively. Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95-98%).[3]

5.5.2.2.1 Pilot Studies 1899 and 1900

The Sponsor conducted two randomized, open label, single-dose, fasting condition, crossover pilot studies in healthy male and female volunteers to assess the bioavailability of study drug in comparison to the same nominal dose of Diastat® AcuDial™ rectal gel. The planned enrollment was 12 subjects in both studies.

Study 1899 compared study drug 5 mg to Diastat® AcuDial™ rectal gel 5 mg. Among the 11 subjects who completed both treatments, DBF 5 mg was bioequivalent to Diastat rectal gel 5 mg with respect to area under the curve (AUC_t and AUC_{inf}), i.e., the 90% confidence interval (CI) for the ratio of geometric means was within the acceptable range of 80%-125%. For C_{max}, the ratio of geometric means was 1.07 with the 90% CI 87.1-131.5%. The median T_{max} was 0.67 hours for the DBF (range 0.33-1.50 hours) and 0.25 hours for the Diastat rectal gel (range 0.15-1.00 hours). The difference in T_{max} values was not statistically significant.[1]

Study 1900 compared DBF 20 mg to Diastat® AcuDial™ rectal gel 20 mg. Evaluable data from 10 subjects who completed both treatments showed that the extent of the absorption of DBF 20 mg was comparable to Diastat® AcuDial™ 20 mg rectal gel, with the ratio of geometric means for AUC_t and AUC_∞ within the acceptable range of 80-125%. For C_{max}, the ratio of geometric means was 158.72% (90% CI 122.81-205.14). The median T_{max} was 1.25 hours for the DBF (range 0.36-2.05 hours) and 1.00 hours for the Diastat® AcuDial™ rectal gel (range 0.25-2.00 hours). The difference in T_{max} values was not statistically significant. Examination of the mean plasma curves for DBF and Diastat® AcuDial™ showed that although the C_{max} was higher for the DBF relative to Diastat® AcuDial™, the pharmacokinetics were comparable in terms of rapid rate of absorption, duration of plateau, and the rate of elimination.[1]

5.5.2.2.2 Study 162013 – Dose-Proportionality

Study 162013 was a single-dose, randomized, open-label, three-period, six-sequence, crossover study conducted to assess dose-proportionality of DBSF at doses of 5, 10, and 15 mg. A total of 30 subjects were randomized and dosed in the study. Analysis of the pharmacokinetic data confirmed that DBSF is dose-proportional over the dose range 5 mg to 15 mg (Table 1). The criteria for dose proportionality were met for diazepam since for both comparisons (A/B: DBSF 5 mg/DBSF 10 mg and C/B: DBSF 15 mg/DBSF 10 mg), the geometric mean 90% CI of the ratios of Least-Squares means from the analysis of variance (ANOVA) of the ln-transformed AUC_t, AUC_∞, and C_{max} were within the acceptable range 80-125%.[1]

Table 1: Study 162013 - Dose-Proportionality of DBSF at Doses of 5, 10, and 15 mg

Parameter[1]	Treatment Comparisons	Geometric Mean Ratio[2]	90% CI[3]	
			Lower	Upper
AUC_t	DBSF 5 mg (A) – DBSF 10 mg (B)	103.53%	99.51%	107.72%
AUC_∞	DBSF 5 mg (A) – DBSF 10 mg (B)	104.08%	99.43%	108.96%
C_{max}	DBSF 5 mg (A) – DBSF 10 mg (B)	104.57%	97.92%	111.67%
AUC_t	DBSF 15 mg (C) – DBSF 10 mg (B)	101.94%	97.62%	106.44%
AUC_∞	DBSF 15 mg (C) – DBSF 10 mg (B)	103.64%	98.52%	109.02%
C_{max}	DBSF 15 mg (C) – DBSF 10 mg (B)	98.84%	92.36%	105.78%

AUC_∞ = area under the concentration-time curve from time zero to infinity; AUC_t = area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t; CI = confidence interval; C_{max}= the maximal observed plasma concentration; DBSF= Diazepam Buccal Soluble Film (equivalent to DBF).
[1] Dose normalized to 10 mg
[2] Calculated using least-squares means according to the formula $e^{DIFFERENCE}$ X 100
90% Geometric Mean Confidence Interval using ln-transformed data.

5.5.2.2.3 Study 162021 – Pivotal Bioavailability Study

This pivotal relative bioavailability study was a four-period, four-sequence randomized crossover in 36 healthy adult males and females. The four treatments were DBSF 15 mg and three doses of Diastat® AcuDial™ rectal gel: 5 mg, 12.5 mg, and 20 mg. These Diastat® AcuDial™ doses span the approved dose range for the rectal gel. The objective of this study was to gain a thorough and precise understanding of the comparative exposure to diazepam and nordiazepam (both AUC and C_{max}) after administration of DBF or Diastat® AcuDial™. A secondary objective was to evaluate the dose proportionality of the three doses of Diastat rectal gel.[1]

Pharmacokinetic parameters (C_{max}, AUC_t, and AUC_∞) were compared pairwise; DBF 15 mg with each of the three doses of the rectal gel (Table 2). Results demonstrate that AUC (both AUC_t and AUC_∞) are dose proportional following single doses for both DBF and for Diastat® AcuDial™ gel over the studied dose. These results, normalized for dose in mg, suggest that the relative bioavailability of diazepam administered as DMF compared with Diastat® AcuDial™ gel is 118% to 128%.[1]

Table 2: Study 162021: Ratios (DBSF 15 mg/Rectal Gel 5, 12.5, 20 mg), 90% Geometric Confidence Intervals for Diazepam: AUC_t, AUC_∞, and C_{max} - PK Population

Treatment Comparison	N	Parameter	Geometric LSM A	Geometric LSM B	Ratio[1]	90% Geometric CI[2] Lower	Upper
DBSF 15 mg (A)	24	AUC_t	11310.33	3181.98	355.45%	292.89%	431.37%
Diastat	24	AUC_∞	13204.10	3730.87	353.91%	295.32%	424.14%
rectal gel 5 mg (B)	24	C_{max}	461.88	116.88	395.18%	291.06%	536.54%
			Geometric LSM A	**Geometric LSM C**			
DBSF 15 mg (A)	23	AUC_t	11381.05	7314.63.	155.59%	127.26%	190.24%
Diastat	23	AUC_∞	12871.61	8370.26	153.78%	126.56%	186.86%
rectal gel 12.5 mg (C)	23	C_{max}	490.93	206.30	237.97%	176.72%	320.45%
			Geometric LSM A	**Geometric LSM D**			
DBSF 15 mg (A)	21	AUC_t	11186.57	12392.66	90.27%	42.23%	112.80%
Diastat	20	AUC_∞	13191.81	14824.85	88.98%	69.28%	114.29%
rectal gel 12.5 mg (D)	21	C_{max}	458.51	327.86	139.85%	140.92%	186.42%

AUC_∞ = area under the concentration-time curve from time zero to infinity; AUC_t = area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t; CI = confidence interval; C_{max}= the maximal observed plasma concentration; DBSF= Diazepam Buccal Soluble Film (equivalent to DBF); LSM = Least-Squares Mean

[1] Calculated least-squares means according to the formula: $e^{(Difference)} \times 100$

[2] 90% Geometric Mean Confidence Interval using ln-transformed data

5.5.2.2.4 Food Effect Studies

Aquestive Therapeutics conducted two food effect studies (Study 162022 in Section 5.5.2.2.5 and Study 172018 in Section 5.5.2.2.6). Results for a high fat meal were consistent across the two studies.[1]

The food effect studies indicate that a high fat or moderate fat meal within 30 minutes prior to dosing of DBF has no effect on diazepam AUC but reduces diazepam C_{max} on average of 45% and 33%, respectively. Bimodal peaks were observed under fed conditions due to the combination of oral transmucosal absorption and intestinal absorption of DBF. The first peak (mean concentration curves) for both high fat and moderate fat meals is observed at 45 minutes (mean of 199.04 ng/mL and 222.37 ng/mL, respectively) and the second peak of the mean concentration curves is observed at 3 hours (mean of 196.22 ng/mL and 261.79 ng/mL, respectively).[1]

5.5.2.2.5 Study 162022

Study 162022 was a single-dose, open-label, two-period, randomized two-sequence crossover study with DBF 15 mg administered under fasted conditions and within 30 minutes following a

high-fat meal. The washout period between doses was 28 days. The study was conducted with 18 healthy male and female subjects aged 18 to 62 years, inclusive. AUC_t and AUC_∞ were not affected by food; however, C_{max} after a high fat meal was approximately 55% of the fasting value, 90% CI 48.6% – 62.7% (ratio of geometric means). Median T_{max} fasting was approximately 0.75 hour with range of 0.25 hour to 2 hours whereas median T_{max} after a high fat meal was 3.0 hours with range 0.5 hour to 6.0 hours, p = 0.0008.[1]

5.5.2.2.6 Study 172018

Study 172018 was a four-period, randomized four-sequence crossover study in 24 male and female adults with four treatments: (A) DBF 15 mg fasted, administered upright; (B) DBF 15 mg fasted, administered reclining; DBF 15 mg within 30 minutes following a standardized high-fat meal, administered reclining; and DBF 15 mg within 30 minutes of a standardized moderate-fat meal, administered reclining.[1]

