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

Protocol Number: 160325 (Crossover)

Amendment 4

Protocol Amendment 4 Date: March 6, 2020
Protocol Amendment 3 Date: September 6, 2018
Protocol Amendment 2 Date: April 16, 2018
Protocol Amendment 1 Date: August 4, 2017
Original Protocol Date: April 16, 2018

Sponsor:
Aquestive Therapeutics
30 Technology Drive
Warren, NJ 07059
USA

Phase 2

IND Number: 129068

Confidentiality Statement

PROTOCOL AMENDMENT: SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Original	June 5, 2017
Amendment 1	August 4, 2017
Amendment 2	April 16, 2018
Amendment 3	September 6, 2018

Protocol 160325 Amendment 4

Date of Amendment: March 6, 2020

Amendment Summary

This summary provides the changes made to Protocol 160325 Amendment 3 (September 6, 2018) as Amendment 4.

The Protocol 160325 Amendment 3 is being amended to: 1) update Diazepam Buccal Soluble Film to Diazepam Buccal Film for consistency with current nomenclature; 2) include the end-date for study enrollment; 3) amend inclusion criterion #3 statement of weight range for study enrollment

Following is a summary of content-oriented changes made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Throughout	Diazepam Buccal Soluble Film has been changed to Diazepam Buccal Film	The generic name of the Investigative Product has been updated for consistency with current nomenclature.
Section 3 Synopsis	New section added: Enrollment End-Date : Enrollment end date is 05 March 2020.	Enrollment end-date is 05 March 2020.
Section 8.1.3 Treatment Periods	Bulleted text added in the section Check-in Procedures: Enrollment end date is 05 March 2020.	

Section	Revision	Rationale
Table 8 Schedule of Events	Footnotes added to the Schedule of Assessments: Check-in † Enrollment end date is 05 March 2020.	Enrollment end-date is 05 March 2020. *Continued→*
Section 9 Subject Selection	Sentence added: Enrollment end date is 05 March 2020.	
Section 3 Synopsis	Experimental Design and Study Population Note added to the description of the study population: Subjects will be 2 to 16 years of age, inclusive, with a body weight of ≥6 kg and ≤111 kg. NOTE: Subjects with body weight in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the Investigator.	Subjects with body weight in the range of 112 to 134 kg are allowed to participate in the study at the discretion of the Investigator.
Table 3 Rationale for Dosage of Diazepam Buccal Film in Section 6.5 Rationale for the Dose Regimen of Diazepam Buccal Film	Note added to the table: [a] Subjects with body weight in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the Investigator.	
Table 9 Calculated Prescribed Dose of Diazepam Buccal Film	Note added to the table: [a] Subjects with body weight in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the Investigator.	
Section 9.2.1 Inclusion Criteria	Note added to criterion #3: 3.Subjects have a body weight of ≥6 kg and ≤111 kg.† † Subjects with body weight in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the Investigator.	

1. PROTOCOL APPROVAL

STUDY TITLE: **A Multicenter, Open Label Crossover Study to Assess the Pharmacokinetics and Safety of Diazepam Buccal Soluble Film (DBSF) in Pediatric Subjects with Epilepsy**

SPONSOR APPROVAL

I have read this protocol and agree that the sponsor will use appropriate control processes to ensure that the sponsor's activities meet the requirements of applicable regulatory agencies.

Gary Slatko MD	Date
Senior Vice President, Chief Medical Officer	
Aquestive Therapeutics	

INVESTIGATOR PROTOCOL AGREEMENT

I have read this protocol and agree to comply with all of the procedures contained within this protocol and requirements of applicable regulatory agencies.

Investigator Date:

Institution: _____

Address: _____

_____

2. CONTACT INFORMATION AND FACILITIES

Sponsor:	Gary Slatko MD Senior Vice President, Chief Medical officer Aquestive Therapeutics 30 Technology Drive Warren, NJ, 07059 USA
Sponsor's Responsible Study Manager:	Frances Ekweonu Clinical Trail Manager, Clinical Operations Aquestive Therapeutics 30 Technology Drive Warren, NJ 07059 USA Telephone: 1-908-941-1941
Clinical Research Organization:	Syneos Health 202 Carnegie Center Princeton, NJ 08540 USA Tel.: 1-609-951-6800
Clinical Laboratory:	Covance Central Laboratory Services 8211 Scicor Drive Indianapolis, IN 46214 USA Tel.: 1-888-268-2623 or 1-317-271-1200
Analytical Facility:	Syneos Health Clinique 2500, rue Einstein Québec City, Québec, Canada, G1P 0A2 Tel.: 1-418-527-4000
Pharmacokinetic/Statistical Facility:	Syneos Health Clinique 2500, rue Einstein Québec City, Québec, Canada, G1P 0A2 Tel.: 1-418-527-4000

Contract Research Organization Safety (Pharmacovigilance) Reporting:	Syneos Health Global Safety & Pharmacovigilance Facsimile: 1-866-856-1649 Telephone Hotline No.: +1-888-750-8020 E-mail: saereceipt.international@syneoshealth.com

3. SYNOPSIS

Title:	A Multicenter, Open Label Crossover Study to Assess the Pharmacokinetics and Safety of Diazepam Buccal Soluble Film (DBSF) in Pediatric Subjects with Epilepsy
Objectives:	The primary objective is to assess the pharmacokinetics of Diazepam Buccal Film (DBF) in pediatric subjects with epilepsy (A) in the interictal state, and (B) in the ictal/peri-ictal state. (A) Subjects are considered to be in an interictal state if an interval of at least 3 hours has elapsed since any clinical observable postictal signs or symptoms (from the last observed seizure) and the subject has been seizure free over this period. Subjects on electroencephalogram (EEG) monitoring can be considered to be in an interictal state if an interval of at least 3 hours has elapsed since any postictal electrical findings on EEG. (B) For the purposes of this study, the ictal state is defined as an ongoing clinically observable seizure or seizure activity as verified via EEG. The peri-ictal state is defined as the subject's immediate postictal state following a generalized tonic-clonic (GTC) seizure or focal seizure with impaired awareness, and within 5 minutes after the last clonic jerk. For subjects on EEG monitoring, the peri-ictal state may be defined as less than 5 minutes after cessation of seizure activity (GTC or focal seizure with impaired awareness) as verified via EEG. Secondary objectives: • Evaluate the safety/tolerability of DBF in pediatric subjects with epilepsy • Evaluate the usability of DBF
Experimental Design and Study Population:	Multicenter, open-label crossover study in pediatric epilepsy subjects to assess the pharmacokinetics and safety of DBF during the interictal state (Treatment Period A) and during the ictal/peri-ictal state (Treatment Period B). Male or female pediatric subjects with a clinical diagnosis of epilepsy admitted to an Epilepsy Monitoring Unit (EMU) or a General Clinical Research Center (GCRC) or similar facility for evaluation of seizures. Subjects will be 2 to 16 years of age, inclusive, with a body weight of

	≥6 kg and ≤111 kg. NOTE: Subjects with body weight in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the Investigator. Subjects aged 2 to 5 years will undergo Treatment B only and will not undergo Treatment A. Subjects aged 6 to 16 years will undergo both Treatment A and Treatment B.
Number of Subjects:	To provide adequate pharmacokinetic, safety, and usability assessment of DBF in the pediatric population, 16 to 18 subjects should complete the study, distributed across three age ranges as follows: 6 subjects aged 2 to 5 years, 6 subjects aged 6 to 11 years, and 4 to 6 subjects aged 12 to 16 years. To ensure an adequate number of completed subjects by age range, efforts will be made to enroll approximately 8 subjects in each range, for a total of 24 enrolled subjects.
Enrollment End-Date:	Enrollment end-date is 05 March 2020.
Phase:	2
Test Drugs:	Diazepam Buccal Film 5 mg (Aquestive Therapeutics) Diazepam Buccal Film 7.5 mg (Aquestive Therapeutics) Diazepam Buccal Film 10 mg (Aquestive Therapeutics) Diazepam Buccal Film 12.5 mg (Aquestive Therapeutics) Diazepam Buccal Film 15 mg (Aquestive Therapeutics) Diazepam Buccal Film 17.5 mg (Aquestive Therapeutics)
Treatments:	In each of the two treatment periods, subjects will receive a single dose of DBF. DBF is provided in a range of doses from 5 to 17.5 mg. The appropriate dose of DBF will be assigned on the basis of age and weight using an interactive web response system (IWRS) during check-in for the subject's first treatment period. The dose for the second treatment period will be the same as that for the first treatment period.
Duration of Treatment Periods:	Each treatment period will last from admission to the EMU/GCRC until 4 hours after DBF administration.

Study Duration:	• The minimum study duration will be approximately 30 days for subjects aged 6 to 16 years (inclusive)*and 15 days for subjects aged 2 to 5 years (inclusive)**, with a maximum of approximately 58 days, consisting of Screening Period: 0 to 28 days prior to Day 1. * Age range 6 to 16 years (inclusive): beginning at the year 6 birthday until the year 17 birthday. **Age range 2 to 5 years (inclusive): beginning at the year 2 birthday until the year 6 birthday. • Treatment Period A (interictal, subjects aged 6 to 16 years): 1 day (from admission to the EMU/GCRC until 4 hours after DBF administration). • Minimum washout period of 14 days between DBF treatment periods • Treatment Period B* (ictal/peri-ictal, all subjects): 1 day (from admission to the EMU/GCRC until 4 hours after DBF administration). * Period A and Period B may occur in either order, depending on seizure occurrence (i.e., if subject experiences a seizure during the first visit to the EMU or GCRC, the Investigator may regard that period as Treatment Period B). • Follow-up Visit: A follow-up visit will be scheduled to obtain safety data 14 days (±2 days) after the second treatment period.
Dosing Time:	The treatment periods will begin at a time of day consistent with usual EMU/GCRC protocol. In Treatment Period A, DBF will be administered as soon as check-in procedures have been completed. In Treatment Period B, the subject will be monitored for seizure activity, and DBF will be administered as soon as possible after detection of seizure activity, within 5 minutes after the last clonic jerk or within 5 minutes of cessation of the seizure as verified via EEG.
Safety Monitoring and Endpoints:	Clinical seizure monitoring (both treatment periods) will start prior to DBF treatment and will continue for 4 hours after dosing, or longer at the discretion of the EMU or GCRC Investigator. Continuous video EEG monitoring for seizure detection will be performed as indicated by EMU or GCRC protocol. Sites will maintain the EEG recordings with the study documents, but data from the EEG recordings will not be collected for the study dataset. The following safety assessments will be performed during the study:

- Columbia Suicide Severity Rating scale (C-SSRS; age-appropriate version) in subjects age 7 and older at Screening, before dosing during Treatment Periods A and B, and at Follow-up
  For non-verbal subjects, the C-SSRS assessments should be personally completed by the subject using non-verbal methods with assistance of site staff trained for these assessments. If the scales cannot be completed, the site must document this.
- Serum pregnancy test in females of childbearing potential, urine drug screen, and breath alcohol test at Screening. Urine pregnancy test, urine drug screen, and breath alcohol test before dosing (Treatment Periods A and B), and at Follow-up
- 12-lead ECG at Screening, and for each treatment period before DBF administration and 4 hours after dose administration.
- Vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], and temperature) will be recorded at Screening and (Treatment Periods A and B) prior to DBF administration. BP, HR, and RR will be recorded post dose at 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes), and 4 hours (240 minutes) and at Follow-up.
- Oxygen saturation (SaO_2) measured via pulse oximetry, Screening and (Treatment Periods A and B) prior to DBF administration and at 5, 10, 20, 30, 40, 50 minutes post dose and thereafter at each time vital signs are recorded: 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes), and 4 hours (240 minutes) and at Follow-up.
- Clinical laboratory tests (hematology, serum chemistry, and urinalysis) at Screening and at Follow-up or at early termination.
- Physical and neurological examination at Screening and at Follow-up or at early termination.
- Oral mucosal inspection to assess for any local irritation conducted by the Investigator at the following times:

- At Screening;
- During Treatment Periods A and B prior to dosing and at approximately 0.25 hours (15 minutes), 0.5 hours (30 minutes), and 1 hour (60 minutes) after application of DBF; and
- At Follow-up or early termination visit*
  * If an enrolled subject's participation is terminated prematurely or the subject withdraws from the study, the procedures scheduled for the follow-up visit will be performed.

- Any abnormalities detected after dosing will be followed as treatment emergent adverse events (TEAEs) until resolution.
- Type, incidence, and severity of adverse events (AEs) at all visits

The Investigator or physician designee will be present from approximately 30 minutes prior to dosing until at least 2 hours post dose for each subject for each treatment period. The Investigator or physician designee will remain on call throughout the duration of each study subject's visit. The Investigator will be responsible for ensuring that a study subject is sufficiently medically stable to be safely discharged from the clinical unit (EMU or GCRC) regardless of whether the subject has received study drug.

Usability Endpoints: The following usability assessments will be performed during the study:

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

Pharmacokinetic Endpoints: The following pharmacokinetic parameters for diazepam will be determined:

- Observed peak drug concentration (C_{max})
- Observed time to reach maximum drug concentration (T_{max})

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

	Collection of plasma samples will continue even if the administration of another anti-eptileptic drug (AED) is needed for rescue.
Total Blood Volume:	A total of approximately 35.4 mL of blood will be taken during the entire study for clinical chemistry, hematology, and pharmacokinetics: 3.7 mL at Screening, 14 mL during Treatment Period A, 14 mL during Treatment Period B, and 3.7 ml at the Follow-up Visit.
Analyte(s) To Be Measured:	Plasma samples will be assayed for diazepam and desmethyldiazepam using a validated analytical method according to the principles of Good Laboratory Practice.
Statistical Analysis:	Summary statistics will be reported for pharmacokinetic, safety, and usability endpoints. No formal statistical tests will be performed to compare Period A vs. Period B on pharmacokinetic, safety, or usability endpoints. All analyses will be descriptive and exploratory. Summary statistics of pharmacokinetic data will include intra-subject comparisons of C_{max} and T_{max} for diazepam. Summary statistics will be presented by age category and weight category, and data will be explored for the potential influence of concomitant medications. No efficacy analysis will be performed. The following age categories will be used for analysis: ages 2 to 5 years, ages 6 to 11 years, and ages 12 to 16 years.

4. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_t	area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first. AUC_t is estimated using the trapezoidal method.
AUC_{inf}	area under the concentration-time curve from time zero to infinity, calculated as $AUC_t + C_{last}/\lambda$, where C_{last} is the last measurable concentration.
BLQ	below the limit of quantitation / below quantitation limit
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CI	confidence interval
C_{last}	the measured last quantifiable concentration.
C_{max}	the maximal observed plasma concentration.
eCRF	electronic case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome
DBF	Diazepam Buccal Film, formerly referred to as Diazepam Buccal Soluble Film
ECG	electrocardiogram
EMU	Epilepsy Monitoring Unit
FDA	Food and Drug Administration
$GABA_A$	gamma-Aminobutyric acid, or γ-aminobutyric acid type A
GCP	Good Clinical Practice
GCRC	General Clinical Research Center
GTC	generalized tonic-clonic (seizure)

Abbreviation	Definition
HIV	human immunodeficiency virus
HR	heart rate
ICF	Informed Consent Form
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliters
ms	millisecond
mmHg	millimeter of mercury
PK	pharmacokinetic(s)
PT	Preferred Term
RBC	red blood cell
RPM	revolutions per minute
RR	respiratory rate
SAE	serious adverse event
SAS®	Statistical Analysis System
SaO_2	(blood) oxygen saturation
SOC	System Organ Classification
SOP	Standard Operating Procedure
$T_{1/2}$	terminal elimination half-life, estimated as $\ln(2)/\lambda$
THC	tetrahydrocannabinol
T_{max}	time when the maximal plasma concentration is observed
UBG	urobilinogen
WBC	white blood cell

5. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

6. BACKGROUND AND PHARMACOKINETICS

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

6.1. Treatment and Management of Refractory Patients with 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 (Cereghino, 2007). When these seizures occur outside a hospital, the patient is often transported to an acute care facility for treatment to prevent prolonged seizures (Lowenstein and Alldredge, 1998). 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 (Bergen, 2006; Matheson et al, 2000; Sankar and Rho, 2007).

In these cases, the primary goals of the treatment are seizure cessation and prevention of seizure recurrence (Cereghino, 2007). 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 (Glauser, 2007).

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. While rectal diazepam gel is currently available in the United States, a portion of the population does not benefit from

this treatment, partly because the rectal route of administration is inappropriate or unacceptable (Fisgin et al, 2002). Therefore, there is an unmet medical need for an effective treatment with a rapid onset of action that is easily administered in the outpatient setting.

6.2. Diazepam

Diazepam is a long-acting "classical" benzodiazepine with potent inhibitory activity at the γ-Aminobutyric acid type A (GABA-$_A$) receptor and demonstrates anticonvulsant properties. It is commonly used to treat a range of conditions including seizures, anxiety, alcohol withdrawal syndrome, benzodiazepine withdrawal syndrome, muscle spasms, trouble sleeping, and restless legs syndrome (Calcaterra and Barrow, 2014). It can be taken by mouth, inserted into the rectum, injected into muscle, or injected intravenously. When given intravenously, effects begin in 1 to 5 minutes. When diazepam is taken orally, effects may be delayed as long as 40 minutes (Riss et al, 2008).

Intravenous diazepam is a first-line treatment for status epilepticus (Riss et al, 2008). Diazepam rectal 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 (Riss et al, 2008). However, diazepam is effective when used intermittently for the prevention of repeated seizures. Like other benzodiazepines, diazepam administration may cause sedation, anxiolysis, and amnesia (Riss et al, 2008).

6.2.1. Mechanism of Action

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 ($GABA_A$). GABA, the major inhibitory neurotransmitter in the central nervous system, acts at this receptor to open the membrane channel allowing chloride ions to flow into neurons (Tan et al, 2011). 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. Excessive depolarization of neurons is implicated in the generation and spread of seizures. It is believed that diazepam enhances the actions of GABA by causing GABA to bind more tightly to the $GABA_A$ receptor.

6.2.2. Metabolism and Elimination

Diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam) (Diastat® AcuDial™ rectal gel prescribing information). 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 (Dean, 2016).

6.2.3. Pharmacokinetics

Per the prescribing information, rectal administration of a 15 mg dose of Diastat® AcuDial™ rectal gel 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 (coefficient of variation [CV] = 43%) and 71 hours (Coefficient of Variation [CV] = 37%), respectively. Both diazepam and its major active metabolite desmethyldiazepam bind extensively to plasma proteins (95-98%).

6.3. Diastat® AcuDial™ Rectal Gel in the Treatment of Seizures

Although the Diastat® AcuDial™ rectal gel formulation is considered generally 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 patient and care-givers alike. For example, the patient or care-giver must first remove articles of clothing and then place the patient 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 patient injury

and leakage of gel from the rectum can result in incomplete dosing and the need for an additional dose to compensate for any loss. Additionally, the attitude of some patients toward a rectal route of drug administration is unfavorable which may negatively impact compliance to treatment (Tatum, 2002). Each of these factors has a potential influence on patient morbidity. Persistent seizure activity is associated with worse outcomes across a spectrum of precipitating conditions (Haut, 2006; Waterhouse et al, 1999). 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 (Kapur and Macdonald, 1997).

6.4. Diazepam Buccal Film

The new route of diazepam administration is via buccal film. Aquestive Therapeutics initiated development of DBF, specifically intended for buccal delivery for patients who require control of intermittent bouts of seizure activity. DBF contains the FDA approved active ingredient diazepam, a benzodiazepine, as a treatment for the management of selected, refractory patients with epilepsy, on stable regimens of antiepileptic drugs who require intermittent use of diazepam to control bouts of increased seizure activity. The DBF products, with a planned dose range of 5 mg to 15 mg, are 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) NDA using Diastat® AcuDial™ rectal gel as the reference therapy.

Buccal diazepam may be particularly well-suited for administration in outpatient settings. The DBF is administered by placing the film against the inner aspect of the cheek, where it adheres, dissolves, and releases the drug onto the buccal mucosa. Although buccal absorption is expected to be the primary route of absorption of the drug, some absorption through the gastrointestinal (GI) tract may be possible due to swallowing of the saliva. It is expected that use of the buccal film will be similar to the use of Diastat® AcuDial™ rectal gel, i.e., the film would be administered during or immediately after a seizure with characteristics for which the Diastat rectal gel would be indicated, and the goal of treatment would be the same as that of the rectal gel—to reduce the overall frequency of acute repetitive seizures.