The primary objective was to assess the effect of a moderate-fat meal on the diazepam PK profile. A secondary objective was to assess the effect of administration of DBF with the subject reclining on his/her side (application site downward) for 15 minutes after application. This was based on aligning treatment administration with the typical posture assumed by subjects in a postictal state and the Sponsor's interest in investigating whether position affected diazepam PK following administration of DBF.[1]

Analysis comprised pairwise comparisons of Treatment C (high-fat meal, reclining) and Treatment D (moderate-fat meal, reclining) with Treatment B (fasting, reclining) as well as a comparison between Treatment B (fasting, reclining) with Treatment A (fasting, upright).[1]

Overall, AUC_t and AUC_∞ were not affected by either food or position. C_{max} after the high fat meal (reclining) was approximately 53% of the fasting value (reclining), 90% CI: 41.1% - 59.5% (ratio of geometric means). C_{max} after the moderate fat meal (reclining) was approximately 67% of the fasting value (reclining), 90% CI 59.8% - 74.6% (ratio of geometric means). Comparison of Treatment B with Treatment A demonstrated that position in the fasting condition (reclining versus upright) had no meaningful effect on either C_{max} or AUC. Diazepam profiles (reclining versus upright) met bioequivalence criteria for the upright and fasting condition. There was no difference in T_{max}, p = 0.4979.[1]

Median T_{max} fasting, upright was 1.00 hour with range 0.28 hour to 2.03 hours. Median T_{max} fasting, reclining was 0.80 hour with range 0.50 hour to 2.03 hours whereas median T_{max} after a high fat meal, reclining was 2.01 hours with range 0.50 hour to 4.06 hours (p = 0.0147 versus fasting, reclining). and median T_{max} after a moderate fat meal, reclining was 3.00 hours with range 0.50 hour to 4.02 hours (p = 0.0005 versus fasting, reclining).[1]

5.6 Rationale for Dose Levels of Diazepam Buccal Film

As described above, the data from Study 162013 and Study 162021 demonstrate that DBF is dose-proportional over the studied dose-range, while Diastat rectal gel is less than dose-proportional with respect to C_{max}. Also, as described above, the data from Study 162022 and Study 172018 demonstrate that food taken within 30 minutes prior to dosing affects the rate (but not the extent) of absorption of diazepam administered as DBF. Accordingly, Aquestive used population PK modeling to select a dosing regimen to compensate for the differences in PK

between DBF and DRG. The recommendation for adults derived from Population PK modelling is a weight-based dosing regimen with doses of 10.0 mg, 12.5 mg, 15.0 mg, 15.0 mg, and 17.5 mg for the five weight bins (weight range 38 to 111 kg) corresponding to the labeled Diastat doses of 10.0 mg, 12.5 mg, 15.0 mg, 17.5 mg, and 20.0 mg (Table 3).[1]

Table 3: Table 3Calculated Prescribed Dose of Study Drug

Weight (Kg)	DRG (mg)	DBF Weight – Adjusted (mg)
38 to 50	10	10
51 to 62	12.5	12.5
63 to 75	15	15
76 to 87	17.5	15
88 to 111	20	17.5

Using data from Study 162013, Study 162021, and Study 172018, population pharmacokinetic modeling was used to model the pharmacokinetic profiles for DBF and Diastat rectal gel under fasted and fed conditions. In brief, the recommended DBF dose for each weight class as defined in the Diastat rectal gel label was selected (1) to provide a dose sufficiently high to ensure that the predicted median of the resulting diazepam C_{max} following a moderate fat meal was similar to the median C_{max} following the labeled dose of Diastat rectal gel, and (2) to provide a dose for which the predicted median of the resulting diazepam C_{max} under fasting conditions would not exceed the median C_{max} values observed and demonstrated as safe in Phase 1 studies with DBF. It was demonstrated that the predicted median diazepam C_{max} values with the proposed regimen administered under fasting conditions did not meaningfully exceed the median C_{max} values observed in the 115 healthy volunteers (adult men and women) who received DBF 15 or 20 mg under fasting conditions in Phase 1 studies conducted by Aquestive. The median C_{max} among these 115 healthy subjects (138 DBF administrations) was 486 ng/mL. Under conditions of a moderate fat meal, the proposed DBF dosing regimen produces a C_{max} similar to the C_{max} expected following the labeled dose of Diastat rectal gel.[1]

5.7 Rationale for Study Design

A prior study to investigate the PK of DBF in patients with epilepsy on a regimen of AEDs (Aquestive Study 160326) indicated that diazepam plasma concentrations observed in patients were on average lower than the concentrations predicted from healthy volunteer data. Lower diazepam concentrations in patients could result from drug interactions with concomitant AEDs by means of induction of enzymes involved in diazepam metabolism and/or displacement of diazepam from binding sites on albumin (as described for valproic acid and sodium divalproex). If the lower plasma diazepam concentrations observed in patients vs. healthy volunteers following DBF is a consequence of enzyme induction and/or protein binding displacement from concomitant AEDs, the same effect of concomitant AEDs would be expected following administration of DRG, and the relative bioavailability of diazepam administered as DBF compared with DRG should be the same in patients as in healthy volunteers.

In the current study, the PK of diazepam will be compared in patients already receiving a stable concomitant AED treatment following single doses of DBF or Diastat® AcuDial™ according to

body weight as described in Table 3. Moreover, the DBF regimen was demonstrated in healthy male and female volunteer simulations to produce within each weight group a median C_{max} value following a moderate-fat meal comparable to the median C_{max} value following DRG administration. Therefore Period 1 and Period 2 of this study will be conducted under fed conditions where DBF and Diastat® AcuDial™ will be administered following intake of a moderate-fat meal. In addition, subjects who volunteer to participate in a third period will receive DBF in Period 3 following a high-fat meal. This third period will allow for the PK evaluation of DBF following a single dose administration under conditions of a high-fat meal.

The study will also aim to obtain PK data for Diastat® AcuDial™ under conditions of use in patient population and to address whether lower concentrations observed in patients versus healthy volunteers following DBF administration are also observed following Diastat® AcuDial™ administration. The study will also determine whether the DBF recommended dose regimen (mapping between DBF and Diastat® AcuDial™) developed from healthy volunteer data is applicable to patients under conditions of use.

The weight-based DBF dose regimen was designed to elicit within each weight group a median C_{max} value following a moderate fat meal comparable to the median C_{max} value following DRG administered according to the current weight-based product labeling for Diastat® AcuDial™. Because of the crossover design, the effect of drug-drug interactions can be expected to be similar for both treatments. Therefore, to the extent that population PK modeling in healthy volunteers is predictive for patients under conditions of use, it can be expected that diazepam C_{max} values observed in this study following a moderate-fat meal will be similar under both treatments. In the event that this is not the case, Aquestive anticipates that results from this study will be used to refine the recommended dose regimen in consultation and collaboration with the Agency.

5.8 Clinical Risks/Benefits of Study Drug

5.8.1 Managing Clinical Risks/Benefits in the Current Study

The available data indicate that study drug is dose proportional over the studied dose-range, while Diastat® AcuDial™ is less than dose proportional with respect to C_{max}.

In this study, dose is based on weight category (Table 3). Subjects will be weighed at screening visit and dose dispensed will be adjusted depending on weight category at that visit. The rationale for the dose regimen for DBF is explained in Section 5.6. Trained study site staff will administer the study drug. The study design includes several study site visits in each period to monitor safety and tolerability.

5.8.2 Overdosage Information Derived from Diastat® AcuDial™ Prescribing Information

According to the prescribing information for Diastat® AcuDial™ rectal gel, previous reports of diazepam overdosage have shown that manifestations of diazepam overdosage include somnolence, confusion, coma, and diminished reflexes. Respiration, pulse, and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal. General supportive measures should be employed, along with intravenous fluids,

and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.[3]

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. Caution should be observed in use of flumazenil in epileptic patients treated with benzodiazepines. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, should be consulted prior to use.[3]

5.9 Rationale for the Study Population

The study employs a 3-period, 2-sequence crossover design enrolling male and female volunteers on a concomitant stable regimen including one or more AED for the treatment of epilepsy. Eligible subjects will be enrolled in an effort to complete Period 2 with at least 16 subjects with representation of both genders, representation of subjects taking/not taking one or more AED known to induce diazepam metabolism, and representation of subjects taking/not taking Sodium divalproex/valproic acid.

No clinical studies have been conducted with diazepam rectal gel in pregnant women. However, an increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested by several studies. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. Children born to mothers receiving benzodiazepines on a regular basis late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period. During labor and delivery, measurable amounts of diazepam have been found in maternal and cord blood, indicating placental transfer of the drug. Additionally, diazepam and its metabolites may be present in human breast milk for prolonged periods of time after acute use. A recent study suggested that paternal exposure may be associated with fetal abnormalities.[1] In humans, measurable amounts of diazepam have been found in maternal and cord blood, indicating placental transfer of the drug.[3]

Since there have been no studies conducted in pregnant women, it is uncertain whether there is human fetal risk associated with the use of diazepam. Therefore, non-pregnant, non-lactating females will be included in the study. Any females of childbearing potential will be included if they use appropriate methods of contraception. In addition, non-surgically-sterile male subjects who are sexually active with non-sterile female partners will be required to use effective contraceptive methods for the duration of the study and for 111 days following administration of the study medication.

6. Objectives

Primary objective:

- Evaluate the PK of single doses of DBF at the recommended dose regimen (range 10 mg to 17.5 mg according to body weight) compared with DRG at the labeled dose regimen (range 10 mg to 20 mg according to body weight) in adult male and female subjects on a stable concomitant regimen of AED for the treatment of epilepsy, following a moderate-fat meal.

Secondary objectives:

- Evaluate the PK of single doses of DBF following a high-fat meal compared with DRG following a moderate-fat meal at the recommended dose regimen in adult male and female subjects on a stable concomitant regimen of AED for the treatment of epilepsy.

- Assess the safety-tolerability of single doses of DBF and DRG administered to adult male and female subjects on a stable concomitant regimen of AEDs under fed conditions.

7. Study Design

This will be a randomized, multiple centers, single-dose, open-label, three-period, three-treatment, two-sequence crossover study under fed conditions.

The study will evaluate single doses of DBF compared with DRG administered according to weight category in adult male and female subjects on a stable concomitant regimen of AED for the treatment of epilepsy. A stable regimen of AED is defined as no change in the prescribed AED regimen during the 30-day period prior to the first study drug administration and no change anticipated in the prescribed AED regimen over the course of study participation until the last PK blood sample collection.

Subjects will receive Treatment A and Treatment B (DBF and DRG following a moderate-fat meal) in Period 1 and Period 2 in a randomized sequence, and at a dosage specific to body weight, as described in Table 4. DBF will be administered according to the currently recommended dose regimen (derived by Aquestive from population PK modeling in healthy volunteers). DRG will be administered depending on weight category according to the current product labeling for Diastat®. **Subjects may be asked to participate in a third period, on a voluntary basis.** Subjects who volunteer to participate in a third period will receive a second dose of DBF administered in exactly the same manner as the earlier dose of DBF with the exception that DBF in Period 3 will be administered following a high-fat meal.

A maximum of 32 eligible subjects will be enrolled in an effort to complete Period 2 with at least 16 subjects with representation of both genders, representation across the five weight categories of subjects taking one or more AEDs known to induce diazepam metabolism, and representation of subjects taking sodium divalproex/valproic acid. Subjects who are eligible may be enrolled without regard to weight category. **Since only exploratory PK data will be gathered from treatment period 3, no more than** 50% of the subjects who complete Period 1 and Period 2 will participate in Period 3.

This study is intended for filing under FDA regulations.

Table 4: Table 4 Study Treatment Administration According to Weight Category

Product	Meal Condition	Weight Category	Weight (kg)	Dose
Test (Treatment A): Diazepam Buccal Film (Aquestive Therapeutics, USA)	**Moderate-Fat Meal**	A1	38-50	1 x 10 mg
		A2	51-62	1 x 12.5 mg
		A3	63-75	1 x 15 mg
		A4	76-87	1 x 15 mg
		A5	88-111*	1 x 17.5 mg
Reference (Treatment B): Diastat® AcuDial™ rectal gel (Valeant Pharmaceuticals, USA)	**Moderate-Fat Meal**	B1	38-50	2 mL (10 mg)
		B2	51-62	2.5 mL (12.5 mg)
		B3	63-75	3 mL (15 mg)
		B4	76-87	3.5 mL (17.5 mg)
		B5	88-111*	4 mL (20 mg)
Test (Treatment C): Diazepam Buccal Film (Aquestive Therapeutics, USA)	**High-Fat Meal**	A1	38-50	1 x 10 mg
		A2	51-62	1 x 12.5 mg
		A3	63-75	1 x 15 mg
		A4	76-87	1 x 15 mg
		A5	88-111*	1 x 17.5 mg

*Subjects eligible for study with weights in the range of 112 to 134 kg will be dosed at the 88-111 kg weight range as shown above.

8. Study Population

8.1 Sample Size

Subjects will be enrolled to attain a sample size of **no more than 32** subjects (and a minimum of 16 completed subjects in Period 2). Because this is not a formal hypothesis testing study, the sample size is proposed based on the desired level of precision for estimating pharmacokinetic parameters and the relationship between pharmacokinetic parameters. In principle, the expected precision of the estimates of the ratios of geometric means of interest can be estimated from the intra-subject variability observed in Aquestive Study 162021 (pharmacokinetic crossover of DBF 15 mg with DRG 5, 12.5, and 20 mg in healthy volunteers). Aquestive has not undertaken a formal analysis to predict the expected precision.

8.2 Inclusion Criteria

Subjects enrolled in this study will be members of the community at large. The recruitment advertisements may use various media types (e.g. radio, newspaper, Web site, volunteer database). Subjects must meet all of the following criteria to be included in the study:

1) Male or female, smoker (no more than 25 cigarettes or equivalent daily) or non-smoker, ≥ 18 and ≤ 65 years of age, with body weight between 38 and 111 kg, inclusive. Potential subjects

with weights in the range of 112 to 134 kg (247 – 249 pounds) may be allowed to participate in the study at the discretion of the Principal Investigator.

2) On a stable and ongoing regimen of at least one AED for treatment of epilepsy. Stable regimen is defined as no change in AED regimen for at least 30 days before the first study drug administration and no change anticipated in the prescribed AED regimen over the course of study participation.
3) Subjects must have a diagnosis of seizure disorder (any seizure type or frequency) under treatment with at least one AED.
4) Healthy (except for seizure disorder), according to the medical history, ECG, vital signs, laboratory results and physical examination as determined by the Principal Investigator/Sub-Investigator.
5) Clinical laboratory values within local laboratories acceptable ranges, unless values are deemed by the Principal Investigator/Sub-Investigator as "Not Clinically Significant".
6) Ability to comprehend and be informed of the nature of the study, as assessed by clinic staff.
7) Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements.
8) Agree not to have a tattoo or tongue or body piercing until the end of the study.
9) Agree not to drive or operate heavy machinery if feeling dizzy or drowsy following drug administration until full mental alertness is regained.
10) Subjects must be able and willing to remove denture or bracing at the time of dosing.
11) Non-vasectomized male subjects must use two forms of medically accepted method of contraception with all sexual partners of childbearing potential during the study and for 111 days following the last dose of study drug. Medically accepted effective forms of contraception include:
    a) simultaneous use of a male condom and
    b) for the female partner, hormonal contraceptives (used since at least 4 weeks) or intra-uterine contraceptive device (placed since at least 4 weeks) or diaphragm or cervical cap with intravaginally applied spermicide.
12) Male subjects must be willing not to donate sperm until 111 days following the last study drug administration.
13) Female subjects who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized since at least 6 months) must fulfill at least one of the following:
    a) Be surgically sterile for a minimum of 6 months;
    b) Post-menopausal for a minimum of 1 year;
    c) Agree to avoid pregnancy and use medically acceptable method of contraception as described below until at least 51 days after the last PK blood sample collection of the study. Medically acceptable methods of contraception include:

- Intrauterine device (hormonal and non-hormonal) placed at least 4 weeks prior to first study drug administration,
- Oral or transdermal hormonal contraceptives with a 28-days treatment cycle taken daily from at least 30 days prior to first study drug administration and with no expected change in dosage throughout the study, or
- Double barrier method (male condom and intravaginally applied spermicide used simultaneously with diaphragm or cervical cap) starting at least 21 days prior to first study drug administration;

d) agree to complete abstinence.

8.3 Exclusion Criteria

Subjects to whom any of the following applies will be excluded from the study:

1) Clinically significant abnormal laboratory test results found during medical screening.
2) Positive pregnancy test at screening.
3) Known presence of any clinically significant: hepatic (e.g. hepatic impairment), renal/genitourinary (renal impairment, kidney stones), gastrointestinal (e.g. ulcerative colitis, ileus, partial or complete intestinal blockage, appendicitis), cardiovascular (e.g. uncontrolled hypertension), cerebrovascular, pulmonary, endocrine (controlled diabetes is acceptable), immunological, musculoskeletal, neurological (other than known seizure disorder), psychiatric, dermatological or hematological disease or condition unless determined as not clinically significant by the Principal Investigator/Sub-Investigator and confirmed by Sponsor via written communication prior to subject enrollment.
4) Presence of any clinically significant gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel disease), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting), or other conditions known to interfere with the absorption, distribution, metabolism or excretion of the study drug experienced within 7 days prior to first study drug administration, as determined by the Principal Investigator/Sub-Investigator.
5) Any clinically significant rectal abnormality suspected by medical history or general physical examination, or any condition, for which, in the judgment of the Principal Investigator/Sub-Investigator, administration of rectal gel would cause a potential risk to the subject.
6) Baseline levels of concomitant AED outside of an acceptable therapeutic range at screening.
7) Presence of any clinically significant illness within 30 days prior to first study drug administration, as determined by the Principal Investigator/Sub-Investigator.
8) Presence of any clinically significant physical or organ abnormality as determined by the Principal Investigator/Sub-Investigator.
9) Presence of any clinically significant lesion of the oral cavity.
10) Clinically significant ECG abnormalities (QTcF interval > 450 msec for males or QTcF interval > 470 msec for females) or vital sign abnormalities (systolic blood pressure lower than 90 or over 160 mmHg, diastolic blood pressure lower than 50 or over 100 mmHg, or

heart rate less than 50 or over 100 bpm) at screening, unless deemed otherwise by the Principal Investigator/Sub-Investigator.

11) A positive test result for HIV, Hepatitis B surface antigen, Hepatitis C.

12) A positive test result for any of the following: drugs of abuse (amphetamines, methamphetamines, barbiturates, cocaine, opiates, phencyclidine, tetrahydrocannabinol, MDMA, methadone, and benzodiazepines, except where a positive test is consistent with a stable regimen of a prescribed medication) and alcohol breath test.