There is no need to disrobe the patient during administration. Additionally, there is less potential for delay in treatment, and greater patient and caregiver acceptance with improved compliance may be expected. For patients with bouts of increased seizure activity, the development of a DBF will meet the treatment need for a form of diazepam that is effective, safe, allows reliable dose administration, and is easier to administer than

the rectal gel. Patients, caregivers, and physicians have indicated that this type of product would be desirable for acute, intermittent treatment of breakthrough, repetitive or cluster seizures.

The Phase 1 clinical studies of DBF have focused on assessing its bioavailability relative to the reference therapy, Diastat® AcuDial™ rectal gel, assessment of dose proportionality, and assessment of food effect. Overall safety and tolerability have been assessed in all clinical trials conducted with DBF. The results of Phase 1 studies to date are summarized in this section.

6.4.1. Pilot Studies 1899 and 1900

The two pilot studies were randomized, open label, single-dose, fasting condition, crossover studies in healthy male and female volunteers to assess the bioavailability of DBF in comparison to the same nominal dose of Diastat® AcuDial™ rectal gel. Study 1899 compared DBF 5 mg to Diastat® AcuDial™ rectal gel 5 mg, with 11 subjects completing both treatments. Study 1900 compared DBF 20 mg to Diastat® AcuDial™ rectal gel 20 mg, with 10 subjects completing both treatments.

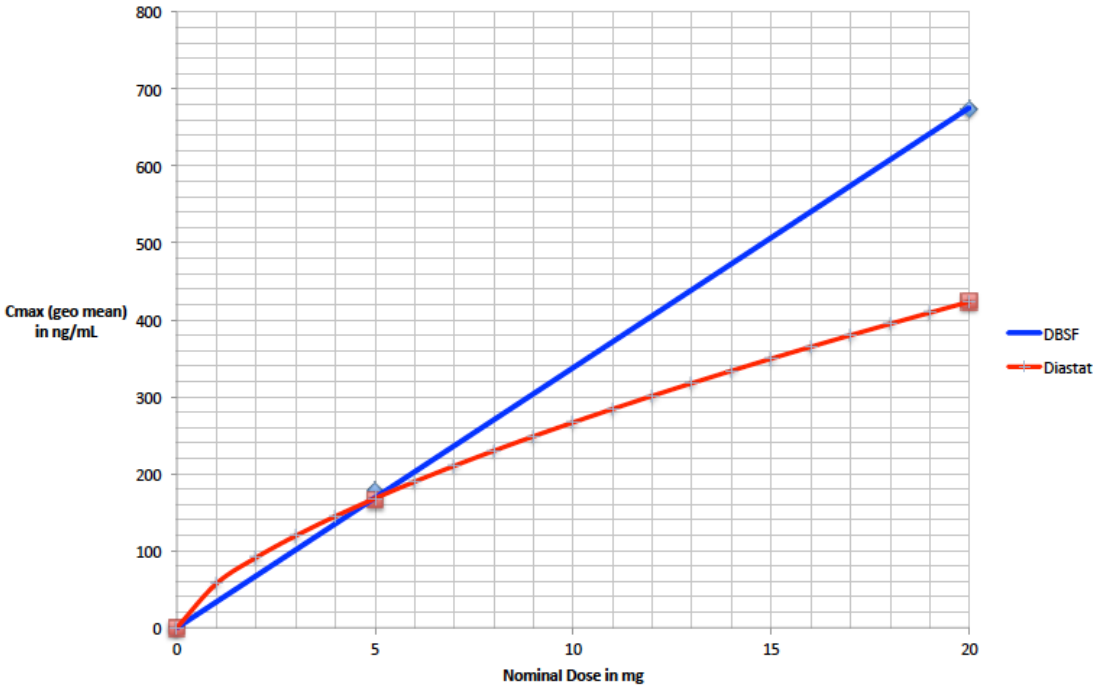
Study 1899 compared DBF 5 mg to Diastat® AcuDial™ rectal gel 5 mg. Among the 11 subjects who completed both treatments, DBF 5 mg was bioequivalent to Diastat® AcuDial™ rectal gel 5 mg with respect to area under the curve from time zero until the last measurable concentration or last sampling time t (AUC_t) and AUC from time 0 extrapolated to infinity (AUC_{inf}), i.e., the 90% confidence interval (CI) for the ratio of geometric means was within the acceptable range of 80-125%. For the observed peak drug concentration (C_{max}), the ratio of geometric means was 1.07 with the 90% CI 87.1 131.5%. The median observed time to reach maximum drug concentration (T_{max}) was 0.67 hours for the DBF (range 0.33-1.50 hours) and 0.25 hours for the Diastat® AcuDial™ rectal gel (range 0.15-1.00 hours). The difference in T_{max} values was not statistically significant.

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® 20 mg rectal gel, with the ratio of geometric means for AUC_t and AUC_{inf} within the acceptable range of 80-125%. For C_{max}, the ratio of geometric means was 158.72% with 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 DSBF and Diastat® showed that although the C_{max} was higher for the DSBF relative to Diastat®, the

pharmacokinetics were comparable in terms of rapid rate of absorption, duration of plateau, and the rate of elimination.

Figure 1 shows the C_{max} values for DBF vs. Diastat® at nominal doses of 5 mg in Study 1899 and 20 mg in Study 1900. These early data suggested that DBF 5 mg was nearly bioequivalent to Diastat® 5 mg. In contrast, because the C_{max} after administration of Diastat® 20 mg is lower than the C_{max} after DBF 20 mg, DBF 20 mg is not bioequivalent to Diastat® 20 mg. While it is difficult to assess dose-proportionality based on pilot studies conducted in separate groups of subjects, the pilot studies suggested that for DBF, both C_{max} and AUC are dose-proportional over the 5 mg to 20 mg dose range, whereas, for Diastat®, although AUC is dose-proportional (data not shown), C_{max} is less than dose-proportional. In light of this observation, at doses above 5 mg, the nominal dose of diazepam administered as DBF was expected to be lower than the therapeutically equivalent nominal dose of Diastat®.

Figure 1. C_{max} Values by Nominal Dose for DBF vs. Diastat®



Data are C_{max} values (geometric means) from pilot Studies 1899 (N=11) and Study 1900 (N=10). As shown in the figure, C_{max} values for DBF were approximately dose-proportional while C_{max} values for Diastat® were less than dose-proportional. ($AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were approximately dose-proportional for both DBF and Diastat® – data not shown.) Analysis of the individual data by linear regression indicated that the observed C_{max} values for DBF were consistent with a direct linear relationship between C_{max} and nominal dose, while the observed C_{max} values for Diastat® appeared to be linearly related to dose to the 2/3 power.

6.4.2. 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 DBF 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 DBF 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: DBF 5 mg/DBF 10 mg and C/B: DBF 15 mg/DBF 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_{0-t}, AUC_{0-inf}, and C_{max} were within 80.0% - 125.0%.

Table 1. Study 162013 – Dose-Proportionality of DBF at Doses of 5, 10, and 15 mg

Parameter[1]	Treatment Comparisons	Geometric Mean Ratio[2]	90% Confidence Interval[3]	
AUC_{0-t}	DBF 5 mg (A) – DBF 10 mg (B)	103.53%	99.51%	107.72%
AUC_{0-inf}	DBF 5 mg (A) – DBF 10 mg (B)	104.08%	99.43%	108.96%
C_{max}	DBF 5 mg (A) – DBF 10 mg (B)	104.57%	97.92%	111.67%
AUC_{0-t}	DBF 15 mg (C) – DBF 10 mg (B)	101.94%	97.62%	106.44%
AUC_{0-inf}	DBF 15 mg (C) – DBF 10 mg (B)	103.64%	98.52%	109.02%
C_{max}	DBF 15 mg (C) – DBF 10 mg (B)	98.84%	92.36%	105.78%

AUC_{0-inf} = area under the concentration-time curve from time zero to infinity; AUC_{0-t} = area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t; C_{max}= the maximal observed plasma concentration; DBF= Diazepam Buccal Film.
[1] Dose-normalized to 10 mg
[2] Calculated using least-squares means according to the formula $e^{DIFFERENCE}$ X 100
[3] 90% Geometric Confidence Interval using ln-transformed data.

6.4.3. 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 DBF 15 mg and three doses of Diastat® rectal gel: 5 mg, 12.5 mg, and 20 mg. These Diastat® 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®.

Pharmacokinetic parameters (C_{max}, AUC_{0-t}, and AUC_{0-inf}) were compared pairwise. DBF 15 mg with each of the three doses of the rectal gel (Table 2). The results suggest that the dose of DBF expected to match the diazepam C_{max} following 20 mg Diastat® gel is lower than 12.5 mg (closer to 11 mg); the dose expected to match the diazepam C_{max} following a 12.5 mg dose of Diastat® gel is lower than 9 mg; and the dose of DBF expected to match the diazepam C_{max} following a 5 mg dose of Diastat® gel is lower than 5 mg

(closer to 4 mg). Results demonstrate that AUC (both AUC_{0-t} and AUC_{0-inf}) are dose proportional following single doses for both DBF and for Diastat® gel over the studied dose. These results, normalized for dose in mg, suggest that the relative bioavailability of diazepam administered as DMSF compared with Diastat® gel is 118% to 128%.

Table 2: Study 162021: Ratios (DBF 15 mg/Rectal Gel 5, 12.5, 20 mg), 90% Geometric Confidence Intervals for Diazepam: AUC_{0-t}, AUC_{0-inf}, and C_{max} - PK Population

Treatment Comparison	N	Parameter	Geometric LSM A	Geometric LSM B	Ratio[1]	90% Geometric CI[2] Lower	90% Geometric CI[2] Upper
DBF 15 mg (A)	24	AUC_{0-t}	11310.33	3181.98	355.45%	292.89%	431.37%
Diastat	24	AUC_{0-inf}	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**			
DBF 15 mg (A)	23	AUC_{0-t}	11381.05	7314.63.	155.59%	127.26%	190.24%
Diastat	23	AUC_{0-inf}	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**			
DBF 15 mg (A)	21	AUC_{0-t}	11186.57	12392.66	90.27%	42.23%	112.80%
Diastat	20	AUC_{0-inf}	13191.81	14824.85	88.98%	69.28%	114.29%
rectal gel 20 mg (D)	21	C_{max}	458.51	327.86	139.85%	140.92%	186.42%

AUC_{0-inf} = area under the concentration-time curve from time zero to infinity; AUC_{0-t} = AUC from time zero until the last measurable concentration or last sampling time t, whichever occurs first; C_{max} = the maximal observed plasma concentration; CI = confidence interval; DBF = Diazepam Buccal Film; LSM = Least-Squares Mean

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

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

6.4.4. Food Effect Studies

The Sponsor conducted two food effect studies (Study 162022 in Section 6.4.4.1 and Study 172018 in Section 6.4.4.2). Results for a high fat meal were consistent across the two studies.

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).

6.4.4.1. 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_{0-t} and AUC_{0-inf} 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.

6.4.4.2. 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.

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 patients in a postictal state and the Sponsor's interest in investigating whether position affected diazepam PK following administration of DBF.

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).

Overall, AUC_{0-t} and AUC_{0-inf} 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}, $p = 0.4979$.

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).

6.5. Rationale for the Dose Regimen 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® 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 Diastat®.

Using data from Study 162013, Study 162021, and Study 172018, population PK modeling was used to model the PK profiles for DBF and Diastat® under fasted and fed conditions (DBF). In brief, the recommended DBF dose for each weight class as defined in the Diastat® 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® , 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 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®.

For the current pediatric study, the DBF dose will be determined according to age and weight category in a manner analogous to the Diastat® label (Diastat® AcuDial™ rectal gel prescribing information December 2016) (Table 3). The proposed dosing regimen is predicted to produce a C_{max} under fasting conditions that is approximately 150% of the C_{max} expected following the labeled dose of Diastat®.

Table 3. Rationale for Dosage of Diazepam Buccal Film

Weight (kg)	Diastat® Dose (mg)	Protocol-Specified Dose (mg)
Age 2–5 Years		
6 to 10	5	5
11 to 15	7.5	7.5
16 to 20	10	10
21 to 25	12.5	12.5
26 to 30	15	15
31 to 35	17.5	15
36 to 44	20	17.5
Age 6–11 Years		
10 to 16	5	5
17 to 25	7.5	7.5
26 to 33	10	10
34 to 41	12.5	12.5
42 to 50	15	15
51 to 58	17.5	15
59 to 74	20	17.5
Age 12–16 Years		
14 to 25	5	5
26 to 37	7.5	7.5
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[a]	20	17.5

[a] Subjects with body weight in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the Investigator.

6.6. Safety

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

6.6.1. Diastat® AcuDial™ Rectal Gel

Diazepam rectal gel was administered to 573 patients with epilepsy during Diastat® clinical trials, only some of which were placebo-controlled (Diastat® AcuDial™ rectal gel prescribing information December 2016). The controlled trials of Diastat® AcuDial™ rectal gel included children 2 years of age and older. Clinical studies have not been conducted to establish the efficacy and safety of Diazepam rectal gel in children under 2 years of age.

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

Table 4 below lists treatment-emergent adverse events (TEAEs) that occurred in >1% of patients enrolled in parallel-group, placebo-controlled trials and that were numerically more common in the diazepam rectal gel group.

Table 4. Treatment-Emergent Adverse Events That Occurred in >1% of Patients Enrolled in Parallel-Group, Placebo-Controlled Trials and were Numerically More Common in the Diazepam Rectal Group

Body System	COSTART Term	Diastat n=101 %	Placebo n=104 %
Body as a Whole	Headache	5%	4%
Cardiovascular	Vasodilatation	2%	0%
Digestive	Diarrhea	4%	<1%
Nervous	Ataxia	3%	<1%
	Dizziness	3%	2%
	Euphoria	3%	0%
	Incoordination	3%	0%
	Somnolence	23%	8%
Respiratory	Asthma	2%	0%
Skin and Appendages	Rash	3%	0%

COSTART = Coding Symbols for a Thesaurus of Adverse Reaction Terms
Source: (Diastat® AcuDial™ rectal gel prescribing information December 2016)

Approximately 1.4% of the 573 patients who received diazepam rectal gel in clinical trials of epilepsy discontinued treatment because of an AE. The AE most frequently associated with discontinuation (occurring in three patients) was somnolence. Other AEs most commonly associated with discontinuation and occurring in two patients were hypoventilation and rash. AEs occurring in one patient were asthenia, hyperkinesia, incoordination, vasodilation, and urticaria. These events were judged to be related to diazepam rectal gel.

6.6.2. Diazepam Buccal Film

A total of 9 clinical studies have been conducted with DBF (6 completed, 3 ongoing). Pooled data for the most frequently reported TEAEs in the 6 completed studies are provided in Table 5. Somnolence was the most frequently reported TEAE in all DBF dose groups followed by dizziness.

Three subjects discontinued study due to a TEAE, all in 15 mg dose groups: blood pressure increased assessed as not related to study drug in Study 162013; severe and serious depressed level of consciousness and severe somnolence in Study 162021.

Table 5: Pooled Data for Most Frequently Reported Treatment-Emergent Adverse Events in Six Completed Studies (1899, 1900, 162013, 162021, 162022, 172018)

	DBF			
MedDRA System Organ Class / **Preferred Term**	**5 mg N = 38 n (%)**	**10 mg N = 26 n (%)**	**15 mg N = 105 n (%)**	**20 mg N = 12 n (%)**
Any TEAE	15 (39.5)	15 (57.7)	92 (87.6)	12 (100)
Nervous System Disorders				
Somnolence	13 (34.2)	10 (38.5)	75 (71.4)	22 (57.9)
Dizziness	1 (2.6)	1 (3.8)	12 (11.4)	1 (8.3)
Headache	0	0	0	1 (8.3)
Gastrointestinal Disorders				
Hiccups	0	0	8 (7.6)[a]	1 (8.3)
General Disorders and Administration Site Conditions				
Gait disturbance	0	0	0	1 (8.3)
Asthenia	0	0	0	1 (8.3)
Feeling of relaxation	0	0	9 (11.1)	0
Investigations				
Aspartate aminotransferase increased	0	0	2 (2.5)	0
Blood creatine phosphokinase increased	0	0	2 (2.5)	0
Psychiatric Disorders				
Euphoric mood	0	0	3 (2.8)	0

DBF = diazepam buccal film; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

[a] Coded to System Organ Class Respiratory, Thoracic, and Mediastinal Disorders

6.6.3. Overdosage

According to the prescribing information for Diastat® AcuDial™ rectal gel (December 2016), 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.

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 re-sedation, 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.

7. STUDY OBJECTIVES

The primary objective is to assess the pharmacokinetics of DBF in pediatric subjects with epilepsy in (A) the interictal state and (B) the ictal/peri-ictal state.

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

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

Secondary objectives:

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

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

8. STUDY DESIGN

8.1. Discussion of Study Design

8.1.1. Study Design

This study uses a multicenter, open-label, crossover design with the following periods: Screening Visit, Treatment Period A (interictal DBF dosing and pharmacokinetic evaluation, subjects aged 6-16 years), minimum washout period of 14 days between DBF treatment periods, Treatment Period B (ictal/peri-ictal DBF dosing and pharmacokinetic evaluation, all subjects), and Follow-up 14 (±2) days after treatment. Definitions of the interictal and ictal/peri-ictal states are given in Section 7. If the subject must remain in the Epilepsy Monitoring Unit (EMU) or General Clinical Research Center (GCRC) for medical reasons after the end of Treatment Period A or B, this time will be designated as Post-treatment. The treatment periods may occur in either order depending on occurrence of seizures.

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

8.1.2. Screening Period

The Screening Period (Section 9.1) will occur 0 to 28 days prior to the first treatment period. The subject or subject's legally authorized representative must provide written informed consent prior to the initiation of any screening procedures, and subjects must provide oral and/or written assent as required by the Institutional Review Board (IRB). During the Screening Period, the subject will be evaluated for study participation as described in Section 9.1 and Section 9.2.

8.1.3. Treatment Periods

The treatment periods (Section 11.2) will begin at a time of day consistent with usual EMU/GCRC protocol. Subjects will arrive at the EMU, GCRC, or similar facility on their scheduled day and time. Subjects are to continue taking their regular AEDs prior to and throughout each Treatment Period (in accordance with EMU or GCRC protocol).

Check-in Procedures: Subjects will undergo standard admission procedures, including the placement of an indwelling cannula for intravenous access, assessment of medical history, medications, vital signs (oxygen saturation [SaO_2) via pulse oximetry, respiratory rate [RR], heart rate [HR], blood pressure [BP], temperature), 12-lead electrocardiogram (ECG), and the Columbia Suicide Severity Rating scale (C-SSRS) as age-appropriate. At the Investigator's discretion, urine drug tests and a breath alcohol test will be performed on all subjects. Urine pregnancy tests will also be performed for women of childbearing potential.

The Investigator or medical staff will review results from the Screening Period and, if applicable, results from the previous treatment period, including vital signs (SaO_2 via pulse oximetry, RR, HR, BP, temperature), 12-lead ECG, clinical laboratory tests, and AEs. The subject's informed consent and/or assent as applicable, medical history, medications, use of restricted substances, and results from the current visit assessments will be reviewed for eligibility and safety. If this is a first treatment visit, subjects who do not meet the inclusion and exclusion criteria will not be enrolled. Subjects who meet inclusion and exclusion criteria will be enrolled.

- Enrollment end-date is 05 March 2020.

If enrolled subjects who have completed a previous treatment visit no longer meet inclusion and exclusion criteria, they will be discontinued from the study.

A study drug kit will be assigned by the Interactive Web Response System (IWRS). Appropriately delegated clinical staff at each clinical site will use the IWRS to assign a kit of the appropriate dose (from the available 5, 7.5, 10, 12.5, 15, and 17.5 mg DBF doses) based on the subject's weight and age.

Clinical monitoring will be initiated. Continuous video EEG monitoring for seizure detection will also be initiated as indicated by EMU or GCRC protocol Sites will maintain the EEG recordings with the study documents, but data from the EEG recordings will not be collected for the study dataset.