13) Known history or presence of:

    a) Alcohol abuse or dependence within one year prior to screening;

    b) Drug abuse or dependence;

    c) Hypersensitivity or idiosyncratic reaction to diazepam, DBF excipients, DRG excipients;

    d) Glaucoma (open or acute narrow angle);

    e) Food allergies and/or presence of any dietary restrictions that, in the judgment of the investigator or the Sponsor, would interfere with study procedures or the subject's safe participation in the study.

    f) Severe allergic reactions (e.g. anaphylactic reactions, angioedema).

14) Intolerance to and/or difficulty with blood sampling through venipuncture.

15) Individuals who have donated, in the days prior to first study drug administration:

    - 50-499 mL of blood in the previous 30 days;
    - 500 mL or more in the previous 56 days.

16) Donation of plasma by plasmapheresis within 7 days prior to first study drug administration.

17) Individuals who have participated in another clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the first dosing, administration of a biological product in the context of a clinical research study within 90 days prior to the first dosing, or concomitant participation in an investigational study including an investigational study involving no drug or device administration.

18) Use of diazepam within 30 days prior to first study drug administration.

19) Use of strong inhibitors of CYP enzymes (e.g. cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) in the previous 30 days before first study drug administration. Use of strong inducers of CYP enzymes (e.g. barbiturates, carbamazepine, glucocorticoids, phenytoin, St. John´s Wort, and rifampicin) and AEDs known to induce CYP enzymes are permitted provided that the regimen of such drugs is stable (taken at least q.d. on a regular basis) within 30 days prior to first study drug administration and until 10 days after last study drug administration.

20) Use of any prescription medication (other than non-systemic topical products) within 30 days prior to first study drug administration. A prescription drug (other than any benzodiazepines, phenothiazines, and strong inhibitors of CYP enzymes) that is part of a stable drug regimen (taken at least q.d. on a regular basis) is allowed if taken from at least 30 days prior to the

first study drug administration and if there is no expected change in dosage throughout the study.

21) Use of any OTC medications (other than spermicidal/barrier contraceptive products and non-systemic topical products), within 30 days prior to first study drug administration. OTC drugs that is part of a stable drug regimen (taken at least q.d. on a regular basis) is allowed if taken from at least 30 days prior to the first study drug administration and if there is no expected change in dosage throughout the study.

22) Natural health products (including oral multivitamins, herbal and/or dietary supplements and/or teas) from 30 days pre-dose until after the last PK blood sample collection of each period.

23) Use of marijuana and THC containing products within 3 months prior to screening unless such products are a part of the subject's stable antiepileptic regimen.

24) Use of any monoamine oxidase (MAO) inhibitors (e.g. phenelzine, tranylcypromine), phenothiazines (e.g. chlorpromazine) within 30 days prior to first study drug administration.

25) Female subjects who have taken oral or transdermal hormonal contraceptives (other than 28-days treatment cycle contraceptive products) within 30 days prior to first drug administration, or have used an implanted, injected, or intravaginal contraceptive within 6 months prior to first drug administration.

26) Individuals having undergone any major surgery within 6 months prior to the start of the study, unless deemed otherwise by Principal Investigator/Sub-Investigator.

27) Presence of mouth jewellery, dentures, 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

28) Dental procedures performed within 14 days of dosing or dental procedures scheduled to occur during study duration.

29) Unable or unwilling to provide informed consent.

30) Have had a tattoo or body/mouth piercing within 30 days prior to first study drug administration.

31) Employee or immediate relative of an employee of Aquestive Therapeutics, any of its affiliates or partners, of the CRO, or the clinical site.

32) Breast-feeding subject.

9. Clinical Procedures

The clinical portion of the study will be conducted at multiple clinical research facilities, as listed in Section 1.2. Unless otherwise specified, procedures, data collection and evaluation will be conducted as per involved clinical facilities SOPs. Subjects' personal information will be stored in electronic data capture (EDC) system or raw data sheets.

9.1 Screening Procedures

Subject screening procedures will be performed within 30 days preceding administration of study medication. Subjects must provide written informed consent prior to initiation of any screening

procedures. The consent to perform some general screening procedures may be obtained on a consent document other than the Informed Consent Form (ICF) specific to this study, and therefore, some screening test results could be obtained before signature of the ICF specific to this study. The study-specific ICF must be signed and dated by the subject before participation to study-specific procedures.

Screening procedures will include: demographic data, medical and medication histories, physical examination, brief neurologic examination, visual inspection of DBF application site, body measurements, ECG (12-lead), vital signs (BP, HR, and RR), oral temperature, digital oxygen monitoring, hematology, biochemistry, HIV, hepatitis B and C tests, urinalysis, baseline AED levels if applicable*, alcohol breath test, urine pregnancy test, and urine drug screen.

* The Investigator should confirm and document, for those AEDs medications that the patient is receiving at baseline screening, that AED drug level testing has been conducted within one year prior to the first dosing, and determine, in consultation with patient's referring neurologist (if not the study Investigator), that AEDs are at acceptable therapeutic levels.

For any AED medication where testing was not conducted within one year before the first dosing or was determined in the past not to be therapeutic, the Investigator should obtain and confirm a blood test result demonstrating a current therapeutic level for that AED medication. If the Investigator determines that a dose adjustment for that AED medication is needed, then the patient will be considered not to be stable on their AED medication regimen, and ineligible for study enrollment.

For eligibility purposes, abnormal laboratory or vital signs results may be repeated once if abnormal result is observed at the initial reading. Moreover, abnormalities found in the ECG may need to be confirmed by repeated measurements. In the event that the participation of a subject in the study is delayed and some screening procedures had been performed outside the prescribed screening window, outdated screening procedures can be repeated.

9.2 Confinements, Visits, and Washout

For each period, subjects will be confined from approximately 14 hours before dosing until after the 24-hour post-dose blood draw. For subsequent blood draw, subjects may come back to the clinical site or have the blood sample collected at home by a home care nurse.

There will be a washout of 28 days between doses. Participation of each subject in this study should last approximately 10 weeks (6 weeks for subjects participating in Period 1 and Period 2 only), excluding the 30 days screening window.

9.3 Randomization and Blinding

Subjects will be administered each treatment according to the 3-period, 2-sequence, block randomization scheme produced by inVentiv. At admission to the clinic, subjects who meet the inclusion/exclusion criteria will be assigned between the 2-sequence arms (ABC or BAC) according to the randomization schedule. inVentiv will inform the site about the medication to be dispensed to each particular subject at the time of subject's randomization and at the prospective protocol visits. The clinic will administer the study treatment as described in Table 4, according to the subject's weight obtained at screening visit.

The randomization code will not be available to the Bioanalytical Division until the clinical and analytical phases of the study have been completed.

9.4 Study Medication

Test product (Treatment A):	Diazepam Buccal Film (DBF) (Aquestive Therapeutics, USA), under fed conditions (breakfast with moderate fat content)
Strengths:	10 mg, 12.5 mg, 15 mg, and 17.5 mg
Doses:	1 x 10 mg, 1 x 12.5 mg, 1 x 15 mg, or 1 x 17.5 mg
Reference product (Treatment B):	Diastat® AcuDial™ rectal gel (Valeant Pharmaceuticals, USA), under fed conditions (breakfast with moderate fat content)
Strengths:	10 mg/2 mL (5 mg/mL), 20 mg/4 mL (5 mg/mL)
Doses:	2 mL (10 mg), 2.5 mL (12.5 mg), 3 mL (15 mg), or 3.5 mL (17.5 mg)
Test product (Treatment C, Period 3):	Diazepam Buccal Film (DBF) (Aquestive Therapeutics, USA), under fed conditions (breakfast with high fat content)
Strengths:	10 mg, 12.5 mg, 15 mg, and 17.5 mg
Doses:	1 x 10 mg, 1 x 12.5 mg, 1 x 15 mg, or 1 x 17.5 mg

9.5 Drug Supplies and Accountability

It is the responsibility of the Sponsor to ensure that study medication provided for this study are manufactured under Good Manufacturing Practices (GMP) and are suitable for human use. It is the responsibility of the Sponsor to ship a sufficient amount of dosage units to allow the clinical sites to maintain an appropriate sampling for the study. Study medication will be stored by the clinical sites as per applicable requirements.

The medications will be stored in a locked, environmentally-controlled medication room with restricted access. Container(s) will bear a label containing at least the name of the study drug, lot and/or batch number, and manufacturing and/or expiry/retest date. Individual subject doses will be dispensed according to the randomization schedule. The medications will be dispensed according to study specific procedure.

All study drug received at each site will be inventoried and accounted for throughout the study by the pharmacy staff.

Further details regarding the proper shipment, storage conditions, dispensing, or responsibilities will be provided by inVentiv in the pharmacy manual.

9.6 Drug Administration

In each period, subjects will undergo a 10-hour overnight fast before the dosing procedure. Subjects will receive a single dose according to their body weight (as described in Table 4). The body weight of each subject will be measured at screening and this value will be used to calculate the exact individual dose of diazepam required.

Following each study drug administration, subjects will remain in a safe comfortable position (sitting or reclining in bed) for at least one hour after dosing to allow for an assessment of drug effect including sedation. After one hour and depending on the assessment of the investigator/clinical staff, the subject may be permitted to ambulate provided that ambulation does not interfere with study procedures.

DBF ease of use will be evaluated by the clinical staff and by the subjects following the first film administration in Period 1 or Period 2. Questions regarding past experience in using DRG or other rescue medication for the treatment of epilepsy will also be asked to subjects prior to DRG administration. Questions are listed in Appendix I – Diazepam PK Study Participant Questions.

Test (Treatment A and Treatment C):

After the overnight fast, subjects will be served a standardized moderate-fat meal (Treatment A, Period 1 or Period 2) or a high-fat, high-calorie meal (Treatment C, Period 3). Subjects will have 20 ± 1 minutes to finish the meal. The study drug will be administered 30 ± 1 minutes after the start of the meal. A single dose of DBF will be administered by placement of the film against the buccal mucosa.

When opening the foil pouch containing the study drug film, the clinical staff will use scissors to carefully cut along the wide edge of the pouch and use gloves when handling and administering the study drug to the subject.

Prior to dosing, the subject will be asked to move his/her tongue around the mouth (front and back part of gums, teeth and palate) two times to note any signs of oral irritation and/or any mouth, tongue or gum ulcer(s). Study staff will check the subjects' mouth to ensure the mouth is clean and free of food before study drug administration. Subsequently, staff will center the DBF against the inner aspect of the right or left buccal mucosa (inside the cheek) and ask the subject to close his/her mouth in a natural way, without swallowing, chewing, biting or breaking the DBF (refer to Appendix III - Placement Diagram for Aquestive Therapeutics Buccal Film). If the subject chews, talks, or moves the study drug within 10 minutes of administration, it is to be noted. Dosing time will be set to the time the film is placed on the buccal mucosa.

The study staff will record the actual time of film placement. Subjects will be instructed to notify study staff if the DBF is accidentally swallowed within 5 minutes of dosing. Study staff will record the time the film was swallowed.

Following the administration of the DBF, hands and mouth will be checked in order to confirm the consumption.

Reference (Treatment B):

Subjects will consume a standardized moderate-fat meal after the overnight fast. Subjects will have 20 ± 1 minutes to finish the meal. The study drug will be administered 30 ± 1 minutes after the start of the meal.

A single dose of DIASTAT® rectal gel will be administered, with subjects lying down on their right side. The tip of the syringe containing the DIASTAT® gel will be inserted gently in the rectum and the gel will be inserted inside the rectum according to the dosing procedure (refer to Appendix IV - Placement Diagram for DIASTAT® AcuDial™ Rectal Delivery System).

9.7 Study Restrictions

If any subject does not comply with the study restrictions, at any time prior to or during the study, continued participation will be re-assessed by the Principal Investigator/Sub-Investigator, CRO PK Scientist and the Sponsor.

If drug therapy other than that specified in the protocol, including any change in the subject's stable AED regimen, is required during the study, the decision whether to continue or discontinue the subject's participation in the study will be made by the Principal Investigator/Sub-Investigator and/or by the CRO PK Scientist in consultation with the Sponsor.

Concomitant drug or non-drug treatment (e.g. prune juice, ginger ale) administered to subjects as per instructions from clinical sites physicians for treatment of any Adverse Events [AEs] (as required) will be permitted. Clinic staff will provide the subjects with the treatment (e.g. medication, fluids) and will document all substances given outside of the protocol specified requirements. All cases of concomitant medication or herbal/dietary supplement administration will be reported as soon as possible to the CRO PK Scientist and/or the Sponsor and will be reviewed on a case by case basis to determine the subject's further participation in the study.

9.7.1 Food and Fluids

After a supervised fast of at least 10 hours, subjects will be served either a standardized moderate-fat meal or a high-fat, high-calorie meal. The standardized moderate-fat meal will contain approximately 625 calories. Approximately 14% of total calories will be derived from protein, 54% from carbohydrates, and 32% from fat.[5] The high-fat, high-calorie meal will contain approximately 800 to 1000 calories (approximately 50% of total caloric content of the meal will be derived from fat). This meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.[7] Subjects will be required to start their meal as soon as it is served and to complete it within 20 ± 1 minutes. Drug administration will occur 30 ± 1 minutes after the meal has been started. Subjects will fast for not less than 4 hours after drug administration. Meals will be standardized and similar in composition between periods.

No water will be allowed during the DBF administration and for at least 15 minutes following DBF administration. Water will be allowed *ad libitum* at all other times.

In addition, subjects will be required to abstain from (refer to Appendix II – Study Restrictions for detailed study restrictions):

- food containing poppy seeds within 48 hours prior to dosing in each period;
- food or beverages containing caffeine/methylxanthines derivatives or energy drinks from 48 hours prior to dosing until after the last PK blood sample collection of each period;
- natural health products (dietary and/or herbal supplements and/or teas) from 30 days pre-dose until after the last PK blood sample collection of each period;
- Food or beverages containing grapefruit, star fruit, and/or pomelo from 30 days prior to the first dosing until the last PK blood sample collection of the study.

9.7.2 Tobacco, Alcohol, and Illicit Drugs

Subjects will be required to abstain from using soft or hard drugs from screening and throughout the study. Subjects will not be allowed to smoke more than 25 cigarettes or equivalent per day. Marijuana and THC containing products may be allowed if prescribed and part of the subject's stable antiepileptic regimen.

Consumption of alcohol-based products will be prohibited from 48 hours prior to dosing until after the last PK blood sample collection of each period.

9.7.3 Medications

Prescription and OTC medications will be prohibited throughout the study except for prescription and OTC drugs that are administered as a stable regimen (taken at least q.d. on a regular basis). Any stable prescription drug and OTC treatment (except any benzodiazepines, phenothiazines, and strong inhibitors of CYP enzymes) will be allowed if taken from at least 30 days prior to the first study drug administration and with no changes expected in dosage regimen through the study (until the last PK sample).

No other concomitant drug therapy will be allowed during the study except one(s) required for the medical management of an AE. In this case, any concomitant medication use will be evaluated on a case-by-case basis by the Principal Investigator or a physician. Concomitant drug or non-drug treatment (e.g. acetaminophen, ibuprofen (or other NSAIDs), prune juice, ginger ale) for the treatment of an AE will be administered as per instructions from clinic physicians. Clinic staff will provide the subjects with the treatment (e.g. medication, fluids) and will document all substances given outside of the protocol specified requirements. All cases of concomitant medication or herbal/dietary supplement administration will be reported as soon as possible to the Sponsor and will be reviewed on a case by case basis to determine the subject's further participation in the study.

Any benzodiazepines (other than study drug), phenothiazines, and strong inhibitors of CYP enzymes (e.g. cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, itraconazole, diltiazem, and HIV antivirals) will be prohibited from 30 days prior to the first dosing until after the last PK blood sample collection of the study. Strong inducers of CYP enzymes (e.g. barbiturates, carbamazepine, glucocorticoids, phenytoin, phenobarbital, St. John´s Wort, rifampicin) and AEDs known to induce CYP enzymes are permitted provided that

the regimen of such drugs is stable (taken at least q.d. on a regular basis) within 30 days prior to first study drug administration and until at least 10 days after last study drug administration.

Subjects will be advised that they are not allowed to take MAO inhibitors for 30 days before dosing and until 14 days after the last study drug administration.

For females, oral or transdermal hormonal contraceptives other than 28-days treatment cycle contraceptives are prohibited within 30 days prior to first study drug administration and implanted, injected, or intravaginal hormonal contraceptive are prohibited within 6 months prior to first study drug administration and through the study.

9.7.4 Posture and Physical Activity

Diazepam may cause sedation. Consistent with intended use of DBF and the use of DRG subjects should be in a safe comfortable position (sitting or reclining in bed) for at least one hour after dosing to allow for an assessment of drug effect including sedation. After one hour and depending on the assessment of the investigator/clinical staff, the subject may be permitted to ambulate provided that ambulation does not interfere with study procedures. Vital signs should be taken in a consistent position (sitting or reclining). Subject visits to the bathroom or washroom will be monitored by clinic staff for 4 hours after each study drug administration, and the following information will be recorded: whether the subject urinated, defecated, or vomited. Subjects will be instructed not to flush if they vomit. Vomitus will be verified and noted in the subject's file for further evaluation if needed.

Because excessive physical activity may increase the level of CK above the upper normal limit value, subjects will be advised to avoid performing vigorous physical activities (e.g., intense or long-distance running or biking, etc.) at all times during the study duration (from at least 5 days prior to admission), including the washout period.

9.8 Sample Collection and Processing

In each period, a total of 19 blood samples will be drawn from each subject for pharmacokinetic analyses. Blood samples will be collected prior to study drug administration and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144, 192, and 240 hours post-dose (3 mL for each sampling time). The time tolerance window for blood samples collected during the confinement period will be ±1 minute for all samples collected before 8 hours post-dose and ±3 minutes for subsequent samples. The time tolerance window for return visit samples will be ±60 minutes. Blood samples will be collected as close as possible to nominal times; exact sample collection times will be recorded on the appropriate source documents and reported for each subject. The actual time of blood sample collection will be used for PK and statistical analysis. Unless otherwise specified or for subject safety, when blood draws and other procedures coincide, blood draws will have precedence. A saline intravenous catheter will be used for blood collection to avoid multiple skin punctures, when appropriate. Otherwise, blood samples will be collected by direct venipuncture.

The total volume of blood including that collected for eligibility and safety purposes should not exceed 313 mL for the whole study.

Further details regarding the proper collection, preparation, labeling, storage, and shipment of plasma samples for PK analysis will be provided by inVentiv in the lab manual.