Treatment Period A (Subjects aged 6-16 years): Subjects will enter Treatment Period A as scheduled if at least a 3-hour interval has elapsed since any clinical postictal signs or symptoms (from the last observed seizure) have been observed and the subject has been seizure free over this period. If clinical assessment (and EEG monitoring, if applicable) show no seizure activity, the subject will receive a single dose of 5 mg, 7.5 mg, 10 mg, 12.5, 15, or 17.5 mg DBF, based on the subject's weight and age (Table 9) (see placement diagram in Appendix A). Safety and PK assessments will be performed as

described below. Clinical monitoring will continue until the end of the treatment period (4 hours), and video EEG monitoring will continue as specified by EMU or GCRC protocol.

If the subject experiences a seizure before dosing during Treatment Period A, and if it has been determined that the subject meets the inclusion and exclusion criteria, the Investigator may regard this visit as Treatment Period B, and Treatment A will be rescheduled. If no seizure occurs and Treatment Period A is completed, the subject will be scheduled for Treatment Period B.

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

Seizure management and the required intervention will be determined by the Investigator. Subjects with a GTC seizure or focal seizure with impaired awareness who are determined to be medically appropriate to receive study drug (DBF) will receive a single dose of 5 mg, 7.5 mg, 10 mg, 12.5, 15, or 17.5 mg DBF, based on the subject's weight and age (Table 9)

- during the seizure, OR
- within 5 minutes after the last clonic jerk, AND/OR
- within 5 minutes after cessation of the seizure as verified via EEG.

If the subject's seizure persists after the single dose of DBF, an alternative anti-epileptic drug (AED) (rescue medication) may be administered as medically required according to the standard-of-care EMU or GCRC treatment protocol. Any alternative AED medications will be recorded in the study CRF. The physician in charge will be encouraged but not required to use intravenous lorazepam for rescue in preference to intravenous diazepam. The Investigator is permitted to discontinue the subject from the study protocol at any time throughout the study protocol. At the end of the treatment period, clinical seizure assessment, AEDs and concomitant medications, and AEs will be reviewed. If AEDs were tapered previously, the Investigator will determine and record the time to restart the subject's AED medications, including the doses administered or prescribed and the schedule for percent dose increase.

8.1.4. Post-treatment

If the subject remains in the EMU, GCRC, or similar facility following the end of the treatment period, that time will be regarded as a post-treatment period. While the subject remains in the EMU, GCRC, or similar facility, general seizure activity, administration of additional AEDs, surgical treatment of their epilepsy, and AEs will be recorded. The subject will be discharged when medically stable.

8.1.5. Follow-up Visit

Safety data (including concomitant medications, vital signs including SaO_2 via pulse oximetry, clinical laboratory tests including urine pregnancy test in females of childbearing potential, AEs, physical and neurological examinations, C-SSRS, and inspection of oral mucosa) will be obtained at a follow-up visit in an outpatient setting (to be determined by Investigator or Staff) at 14 ± 2 days after the last treatment period (A or B).

8.1.6. Pharmacokinetic and Safety Assessments

The following assessments will be performed (see Section 11.4 for details):

Diazepam PK (Section 11.4.1). In the two pilot studies conducted by the Sponsor in healthy male and female volunteers to assess the bioavailability of DBF, the median T_{max} for DBF was 0.67 hours (range 0.33-1.50 hours) in Study 1899 and 1.5 hours (range 0.36-2.05 hours) in Study 1900. Therefore, in both treatment periods in the present study, plasma samples for diazepam and the active metabolite desmethyldiazepam PK will be obtained before DBF administration and post dose at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), and 4 hours (240 minutes). Collection of plasma samples will continue regardless of whether another AED is administered for rescue.

Vital Signs. The subject's SaO_2, BP, HR, RR, and temperature will be recorded at Screening, at check-in predose, during the treatment visits and post dose, and at Follow-up as described in Section 11.6.

Oral Mucosal Inspection. As described in Section 11.9, to check for any mucosal irritation, an illumination-assisted visual inspection of the DBF application site will be performed at Screening; at each treatment visit prior to study drug administration and approximately 0.25 hours (15 minutes), 0.5 hours (30 minutes), and 1 hour (60 minutes) after application of the film (±5 minutes for all time points); and at Follow-up.

Usability. The usability of DBF will be evaluated by assessing oral cavity insertion, retention, and placement after each administration during the treatment periods as described in Section 11.10.

Laboratory Safety. Blood samples will be collected for laboratory safety at Screening and at Follow-up or upon early termination (Section 11.4.2).

ECG. A 12-lead ECG will be obtained at Screening and at each treatment period, both predose and 4 hours after dosing (Section 11.7).

8.2. Study Duration and Washout

The study includes the Screening Period 0-28 days before Day 1; Treatment Period A (interictal, for subjects aged 6 to 16 years (inclusive) 1 day; a minimum washout period of 14 days between DBF treatment periods; Treatment Period B (ictal/peri-ictal, for all subjects) 1 day; and Follow-up 14 days (±2 days) after the second treatment period. Thus, the minimum study duration will be approximately 30 days for subjects aged 6 to 16 years (inclusive) and 15 days for subjects aged 2 to 5 years (inclusive). The maximum study duration (including screening) will be approximately 58 days for subjects aged 6 to 16 years and 43 days for subjects aged 2 to 5 years.

8.3. Randomization and Blinding

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

9. SUBJECT SELECTION

Enrollment end-date is 05 March 2020.

9.1. Screening Procedures

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

- Obtain written informed consent as evidenced by potential subject's parent(s) or legally authorized representative signing an Informed Consent Form (ICF). Obtain verbal and/or written assent from the subject as required by the IRB. Subjects, parents, and legally authorized representatives will be given an opportunity to ask questions about the study before giving consent/assent.
- Register subject in IWRS.
- Record medical/medication history (including diazepam or benzodiazepines, smoking history, etc), and demographic information based on existing medical records and an interview with the potential subject.
- Administer age-appropriate versions of the Columbia-Suicide Severity Rating Scale (subjects age 7 and older – see Section 11.5). For non-verbal subjects, the C-SSRS assessments should be personally completed by the subject using non-verbal methods with assistance of site staff trained for these assessments. If the scales cannot be completed, the site must document this.
- Collect urine samples for urinalysis and drug screening (see Section 11.4.2).
- Receiving any dosage form of diazepam or other benzodiazepines with the 2 weeks prior to the screening is not a reason to postpone screening procedures. However, if the subject or subjects' parent(s) or legally authorized representative reports that the subject has received any dosage form of diazepam (all other benzodiazepines are allowed) within the 2 weeks prior to the day of admission to clinic, then the clinic admission for treatment should be deferred for a minimum of 2 weeks and a maximum of 4 weeks. If the subject or parent(s) or legally authorized representative reports that the subject has taken no diazepam and the urine test is positive for benzodiazepines, then the Investigator should review the medication history to determine whether it is consistent with the positive urine test for benzodiazepines.

- To allow a subject who tests positive for tetrahydrocannabinol (THC) at screening to continue in the study, verify and affirm in writing that the use of a medical marijuana product is part of the subject's treatment plan as recommended by a physician for treatment of a medical condition.
- Obtain height and body weight.
- Obtain vital signs (SaO_2, temperature, RR, HR, BP) and 12-lead ECG.
- Collect blood samples for hematology, chemistry, and pregnancy testing (for females of childbearing potential). For a complete listing of all tests to be performed, see Section 11.4.2.
- Perform breath alcohol test in subjects.
- Perform a physical and neurological examination.
- Dispense seizure diaries, with instructions to subjects or parent(s) or legally authorized representatives to record the number of seizures, AED dosing, use of rescue, and any AEs.
- Investigator reviews inclusion/exclusion criteria and all screening results/data to assess eligibility of each potential subject.

9.2. Inclusion/Exclusion Criteria

9.2.1. Inclusion Criteria

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

1. Subjects have a clinical diagnosis of epilepsy (GTC seizures or focal seizures with impaired awareness) and are scheduled for admission to an Epilepsy Monitoring Unit (EMU), General Clinical Research Center (GCRC), or similar facility for evaluation.
2. Male and female subjects between 2 and 16 years of age, inclusive.
3. Subjects have a body weight of ≥6 kg and ≤111 kg.†

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

4. Subjects have an average frequency of ≥1 clinically apparent seizures every 3 days or ≥10 clinically apparent seizures per month, with alteration of

consciousness as documented by reliable subject report, personal seizure diary records, and/or by seizure diaries dispensed at Screening and verified prior to Treatment Period A or Treatment Period B.

5. Female subjects of childbearing potential (i.e., are having periods, are not surgically sterile) must have a negative serum pregnancy test (ß-hCG) at Screening and a negative urine pregnancy test on Day 1 prior to drug dosing. Female subjects of childbearing potential must agree to abstinence, have a partner who is sterile, or be practicing double barrier contraception or have been using an FDA-approved contraceptive (e.g., licensed hormonal or barrier methods) for greater than 2 months prior to screening visit, and must commit to an acceptable form of birth control for the duration of the study and for 30 days after participation in the study.
6. Male subjects with a female sexual partner of childbearing potential must agree to abstinence or practice adequate birth control during the study, including at least 1 barrier method such as a condom, diaphragm, or spermicide for greater than 2 months prior to screening visit, and must commit to an acceptable form of birth control for the duration of the study and for 30 days after participation in the study. Also, male subjects must agree to not donate sperm during the study and for 90 days after the follow-up visit.
7. Subjects are currently receiving at least one antiepileptic medication.
8. Subject's parent or legally authorized representative must be willing and able to complete informed consent and HIPAA authorization. Subjects must be willing to give assent as required by the IRB.
9. Subject must agree to be available or subject's parent(s) or legally authorized representative must agree to have the subject be available for both treatment periods and the follow-up visit and must be willing to comply with all required study procedures and adhere to all protocol requirements.
10. Subject or subject's parent(s) or legally authorized representative must be able to comprehend and be informed of the nature of the study, as assessed by the Investigator.