9.9 Subject Monitoring

Subjects will be monitored throughout the study by the clinical staff for adverse events. In each period, the Principal Investigator or Sub-Investigator will be on site for drug administration and until 8 hours after administration of the study medication to the last subject. A Principal Investigator or Sub-Investigator will also be on call for the remainder of the study. If necessary, a physician, either at the clinic or in a nearby hospital will administer treatment for any AEs. A crash cart or emergency bag containing the necessary rescue material and appropriate medications will be available in the clinic to allow for rapid intervention in case of emergency.

Safety parameters, including laboratory results and ECG, will be assessed by the Principal Investigator or delegate, using local laboratories acceptance ranges criteria for biomedical laboratory as suggested guidelines in making the medical assessment.

Scheduled safety measurements will be repeated according to appropriate ranges or upon request from a physician. Any abnormal repeated measurement will be evaluated by a physician and repeated if judged necessary. Further action may be taken upon physician's request.

Subjects will be advised to notify their health care professional(s) (e.g., physician, dentist, and/or pharmacist) that they are participating in a clinical research study on a new formulation of diazepam before taking any medicines or undergoing any medical procedure.

9.9.1 Vital Signs

Vital signs (BP, RR, HR) and digital oxygen monitoring will be measured in a sitting position (except for safety reasons) at screening and at study exit. Oral temperature will be measured at screening and at study exit.

Vital signs and digital oxygen monitoring will be measured before dosing and approximately 0.5, 1, 1.5, 2, 4, and 8 hours post-dose (and beyond if clinically indicated).

Vital signs will also be measured approximately 12 and 24 hours post-dose.

When vital signs measurements coincide with a blood draw, they should preferably be performed a few minutes before the blood collection whenever possible.

9.9.2 ECG

Supine ECG will be performed at screening and study exit. Continuous ECG monitoring will be performed from approximately 1 hour prior to dosing until 8 hours post-dose (and extended if clinically indicated).

9.9.3 Physical Examination

A physical examination will be performed at screening and study exit. The physical examination includes at least the following components: HEENT (head, eyes, ears, nose, and throat), neck, chest and lungs, cardiovascular, abdomen, skin, and musculoskeletal evaluation.

A brief neurologic examination will be performed at screening and study exit. The neurologic assessment involves at least the following evaluation: mental status, cranial nerves, motor system, sensory system, cerebellar disorder, gait, and reflexes.

9.9.4 DBF Application Site Inspection

The Investigator or designee will make a visual inspection of the oral mucosa at screening. The application site will also be inspected prior to DBF administration and approximately 6 and **24** hours after administration. Assessments of the oral mucosa (normal/abnormal) will be conducted by the Principal Investigator/Sub-Investigator or a trained nurse.

Abnormalities observed before dosing will be recorded and evaluated regarding exclusion criteria but will not be considered AEs. Any post-dose abnormalities will be reported as AEs and followed until resolution.

9.9.5 Drug and Alcohol Screen

A urine drug screen (amphetamines, methamphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, opiates, PCP, MDMA, methadone) and an alcohol breath test will be performed at screening and before dosing of each period.

9.9.6 Pregnancy Test

A urine pregnancy test will be performed at screening and at study exit, and a serum pregnancy test will be performed at check-in of each period.

9.9.7 Laboratory Assessments

9.9.7.1 Hematology

Hematology will be performed at screening and at study exit. The following will be assessed: complete blood count with differential, hemoglobin, hematocrit and platelet count.

9.9.7.2 Biochemistry

Biochemistry will be performed at screening and at study exit. The following will be assessed: albumin, alkaline phosphatase, AST, ALT, urea, calcium, chloride, glucose, phosphorus, potassium, creatinine, sodium, total bilirubin, CK, lactate dehydrogenase, uric acid, total protein, magnesium, bicarbonates, and ammonia.

9.9.7.3 Serology

Hepatitis B (HBs Ag), Hepatitis C (HCV) antibody, and HIV antigen and antibody detection will be performed at screening.

9.9.7.4 Urinalysis

Urinalysis will be performed at screening and at study exit. The following will be assessed: macroscopic examination, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, **nitrite, and** leukocytes. Unless otherwise specified, microscopic examination will be performed on abnormal findings.

9.10 Study Exit Procedures

Physical examination, brief neurologic examination, hematology, biochemistry, urinalysis, vital signs (blood pressure, heart rate, respiratory rate), oral temperature, digital oxygen monitoring, ECG, urine pregnancy test, and AE monitoring will be performed on the last study day. If not possible, all efforts will be made to complete study exit procedures within 14 days after the last participation of the subject in the study.

9.11 Data Collection and Evaluation

All clinical raw data will be recorded promptly, accurately, and legibly as e-source data or indelibly on paper (e.g. ECG readings). A detailed list of the type (electronic or paper) and location for all source data will be included in the Trial Master File. All raw data will be conserved in order to maintain data integrity. A physician and/or the clinical staff will assume the responsibility of ensuring the completeness and accuracy of the clinical data.

9.12 Subject Withdrawal and Replacement

Subjects will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or a delegate may withdraw any subject from the study for one of the reasons described below:

- safety reason;
- non-compliance with protocol requirements;
- significant protocol deviation;
- positive alcohol breath test;
- positive drug screen (except for subjects using prescribed marijuana and THC containing products as AED treatment);
- positive pregnancy test.

Positive result to the urine benzodiazepine screen (urine drug screen) in Period 2 and Period 3 may derive from residual concentrations from study drug administered in the previous period(s). Therefore, it is not required that subjects with a positive result to that test in Period 2 and Period 3 be withdrawn from the study. Continued subject participation in the study will be evaluated by the Principal Investigator.

Subjects experiencing emesis within 4 hours following DBF adminsitration will be evaluated on a case-by-case basis by the Principal Investigator/Sub-Investigator, the CRO PK Scientist, and the Sponsor, and a decision on their continued participation will be made. Subjects experiencing a bowel movement within 4 hours following DRG administration or clinically significant leakage of the rectal gel within 4 hours post-dose will be evaluated on a case-by-case basis by the Principal Investigator/Sub-Investigator, the CRO PK Scientist, and the Sponsor, and a decision on their continued participation will be made. All decisions will be made prior to the bioanalytical laboratory commencing bioanalysis.

Subjects who withdraw or are withdrawn from the study after dosing will not be replaced. However, in the event that the number of drop-outs exceeds initial expectations, subjects who withdraw or are withdrawn might be replaced at the discretion of the Sponsor. Such replacement

resulting in dosing of more subjects than planned in this protocol would be documented in a protocol amendment.

Subjects who withdraw or are withdrawn will be asked to remain at the clinic until the Investigator or a delegate agrees that the subject is fine and can be discharged. As soon as subject withdrawal is confirmed, blood sampling will be stopped. Study exit procedures will be performed at the time of withdrawal from the study or as soon as possible thereafter.

9.13 Adverse Events

9.13.1 Adverse Event Recording and Follow-up

Subjects will be instructed to inform clinical personnel of any untoward medical symptoms and/or events that may arise during the course of the study. AEs/SAEs will be collected and documented from the signing of the ICF until at least 10 days following the last study drug administration, and as observed or reported spontaneously by study participants.

Prior to subsequent dosing, subjects will be questioned concerning symptoms that may have occurred after the previous administration of the study drug. The incidence, seriousness, severity, duration, and relation to study drug of all AEs will be recorded.

9.13.1.1 Serious Adverse Events

An SAE is an AE that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- 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 or birth defect (in the child of a subject who was exposed to the study drug)

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

9.13.1.2 Evaluation of Severity of AEs

Severity will be evaluated according to the following scale:

Mild	Adverse event resulting in discomfort, but not sufficient to cause interference in normal daily activities.
Moderate	Adverse event resulting in discomfort that is sufficient to cause interference in daily activities.
Severe	Adverse event resulting in discomfort causing an inability to carry out normal daily activities.

Adverse Event monitoring and reporting will be followed-up until resolution or for up to 2 weeks following completion of the study, after which the Investigator will decide the course of action.

9.13.1.3 Assessing Relationship to Study Drug

The Investigator will assess the relationship of all AEs to the drug, using the following scale:

Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanation.
Unrelated	This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

All AEs will be evaluated by the Investigator, who must approve the subject for subsequent dosing.

The Investigator or designee will be present from approximately 30 minutes prior to each dosing until at least 8 hours post-dose for each subject. The Investigator or designee will remain on-call throughout the duration of each study subject's visit.

9.13.1.4 Follow-up of AEs

Any AEs, whether serious or non-serious, will be monitored throughout the study and followed to resolution or for up to 2 weeks after the last PK blood draw, after which the Investigator will decide the course of action.

9.13.2 Procedures for Reporting Adverse Events

Subjects will be instructed to inform clinical personnel of AEs that may arise during the course of the study. Treatment of any AEs will be administered under the direction of the Investigator.

All symptoms will be recorded by clinical staff and will be reviewed by the Investigator prior to any subsequent dosing.

When appropriate, medical tests and examinations will be performed to document resolution of the event(s).

Adverse events will be coded into the Preferred Term (PT), classified according to the current version of Medical Dictionary for Regulatory Activities (MedDRA) with System Organ Classification (SOC) and reported with severity, duration, onset time and relationship to study drug and action taken.