9.2.2. Exclusion Criteria

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

1. Subjects with a progressive neurological disorder such as a brain tumor, demyelinating disease, or degenerative central nervous system (CNS) disease that is likely to progress in the next 12 months.
2. Subject has respiratory failure (or is at risk for respiratory failure) or other severe cardiorespiratory disease with New York Heart Association Class III or IV functional status or requires supplemental oxygen.
3. Female subjects who are lactating, have a positive serum pregnancy test (ß-hCG) at screening, or have a positive urine pregnancy test at Check-in for treatment periods.
4. Subjects with psychiatric disease that in the Investigator's judgment would prevent the subject's successful completion of the study.
5. Subject has a recent history of suicide attempt (defined as an active, interrupted, or aborted attempt with the past five years) or reports suicidal ideation in the past six months as indicated by a positive response (“Yes”) to either Question 4 or Question 5 of the C-SSRS performed at the Screening Visit.
6. Subjects with known history or presence of any clinically significant hepatic (e.g., hepatic impairment), renal/genitourinary (renal impairment, kidney stones), psychiatric, dermatological, or hematological disease or condition, unless determined as not clinically significant by the Investigator or designee and confirmed by Sponsor via written communication prior to subject enrollment. Abnormal laboratory results considered clinically significant by the Investigator or designee will be evaluated by the Investigator in consultation with the Medical Monitor.
7. Subjects with any clinically significant illness other than epilepsy within 30 days prior to study drug administration, as determined by the Investigator.
8. Subjects with any significant physical or organ abnormality or other condition that would interfere with study participation or constitute a safety risk in the judgment of the Investigator.
9. Subjects with any significant lesion of the oral cavity or having oral prophylactic or dental procedures within 30 days prior to study drug administration.
10. Subjects with a QTcF (QT with Fredericia's correction) interval ≥450 msec for males or QTcF ≥470 msec for females on screening ECG, unless determined to be not clinically significant by the Investigator.

11. Subjects with a positive test result for any of the following drugs of abuse: amphetamines, cocaine, opiates, phencyclidine, or a positive breath alcohol test. Subjects who test positive for tetrahydrocannabinol (THC) at screening will be excluded unless the Principal Investigator is able to affirm in writing that the use of a medical marijuana product is part of the subject's treatment plan as recommended by a physician for treatment of a medical condition. In such case, the subject will be allowed to continue with screening, and the medical marijuana product will be recorded as a concomitant medication.
12. Subjects with a known history or presence of:
    a. Substance abuse or dependence (including alcohol) within one year prior to first study drug administration
    b. Hypersensitivity or idiosyncratic reaction to diazepam, its excipients, sodium phosphates, and/or related substances, e.g., benzodiazepines
    c. Glaucoma (open or acute narrow angle)
    d. Severe allergic reactions (e.g., anaphylactic reactions, angioedema) to investigational product and excipients
13. Subjects who have participated in another clinical trial or who received an investigational drug within 30 days prior to study drug administration or 5 half-lives of the investigational drug—whichever is the longer period.
14. Subjects with presence of mouth jewelry, dentures, oral implants, braces, or piercings in the mouth or tongue that, in the opinion of the Principal Investigator, would be likely to interfere with successful completion of the dosing procedure.
15. Subjects with a blood or plasma donation within 30 days prior to Screening.
16. Subjects not willing or unable to tolerate blood draws.
17. Consumption of alcohol within 48 hours before dosing; or food or beverages containing grapefruit, star fruit, Seville oranges, and/or pomelo, or their derived products (e.g., fruit juice) within 10 days prior to study drug administration.
18. Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome (CYP) 450 enzymes (e.g., cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem, or human immunodeficiency virus [HIV] antivirals) and strong inducers of CYP enzymes (e.g., glucocorticoids, St. John´s Wort, or rifampicin), in the previous 30 days prior to

study drug administration. (Barbiturates, carbamazepine, phenytoin, and other enzyme-modifying AEDs that are medically needed are permitted.)

19. Use of any monoamine oxidase (MAO) inhibitors (e.g., phenelzine, tranylcypromine), phenothiazines (chlorpromazine) within 30 days prior to first study drug administration.
20. Employee or immediate relative of an employee of Aquestive Therapeutics, any of its affiliates or partners, or Syneos Health.

9.3. Permitted and Restricted Items

Study restrictions are summarized in Table 6. If any subject does not comply with these restrictions, at any time prior to or during the study, continued eligibility will be re-assessed by the Investigator in consultation with the Sponsor.

Subjects may take concomitant drug or non-drug treatment as needed during study participation, unless specified within the protocol as excluded or restricted. Any excluded or restricted concomitant drug or non-drug treatments taken will be reported as soon as possible to the Sponsor or designee and will be reviewed on a case by case basis to determine the subject's further participation in the study.

Treatment with a medical marijuana product during the course of the study is acceptable as concomitant medication if the Principal Investigator is able to affirm in writing that such treatment is a part of the subject's treatment plan as recommended by a physician for treatment of a medical condition.

All cases of concomitant medication, herbal/dietary supplement administration, or consumption of restricted food or beverages from Screening through Follow-up will be documented in the CRF.

Table 6 Study Restrictions

Restriction Period	Item Restricted	Examples
30 days prior to drug administration until after the last blood draw in the final study period	Enzyme-modifying drugs	Strong inhibitors of CYP enzymes (e.g., cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem, or HIV antivirals) Strong inducers of CYP enzymes (e.g., glucocorticoids, St. John´s Wort, or rifampicin). [Barbiturates, carbamazepine, phenytoin, and other AEDs affecting CYP enzymes are allowed if medically indicated.
	Monoamine oxidase (MAO) inhibitors	Phenelzine, tranylcypromine
	Phenothiazines	Chlorpromazine
	Note: Spermicidal/barrier contraceptive products may be permitted.	
10 days prior to drug administration until after the last blood draw in the final study period	Foods and/or beverages containing grapefruit	Grapefruit, grapefruit juice, grapefruit candies, star fruit, Seville oranges, and/or pomelo, or their derived products (e.g., fruit juice)
48 hours prior to drug administration until after the last blood draw in each study period	Alcohol of any kind	Wine, beer, liquor, cocktails
1 hour after dosing	Food and water intake	

9.4. Sample Size

To provide adequate pharmacokinetic, safety, and usability assessment of DBF in the pediatric population, 16 to 18 subjects should complete the study, distributed across three age ranges as follows: 6 subjects aged 2 to 5 years, 6 subjects aged 6 to 11 years, and 4 to 6 subjects aged 12 to 16 years. To ensure adequate numbers of completed subjects,

efforts will be made to enroll 8 subjects in each age group, for a total of 24 enrolled subjects.

9.5. Dropout and Withdrawal/Termination

Subjects whose participation in the study is discontinued (for any reason) will not be replaced.

A subject is free to withdraw at any time, for any reason. Every attempt will be made to record reasons for withdrawal.

Enrolled subjects who have an episode of status epilepticus at any time during either treatment period may be excluded from further study participation at the Investigator's discretion in consultation with the Sponsor. Subjects experiencing emesis after dosing will be evaluated (to assess subject safety) on a case-by-case basis by the Investigator and the Sponsor, and they will decide on the subject's continued participation. A subject may also be removed if necessary to protect their health or the integrity of the study. This determination will be made by the Investigator in consultation with the Medical Monitor. Removal of a subject from the study will only be permitted prior to commencement of bioanalysis.

If an enrolled subject's participation is terminated prematurely or the subject withdraws from the study, the cause, date, and time of the early termination or withdrawal will be documented on the source documents and in the final study report. Efforts will be made to obtain an early discontinuation visit at which clinical seizure assessment will be done, vital signs including SaO_2 will be recorded, physical and neurological examination and clinical laboratory tests will be performed, an oral mucosal inspection will be performed, and any concomitant medications, including AEDs, will be recorded.

10. INVESTIGATIONAL PRODUCT

10.1. Drug Information

Information on the study drug is given in Table 7.

Table 7. Study Drug Information

Drug Name:	Diazepam
Strengths:	5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, and 17.5
Dosage Form:	Buccal Film
Manufacturer:	Aquestive Therapeutics
Dose:	1 x 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, or 17.5 mg, depending on weight and age (see Table 3)

10.1.1. Controlled Substance Documentation

Diazepam Buccal Film is designated as a Schedule IV controlled substance with abuse potential by the US Controlled Substances Act (21 Code of Federal Regulations [CFR] §1308). Because the study drug is a controlled substance, drug supplies must be kept in a secure, double-locked, substantially constructed enclosure with restricted access.

Prior to shipment of study drug, the Investigator must provide the Sponsor with a copy of a controlled substance license that clearly identifies the registrant and address of the registrant. Study drug supplies will be shipped to the registrant and address noted on the certificate.

10.1.2. Description of Investigational Product

Diazepam Buccal Film (DBF) contains the active ingredient diazepam incorporated into a polymer-based film matrix utilizing Aquestive Therapeutics' PharmFilm® technology. For the purposes of this pediatric study, the investigational product will be provided at the following strengths: 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg and 17.5 mg.

The film is intended for application to the inner aspect of the cheek where the film immediately adheres and begins to hydrate. During the hydration process, the drug, along with associated solubility enhancers, are rapidly released onto the buccal mucosa for dissolution and absorption. The DBF doses up to 20 mg were tested in a pilot clinical study. The inactive ingredient composition, the film dimensions, and the manufacturing

process selected for this drug product are based on the information gained from the development of the DBF and other film products produced by Aquestive Therapeutics (ZUPLENZ® 4 and 8 mg and SUBOXONE® 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, and 12 mg/3mg Sublingual Films). The DBF product is a green rectangular film.

The primary package used for DBF is a polyester/foil laminate provided by Amcor Flexibles (Madison, WI). The material (product code RFE-013) is a multi-layer composite consisting of (1) a 12.2-micron layer of polyethylene phthalate, (2) a 25.4-micron layer of low-density polyethylene, (3) an 8.9-micron layer of aluminum foil, and (4) a 38.1-micron layer of low-density polyethylene, and is heat sealed at the edges. Each pouch contains one DBF.

10.2. Labeling, Maintenance, and Retention of Study Drugs

It is the responsibility of the Sponsor to ensure that all drug supplies provided for the study are manufactured under current Good Manufacturing Practices and are suitable for human use. The Sponsor will supply an authorized clinical supplies vendor with a sufficient quantity of the study formulation(s) to allow completion of this study, including some spares for replacement drugs. The clinical supply vendor will ship the packaged and labeled study drugs for each participating investigator to the Pharmacy or Investigator at the address specified on the DEA Controlled Substance certificate.

The study drugs will be sent to the Site Pharmacy already packed in individual unit-dose packages. Each unit-dose package will be labeled in English containing at a minimum the Protocol Number, Drug Name, Strength, Kit Identification Number, Route of Administration, and a statement “For clinical trial use only.”

Upon receipt of the study drugs, the Investigator, Pharmacist, or designee will inspect the shipment to ensure study drugs are received in good condition. Study drug receipt and condition will be promptly registered in the IWRS. The Investigator, Pharmacist, or designee will ensure records of receipt and dispensing of study drugs supplied are maintained for the duration of the study.

The Investigator or designee will log into the IWRS to register the subject’s visit and have the study drug kit number assigned to the subject. Only this kit will be removed from inventory.

At the completion of the study, all unused study drugs, including the spares, will be retained by the Study Site until the authorization to return or destroy is received from the Sponsor.

11. STUDY PROCEDURES

11.1. Schedule of Events

The schedule of study events is given in Table 8.

Table 8. Schedule of Events

		Treatment A[a]		Treatment B[a]		FU
Procedure/Activity	**Screening (Day -28 to Day 0)**	**Check-in† (predose)**	**Dosing/ (postdose)**	**Check-in (predose)**	**Dosing/ (postdose)**	**(14 ±2 d post last treatment)**
ICF and assent[b]	X					
Inclusion/Exclusion assessment	X	X		X		
IWRS: Register subject, determine DBF dose, update status	X	X		X		X
Medical history/demographics	X	X		X		
Concomitant medication review	X	X		X		X
Date/time of the subject's last meal before DBF dose		X		X		
Review of restrictions	X	X[c]	X[c]	X[c]	X[c]	
C-SSRS (age-appropriate versions)	X	X		X		X
Height and body weight	X[d]	X		X		
Oxygen saturation	X	X[e]	X[e]	X[e]	X[e]	X
Blood pressure	X	X[f]	X[f]	X[f]	X[f]	X
Heart rate	X	X[f]	X[f]	X[f]	X[f]	X
Respiratory rate	X	X[f]	X[f]	X[f]	X[f]	X
Temperature	X	X[f]		X[f]		X
Physical/neurological exam	X[g]					X
ECG	X[h]	X[h]	X[h]	X[h]	X[h]	
Pregnancy test	X[i]	X[i]		X[i]		X[i]
Clinical laboratory tests	X					X

		Treatment A[a]		Treatment B[a]		FU
Procedure/Activity	**Screening (Day -28 to Day 0)**	**Check-in† (predose)**	**Dosing/ (postdose)**	**Check-in (predose)**	**Dosing/ (postdose)**	**(14 ±2 d post last treatment)**
Drug screen (urine)	X[j]	X[j]		X[j]		
Breath alcohol test	X	X		X		X
Oral mucosal inspection	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]
Dispense/collect seizure diaries	X	X		X		X
Continuous video EEG		X[l]	X[l]	X[l]	X[l]	
Study drug dosing			X		X	
PK sampling		X	X[m]	X	X[m]	
Assessment of usability			X[n]		X[n]	
Adverse event reporting		X[o]	X[o]	X[o]	X[o]	X[o]

C-SSRS = Columbia-Suicide Severity Rating Scale; DBF = Diazepam Buccal Film; ECG = electrocardiogram; EEG = electroencephalogram; FU = Follow-up; ICF = informed consent form; PK = pharmacokinetics.

† Enrollment end date is 05 March 2020.

a. Only subjects aged 6-16 will undergo Treatment Period A. Treatment Periods A and B may occur in either order, depending on seizure occurrence, e.g., if a subject experiences a seizure during the first visit to the EMU or GCRC. In such cases, if feasible after IWRS registration, dose determination, and review of inclusion/exclusion criteria, the Investigator may regard that period as Treatment Period B and schedule another visit for Treatment Period A.

b. Obtain written informed consent from parent(s) or legally authorized representative. Obtain verbal and/or written assent from subjects as required by Institutional Review Board.

c. Confirmed at each ambulatory blood draw, if applicable.

d. Height measured at Screening only.

e. At both treatment visits, SaO_2 via pulse oximetry will be recorded predose and at 5, 10, 20, 30, 40, 50 minutes post dose and thereafter at each time vital signs are recorded: 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes), and 4 hours (240 minutes).

f. At both treatment visits, vital signs (BP, HR, RR, and temperature) are to be recorded predose. BP, HR, and RR are to be recorded post dose at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes, even though no blood will be drawn at this time point), and 4 hours (240 minutes) after dosing. The subject's position may be seated or supine but should be consistent throughout.

g. Physical/neurological examination will be performed at Screening and at Follow-up or at an early discontinuation visit.

h. A 12-lead ECG will be obtained at Screening, at the beginning of each treatment period, and at 4 hours after dose administration.

i. A serum pregnancy test will be performed for females of childbearing potential at Screening; a urine pregnancy test will be performed at each treatment period Check-in and at Follow-up.

j. Screening: Receiving any dosage form of diazepam or other benzodiazepines within the 2 weeks before screening is not a reason to postpone screening.
Treatment periods: If the subject or parent(s) or legally authorized representative reports that the subject received any dosage form of diazepam (all other benzodiazepines are acceptable) within 2 weeks prior to the day of admission to the clinic when Treatment Period A or B may be conducted, then the admission should be deferred for a minimum of 2 weeks and a maximum of 4 weeks. If the subject or parent(s) or legally authorized representative reports that the subject has taken no diazepam in the previous 2 weeks but the urine test is positive for benzodiazepines at Check-in the Investigator should consider the subject's drug history and evaluate whether the drug history is consistent with the positive urine result. Considering both the drug history and the urine test positive for benzodiazepines, the Investigator may choose to reschedule the clinical admission, but the protocol does not require the Investigator to reschedule. Subjects who test positive for THC at screening may participate if the Principal Investigator is able to affirm in writing that the use of a medical marijuana product is part of the subject's treatment plan as recommended by a physician for treatment of a medical condition. In such case, the medical marijuana product will be recorded as a concomitant medication.

k. The Investigator will make an illumination-assisted visual inspection of the oral mucosa during Screening and during each treatment period prior to study drug administration and at approximately 15 minutes, 30 minutes, and 60 minutes after film placement. A further inspection of oral mucosa will be made at Follow-up.

l. If indicated by EMU or GCRC protocol, continuous video EEG monitoring for seizure detection will be performed throughout each treatment period (4 hours). Sites will maintain the EEG recordings with the study documents, but data from the EEG recordings will not be collected for the study dataset.

m. For both treatment periods, plasma samples for determination of diazepam and desmethyldiazepam PK samples are to be obtained at predose and post dose at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), and 4 hours (240 minutes) after dosing. Collection of plasma samples will continue even if the administration of another AED is needed for rescue.

n. The study staff will evaluate the insertion process to determine usability of the film as described in Section 11.10.

o. AEs are to be collected from time of consent throughout the study.

11.2. Treatment Periods A and B

11.2.1. Check-in Procedures

For each treatment period, subjects will undergo standard admission procedures as described below, including the placement of an indwelling cannula for intravenous access, assessment of medical history, medications, date/time of the subject's last meal before the DBF dose, vital signs, urine pregnancy test in females of childbearing potential, urine drug screen, breath alcohol test, 12-lead ECG, and the Columbia Suicide Severity Rating scale (C-SSRS), as age appropriate.

Subjects and their parent(s) or legally authorized representatives will be questioned about whether they have complied with the study restrictions. If a restricted drug or non-drug therapy specified in the protocol was used, a decision to continue or discontinue the subject's participation will be made by the Investigator and/or by the Sponsor.

If the subject or subjects' parent(s) or legally authorized representative reports that the subject received any dosage form of diazepam (all other benzodiazepines are acceptable) within the 2 weeks prior to the day of admission, then the admission should be postponed for a minimum of 2 weeks and a maximum of 4 weeks. If the subject, parent(s) or legal representative reports that the subject has taken no diazepam and the urine test is positive for benzodiazepines, then the Investigator may choose to postpone the clinic admission after considering both the subject's drug history and the urine test positive for benzodiazepines.

At each period check-in, the Investigator will review results from the Screening Period and, if applicable, results from the previous treatment period, including vital signs (SaO_2, BP, HR, RR, temperature), 12-lead ECG, and clinical laboratory tests, informed consent, medical history, medications, seizure diaries, use of restricted substances, results of drug tests, breath alcohol test, and pregnancy test. Results from the current visit assessments will also be reviewed for eligibility and safety. If this is a first treatment visit, subjects who do not meet the inclusion and exclusion criteria will not be enrolled. Subjects who meet inclusion and exclusion criteria will be enrolled. If enrolled subjects who have completed a previous treatment visit no longer meet inclusion and exclusion criteria, they will be discontinued from the study.

A study drug kit will be assigned by the Interactive Web Response System (IWRS). Appropriately delegated clinical staff at each clinical site will use the IWRS to assign a kit of the appropriate dose (from the available 5, 7.5, 10, 12.5, 15, and 17.5 mg DBF doses) based on the subject's weight and age.

Clinical monitoring will be initiated. Continuous video EEG monitoring for seizure detection will be initiated as indicated by EMU or GCRC protocol. Sites will maintain the EEG recordings with the study documents, but data from the EEG recordings will not be collected for the study dataset.

11.2.2. Treatment Period A (Subjects Age 6-16 Years)

Subjects will enter Treatment Period A as scheduled if at least a 3-hour interval has elapsed since any clinical postictal signs or symptoms (from the last observed seizure) have been observed and the subject has been seizure free over this period. If clinical and/or EEG monitoring show no seizure activity, the subject will receive a single dose of DBF as assigned by the IWRS (see placement diagram in Appendix A). Safety and PK assessments will be performed as described below. Clinical monitoring will continue until the end of the treatment period (4 hours post dose), and video EEG monitoring will continue as specified by EMU or GCRC protocol.

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

11.2.3. Treatment Period B (All Subjects)

During Treatment Period B, the subject will be monitored until a GTC or focal seizure with impaired awareness is detected or the Investigator terminates the monitoring period. If the subject's AEDs are to be tapered as per EMU or GCRC protocol, and the Investigator will determine and record the time to begin tapering the AEDs, including the percent dose reduction and tapering rate.

Seizure management and the required intervention will be determined by the Investigator. Subjects with a GTC seizure or focal seizure with impaired awareness who are determined to be medically appropriate to receive study drug (DBF) will receive a single-dose of DBF (dose level determined via the IWRS) during the seizure or within 5 minutes after the last clonic jerk or within 5 minutes after cessation of the seizure as verified via EEG.