Female subjects of child-bearing potential must have a negative serum pregnancy test at all treatment visits. Following administration of study drug, any known cases of pregnancy in female subjects will be reported until the subject completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed Pregnancy Report to the Sponsor's safety representative, Syneos Health Safety & Pharmacovigilance within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor's safety representative, Syneos Health Safety & Pharmacovigilance of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by emailing/faxing a completed SAE form to the Sponsor's safety representative, Syneos Health Safety & Pharmacovigilance within 24 hours of knowledge of the event.

SAEs will also be reported to the Sponsor's safety representative, Syneos Health Safety and Pharmacovigilance via e-mail (preferred) or fax within 24 hours of first knowledge by the Investigator. The notification must be directed to:

Syneos Health Safety and Pharmacovigilance Fax Number: +1 866 856 1649 Email: SafetyPV@syneoshealth.com

The following Sponsor personnel are to be contacted on the occurrence of a SAE:

Allen H. Heller, MD, MPH Pharma Study Design LLC Office phone: 203-389-2324 24-hour phone: 908 300 7986

9.14 Reportable Disease

In the case a subject has or manifested any clinical signs characteristic of a reportable disease or condition (e.g., HIV, Hepatitis B or C), it is the responsibility of the Principal Investigator to notify the public health department of the State of Florida by telephone or fax, as soon as possible and within the appropriate timelines.

10. Study Termination

The study may be terminated by the Principal Investigator following consultation with the Sponsor, by the Sponsor or by the regulatory authorities. Following a decision to discontinue the trial, the Principal Investigator will immediately inform the active study subjects and the IRB/IEC responsible for this trial, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study subjects or other persons. It is the Sponsor's responsibility to report the premature termination of the study to the regulatory authority(ies), when required by the applicable regulatory requirement(s).

11. Analytical Methodology

Each plasma sample for PK analysis will be aliquoted in 2 samples. One set of aliquots from all subjects will be delivered to the analytical facility packed on a sufficient amount of dry ice so that the samples remain frozen for at least 72 hours. Once the initial set has been confirmed to have been received by the analytical facility, the second set of aliquots will then be delivered, if requested.

All shipments will be accompanied by an inventory list and delivered to the following address:

inVentiv
2500, rue Einstein
Québec (Québec), Canada, G1P 0A2
Attn: Sample Management
Tel.: 1-418-527-4000
Fax: 1-418-527-3456
E-mail: DL-SamplesControllerQuebec@syneoshealth.com

Clinical personnel will notify the analytical laboratory prior to shipment by phone, fax or e-mail.

The Bioanalytical Division of inVentiv will analyze diazepam and nordiazepam in plasma samples using a validated method.

Analyst and Watson LIMS (Laboratory Information Management System) will be used at different steps of the analysis.

Samples from subjects included in the pharmacokinetic population (see section 12.2.2) and from subjects who were withdrawn from the study due to adverse events or vomiting episodes will be analyzed.

12. Pharmacokinetic and Statistical Analyses

Pharmacokinetic analysis will be performed using Phoenix® WinNonlin®, which is validated for bioequivalence/bioavailability studies by inVentiv. Inferential statistical analyses will be performed using SAS® according to FDA guidelines.

12.1 Pharmacokinetics

The following pharmacokinetic parameters will be calculated by standard non-compartmental methods for diazepam and nordiazepam:

1) AUC_{0-t}: area under the concentration-time curve from time zero to the last non-zero concentration
2) AUC_{0-inf}: area under the concentration-time curve from time zero to infinity (extrapolated)
3) C_{max}: maximum observed concentration
4) Residual area: calculated as $100*(1- AUC_{0-t} /AUC_{0-inf})$
5) T_{max}: time of observed C_{max}
6) $T_{½\ el}$: elimination half-life
7) K_{el}: elimination rate constant
8) Cl/F: Apparent Total Clearance (L/hr) estimated from dose/AUC_{0-inf}
9) V_d/F: Apparent Volume of distribution (L) estimated from Cl/K_{el} (β)
10) Cl/F/kg: Apparent Total Clearance/kg (L/hr) estimated from dose/kg/AUC_{0-inf}
11) V_d/F/kg: Apparent Volume of distribution/kg (L) estimated from Cl/K_{el} (β)/kg

12.2 Analysis Populations

12.2.1 Safety Population

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

12.2.2 Pharmacokinetic Population

The pharmacokinetic population will include all subjects completing at least Period 1 and Period 2 with no significant violation of study restrictions, and for whom the pharmacokinetic profile can be adequately characterized. Any subject who completes only one period will be presented in the concentrations and pharmacokinetic tables but excluded from descriptive statistics and ANOVA.

A violation of the requirement to maintain a stable regimen of AEDs or a stable regimen of other concomitant drugs with the potential to influence diazepam pharmacokinetics will be considered a significant violation of study restrictions. A change of drug in the prescribed AED regimen and/or change in the dose of a prescribed AED will be considered a departure from a stable regimen. Any subject who does not maintain a stable AED regimen in the course of the study will be presented in the concentrations and pharmacokinetic tables but excluded from descriptive statistics and ANOVA. For cases in which a departure from a stable AED regimen is a matter of judgment, the decision will be made by the Principal Investigator/Sub-Investigator and/or by the CRO PK Scientist in consultation with the Sponsor prior to bioanalysis.

Any subject with diazepam or nordiazepam pre-dose concentrations will be presented in the concentrations and pharmacokinetic tables but excluded from descriptive statistics and ANOVA if the pre-dose concentration is greater than 5% of the C_{max} value for that analyte of that period for that subject.

Subjects withdrawn due to vomiting episodes as per criterion established under section 9.12 or due to adverse events will be presented but excluded from the statistical analyses (i.e., descriptive statistics and ANOVA).

Data from subjects who experienced emesis during the sampling interval and who were not withdrawn as per criterion established under section 9.12 may be evaluated after completion of the pharmacokinetic analysis. Any subject who experienced emesis within 2 times median T_{max} of the current study (based on the reference product) will be excluded from the statistical analysis (i.e., descriptive statistics and ANOVA).

12.3 Statistical Analyses

Demographic parameters will be summarized descriptively. Treatment-emergent adverse events will be summarized descriptively by treatment for all subjects who were dosed (safety population). No inferential statistical analysis of safety data is planned.

Individual and mean plasma concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation [SD], coefficient of variation [CV%], minimum [Min], maximum [Max], and median) of the plasma concentrations versus time and the pharmacokinetic parameters will be presented for the Test and the Reference products for each weight category as well as irrespective of weight category.

For diazepam and nordiazepam, using GLM procedures in SAS, ANOVA will be performed on untransformed T_{max}, K_{el}, and $T_{½\ el}$ and on ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, Cl/F, Cl/F/kg, V_d/F, and V_d/F/kg at the alpha level of 0.05. Factors incorporated in the model will include: Sequence, Subject(Sequence), Period, and Treatment. T_{max} will be analyzed using an additional non-parametric test (Wilcoxon signed-rank test).

12.3.1 Treatment Comparison DBF (Test) versus DRG (Reference) Following a Moderate-Fat Meal

The ratio of geometric means will be calculated for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} for the Test product versus the Reference product (Treatment A/Treatment B) irrespective of weight category. The 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data will also be calculated. Intra and inter-subject coefficient of variation will be estimated.

12.3.2 Treatment Comparison DBF (Test) versus DRG (Reference) Following Different Meal Conditions

An exploratory pair-wise analysis comparing DBF following a high-fat meal (Treatment C) with DRG following a moderate-fat meal (Treatment B) will be conducted and reported.

The ratio of geometric means will be calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max} for Treatment C versus Treatment B, irrespective of weight category. The 90% confidence interval for the ratio of geometric means, based on least-squares means from the ANOVA of the ln-transformed data will also be calculated. Intra and inter-subject coefficient of variation will be estimated.

Additional analyses may be performed.

Details of the pharmacokinetic and statistical analyses will be provided in the SAP.

12.4 Safety and Tolerability Parameters and Analyses

Demographic parameters will be summarized descriptively.

Safety and tolerability to DBF will be evaluated through the assessment of AEs (i.e., seriousness, severity, relationship to the study drug, outcome, duration, and management), vital signs, clinical laboratory parameters and physical examination. Treatment-emergent AEs will be summarized descriptively by treatment for all subjects who were dosed (safety population). Changes from baseline values in vital signs, ECG, and clinical laboratory parameters will be evaluated. Safety and tolerability data will be reported using descriptive statistics. No inferential statistical analysis of safety data is planned.

Details of the safety and tolerability analyses will be provided in the SAP.

13. Final Report

A final report including clinical, bioanalytical, and statistical sections will be the responsibility of inVentiv.

In the event that the study is prematurely terminated, inVentiv will produce an abbreviated safety report. In such an event, raw data will not be submitted with the abbreviated report but will be archived at inVentiv, unless requested by the Sponsor.

14. Regulatory Considerations and Quality Assurance

14.1 Independent Ethics Committee Approval of Protocol and Other Study Documents

The Investigator(s) agree to provide the IRB/IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's Brochure (if any) and any other written information provided to study subjects. The trial will not begin until the Investigators have obtained the IEC favourable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each subject prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept by the Investigator and a copy will be given to the subject.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each subject's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each subject's consent.

The Investigators and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary.

14.2 Compliance

This study will be conducted in compliance with the protocol, GCP, GLP, and all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), and any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory.

14.3 Audits, Inspections and Monitoring

All source documents and laboratory reports will be Quality Control reviewed to ensure accuracy and completeness. Adverse events will be reviewed and assessed for severity and causality by the Principal Investigator/Sub-Investigator.

In accordance with the principles of GCP and GLP, the study may be inspected by regulatory authorities, the Sponsor, and the CRO. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

15. Confidentiality

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

All information on a subject obtained during the conduct of the study will be kept confidential. Subjects will be identified by an anonymized identifier on all samples and study records provided to the Sponsor or designee. In compliance with ICH GCP, the Sponsor's authorized representatives, monitor(s), auditor(s), IEC, and regulatory authority(ies) will be granted direct access to the subject's original trial-related records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations. Consent from the subject for disclosure of such information will be obtained in writing in the ICF. In addition, should a subject requires medical care or hospitalization during the course of the study, the clinical site's representatives may contact the treating physician with the subject's consent, except that consent may not be requested if there is an emergency situation. If the results of the study are published, the subject's identity will remain confidential.

16. References

1 Diazepam Buccal Film (DBF) Investigator's Brochure_4.0_XX Dec 2018

2 Physician's Desk Reference (PDR). Diazepam – drug summary. http://www.pdr.net/drug-summary/Valium-diazepam-2100. Accessed 01 October 2018.
3 Diastat® AcuDial™ C-IV label, FDA revision date 12/2016, available at: www.accessdata.fda.gov/drugsatfda_docs/label/2013/013263s092lbl.pdf.
4 Valium® (diazepam) label, FDA revision date 12/16/2016, available at: www.accessdata.fda.gov/drugsatfda_docs/label/2013/013263s092lbl.pdf.
5 Bonate PL, Howard D. Pharmacokinetics in drug development: Problems and Challenges in Oncology. Switzerland: Springer; 2016.
6 Bonate PL, Howard D. Pharmacokinetics in drug development: Problems and Challenges in Oncology. Switzerland: Springer; 2016.
7 FDA Guidance for Industry – Food-Effect Bioavailability and Fed Bioequivlence Studies, 2002.

17. Appendix I – Diazepam PK Study Participant Questions

SECTION 1

Audience: Study Participants – Subjects Enrolled in Study 180323

Timeframe: Prior to Dosing

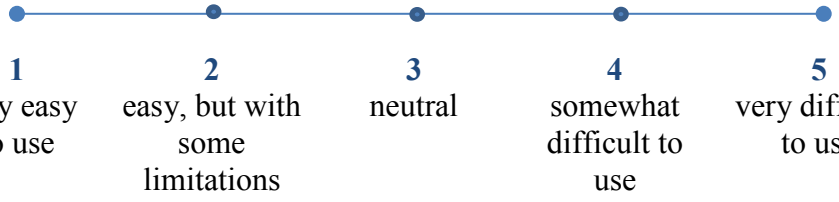
Areas of Interest: Current rescue medication, previous experience with Diastat (if any), preferred route of administration

Questions:

1) What is your current rescue medication treatment?

A) Diastat
B) Extra dose of usual maintenance medication
C) Oral diazepam
D) ER visit/call 911
E) No treatment

2) If you have used Diastat (diazepam rectal gel) in the past, how would you rate the experience in terms of ease of use for your caregiver?



3) How would your ideal rescue medication be taken?

A) orally – via the mouth
B) rectally
C) nasally – as a nasal spray

SECTION 2

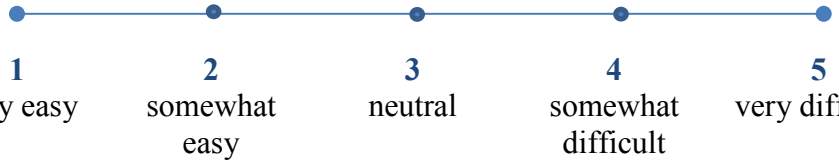
Audience: Study Participants – Subjects Enrolled in Study 180323

Timeframe: Post Diazepam Buccal Film (DBF) Dosing

Areas of Interest: Experience with DBF, perceptions of ease of use, comparison to Diastat experience, ability to self-administer

Questions:

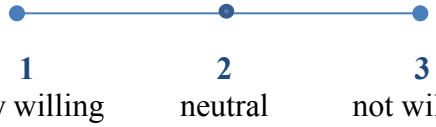
1) How would you rate the experience of taking DBF?



2) Do you prefer DBF over DRG?

A) yes
B) no

3) How willing would you be to use DBF in public following a seizure (at work, in a public setting, etc.)?



4) Do you prefer DBF vs a medication that requires a device to use?

A) yes
B) no

SECTION 3

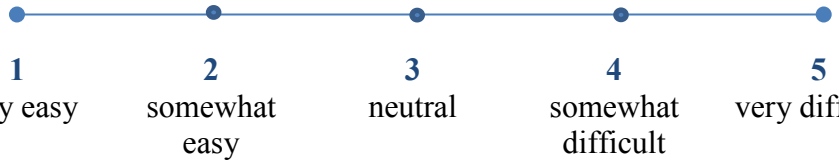
Audience: Study Administrators

Timeframe: Post DBF Dosing

Areas of Interest: Experience with DBF, ease of administration

Questions:

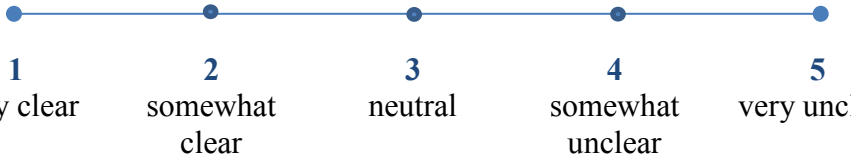
1) How would you rate the experience of administering DBF?



2) Do you prefer to administer DBF over Diastat?

A) yes
B) no

3) How clear were the administration instructions for DBF?



1	2	3	4	5
very clear	somewhat clear	neutral	somewhat unclear	very unclear

18. Appendix II – Study Restrictions

Restriction Period	Item Restricted	Examples
6 months prior to first study drug administration until the last blood draw in the final study period	Females: implanted, injected, or intravaginal hormonal contraceptive	
3 months prior to screening until the last blood draw in the final study period	Marijuana and THC containing products other than as a prescribed AED	
30 days prior to first drug administration until the last blood draw in the final study period	Enzyme-modifying drugs (Strong Inhibitors)	Strong inhibitors of CYP enzymes (e.g. Cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals);
	Females: oral or transdermal hormonal contraceptives other than a continuous 28-days treatment cycle	
	Monoamine oxidase (MAO) inhibitors Note: until 14 days after the last study drug administration	Phenelzine, tranylcypromine
	Phenothiazines	Chlorpromazine
	Diazepam and any benzodiazepines	
	Prescription medication other than a prescribed drug that is part of a stable drug regimen*	Prescription pills, topical systemic creams, inhalants, sprays.
	OTC medication other than an OTC drug that is part of a stable drug regimen* Note: Spermicidal/barrier contraceptive products may be permitted	
	dietary and/or herbal supplements and/or teas	Ricola, oral multivitamins
	Foods and/or beverages containing grapefruit, star fruit and/or pomelo	Grapefruit, grapefruit juice, grapefruit candies, pomelo, star fruit, etc.

Restriction Period	Item Restricted	Examples
48 hours prior to drug administration until after the last blood draw in each study period.	Products containing caffeine/methylxanthines	Coffee, tea, chocolate, caffeine-containing soft drinks (e.g. Coke, Pepsi, Red Bull)
	Alcohol of any kind	Wine, beer, liquor, cocktails
	Poppy seeds Note: 48 hours prior to drug administration in each period only	Poppy seed cake, cookies, bagels

*A stable drug regiment is defined as at least once a day administration from at least 30 days prior to the first study drug administration and with no changes expected in dosage regimen through the study (until the last PK sample).

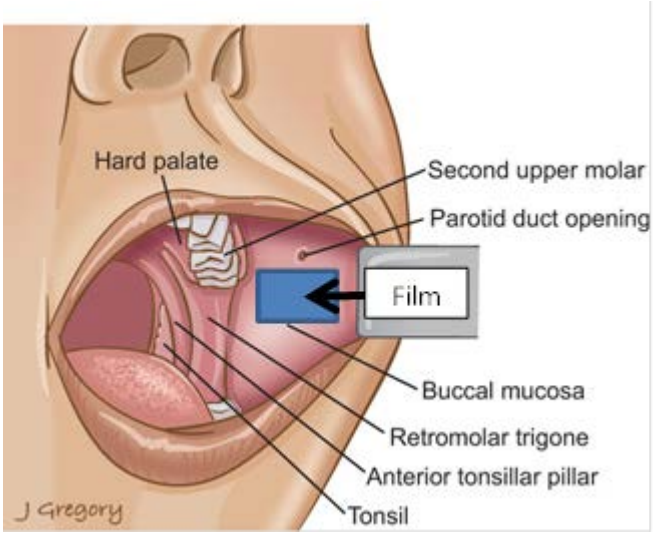
19. Appendix III - Placement Diagram for Aquestive Therapeutics Buccal Film

Test Drug: Placement against the buccal mucosa (either side of film can be placed against the buccal mucosa):

Aquestive Therapeutics film is to be centered against the inner aspect of the right or left cheek, as illustrated by the Figure below. The film may be placed without regard to the location of the parotid duct.

Ensure film is completely adhered to the mucosal surface.

Note: Figure is for illustrative purposes and not drawn to scale.



20. Appendix IV - Placement Diagram for DIASTAT® AcuDial™ Rectal Delivery System