If the subject's seizure persists after the single dose of DBF, an alternative AED medication (rescue medication) can be administered as medically required and according to the standard-of-care EMU or GCRC treatment protocol and recorded in the study CRF.

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

11.2.4. Dosing

DBF is provided in a range of doses from 5 to 17.5 mg to facilitate optimal dosing (see Section 6.5). The recommended dose of DBF is dependent on the subject's age and weight. The Investigator or attending EMU or GCRC medical staff will use the IWRS (based on Table 9) to choose appropriate doses for pediatric subjects.

Table 9. Calculated Prescribed Dose of Diazepam Buccal Film

Weight (kg)	Protocol-Specified Dose (mg)
Age 2–5 Years	
6 to 10	5
11 to 15	7.5
16 to 20	10
21 to 25	12.5
26 to 30	15
31 to 35	15
36 to 44	17.5
Age 6–11 Years	
10 to 16	5
17 to 25	7.5
26 to 33	10
34 to 41	12.5
42 to 50	15
51 to 58	15
59 to 74	17.5
Age 12–16 Years	
14 to 25	5
26 to 37	7.5
38 to 50	10
51 to 62	12.5
63 to 75	15
76 to 87	15
88 to 111[a]	17.5

[a] Subjects with body weight in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the Investigator.

Before administration of the DBF, the Investigator will perform an oral safety inspection as described in Section 11.9. The dosing process will consist of the following steps:

- When opening the foil pouch containing the study drug, staff are to 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.
- Subjects will be instructed to swallow saliva and then open their mouth.
- If the predose oral safety assessment reveals evidence of mucosal injury or irritation (e.g., a cheek bite resulting from a seizure), care should be taken to avoid placement of DBF in that area.
- Staff will place the film on the tip of a finger and then use the finger to insert the film into the subject's mouth.
- The film is to be centered against the inner aspect of the right or left cheek, so that it adheres to the buccal mucosa (refer to Appendix A for a diagram of film placement). The film may be placed without regard to the location of the parotid duct.
- Subjects should be placed in a comfortable position.
- The subject will be instructed to close his/her mouth in a natural way, without swallowing, chewing, biting, or breaking the DBF.
- Staff will observe the patient during this 15-minute period. It should be noted whether the subject chews, talks, moves the film, spits it out, or blows it out of his or her mouth. If the subject spits the film out or blows it out of his or her mouth, Staff should try to reinsert the film, if possible. No second film should be applied.
- Dosing time will be set to the time the film is placed on the buccal mucosa. At 15 minutes after film placement, the subject will be asked to swallow any remaining film remnants, and the subject's hands will be inspected to check whether the subject had removed the film (or a part of the film) from the mouth.
- The study staff will evaluate the insertion process to determine usability of the film as described in Section 11.10. As noted in Section 11.9, the Investigator will again perform post-dose oral safety assessments at 15, 30, and 60 minutes after film placement.

11.2.5. Post-treatment

If the subject remains in the EMU, GCRC, or similar facility following the end of Treatment Period A or B, that time will be regarded as a post-treatment period. While the subject remains in the EMU, GCRC, or similar facility, general seizure activity, administration of additional AEDs, surgical treatment of their epilepsy, and AEs will be recorded. The subject will be discharged when medically stable.

11.3. Follow-up

Safety data including concomitant medication, vital signs, clinical laboratory tests (hematology, serum chemistry, urinalysis, including urine pregnancy test, as described in Section 11.4.2), AEs, physical and neurological examinations, C-SSRS, inspection of oral mucosa), and review of personal seizure diary records will be obtained at a follow-up visit in an outpatient setting (to be determined by Investigator or Staff) at 14 ± 2 days after the last treatment period (A or B), or after withdrawal/ discontinuation of a subject from the study (where possible).

11.4. Blood Sampling Schedule, Sample Collection, Processing, and Storage

Blood will be obtained by direct venipuncture in the arm, or via an indwelling cannula. Subjects may use up to a total of 2 indwelling cannulas in each study period. A third indwelling cannula may only be used upon authorization by the Investigator or qualified designee. If the cannula fails to work (i.e., it becomes clogged), the remaining samples will be taken by direct venipuncture.

Blood sample collection times will be recorded on the appropriate source documents and reported for each subject.

11.4.1. Pharmacokinetic Assessments

During both treatment periods, plasma samples for determination of diazepam and the active metabolite, desmethyldiazepam PK will be obtained at predose (0 hours), and at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), and 4 hours (240 minutes) after dosing. Collection of plasma samples will continue even if the administration of another AED is needed for rescue.

Blood PK samples will be placed in a refrigerated centrifuge within 30 minutes from the time of collection and centrifuged at approximately 3000 revolutions per minute (RPM) for 10 minutes under refrigerated (approximately 4°C) conditions.

After centrifugation, the plasma will be aspirated and aliquoted into 2 pre-chilled clear polypropylene tubes. A minimum of 1 mL plasma will be transferred to the first tube, and the remaining plasma (if any) will be aliquoted into a second tube. Samples that are disturbed during the separation process will be re-spun under the same conditions in an attempt to obtain the maximum amount of plasma from each sample. Polypropylene tubes will be pre-chilled and pre-labeled with at least the following information: Time point, Protocol Number, Study Period, Aliquot Number, Matrix, and Subject Number. The samples will be stored at -20°C or colder in a freezer pending shipment. Samples must be placed in the freezer within 70 minutes from the start of centrifugation.

Throughout sample collection and following centrifugation, the samples will be maintained in an ice-bath until stored in the freezer.

Details regarding the proper collection, preparation, labeling, storage, and shipment of plasma samples for PK analysis will be provided by the central laboratory in a lab manual.

11.4.2. Clinical Laboratory Assessment

Blood samples will be collected for laboratory safety tests at Screening and at Follow-up or upon early study discontinuation.

Blood and urine specimens will be collected by qualified study center personnel at all visits and sent to a central laboratory for analysis of the parameters specified in Table 10. Abnormal laboratory test results will be flagged by the central laboratory. Detailed instructions of sample collection, storage, and shipping will be provided by the central laboratory in a lab manual.

All clinically important abnormal laboratory tests occurring during the study will be repeated and followed until they resolve (return to normal or baseline values) or stabilize, or until they are considered by the Investigator to be no longer clinically significant.

Table 10 Clinical Laboratory Assessments

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cells; THC = tetrahydrocannabinol; UBG = urobilinogen; WBC = white blood cells.
[a]Serum and urine pregnancy tests for females of child-bearing potential only

11.4.3. Number and Volume of Blood Samples

The number and volume of blood samples and total blood volume collected per subject are shown in Table 11.

Table 11 Number and Volume of Blood Samples and Total Blood Volume Collected per Subject

		Maximum # Samples				
	Volume (mL) per sample	**Screening**	**Period A**	**Period B**	**Follow-up**	**TOTAL Blood (mL)**
Clinical Chemistry [a]	2.5	1	-	-	1	**5**
Hematology [a]	1.2	1	-	-	1	**2.4**
PK [b, c]	2		7 [b]	7 [b]		**28**
		Maximum Blood Volume (mL)				
TOTAL (mL)		**3.7**	**14**	**14**	**3.7**	**35.4**

Type of Vacutainer (pediatric)	PK – pre-chilled K_2EDTA Vacutainer®, 2 mL Chemistry – Vacutainer®, 2.5 mL Hematology – Vacutainer®, 1.2 Ml
Blood sampling time points	a. Samples for the clinical laboratory tests will be obtained at Screening and at Follow-up (or at early discontinuation). b. Plasma samples for diazepam and desmethyldiazepam PK will be obtained during both treatment periods at predose (0 hours) and at the following time points (±5 minutes): 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), and 4 hours (240 minutes) after dosing. c. The actual time of blood sample collection will be used for PK and statistical analysis.

11.5. Columbia-Suicide Severity Rating Scale

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

For non-verbal subjects, the C-SSRS assessments should be personally completed by the subject using non-verbal methods with assistance of site staff trained for these assessments. If the scales cannot be completed, the site must document this.

Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with specific plan and intent) suicidal ideation are exclusionary for enrollment and, if found during the study, the subject will be discontinued from the study and referred to a mental health professional.

11.6. Vital Signs

The subject's vital signs (oxygen saturation [SaO_2] measured via pulse oximetry, BP, HR, RR, and temperature) will be recorded at Screening and during both treatment periods, and at the Follow-up Visit.

Vital signs (BP, HR, RR, and temperature) will be recorded at Screening and (Treatment Periods A and B) prior to DBF administration. BP, HR, and RR will be recorded post dose at 0.25 hours (15 minutes), 0.5 hours (30 minutes), 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes), and 4 hours (240 minutes) and at the follow-up visit. The subject's position may be seated or supine but should be consistent throughout.

SaO_2 measured via pulse oximetry, will be recorded Screening and (Treatment Periods A and B) prior to DBF administration and at 5, 10, 20, 30, 40, 50 minutes post dose and thereafter at each time vital signs are recorded: 1 hour (60 minutes), 1.5 hours (90 minutes), 2 hours (120 minutes), 3 hours (180 minutes), and 4 hours (240 minutes) and at the follow-up visit.

For subjects with pre- or post-dose vital signs outside of the acceptable range for systolic blood pressure (90-140 mmHg, inclusive), diastolic blood pressure (50-90 mmHg, inclusive), or heart rate (50-100 bpm, inclusive), the measurement will be repeated up to two times (at rest, after 5 minutes in a sitting position). If vital signs are still outside of the acceptable range, the Investigator will determine the appropriate course of action.

Methods for the administration of oxygen should be readily available for saturation dropping below 90%. The Investigator will determine management of hypoxemia until recovery.

Additional measurements of vital signs will be made if deemed necessary by the Investigator. Should a timing conflict arise, blood draws will take precedence over vital sign measurements and other scheduled activities, unless deemed otherwise by the Investigator.

11.7. 12-Lead Electrocardiogram

A 12-lead ECG will be obtained at Screening and at the beginning and end of each treatment period.

11.8. Physical/Neurological Examination

A physical and neurological examination will be performed at Screening and at Follow-up or prior to early termination.

11.9. Oral Safety Assessments

The Investigator will make an illumination-assisted visual inspection of the oral mucosa, including the DBF application site, at the following times:

- At Screening;
- During Treatment Periods A and B prior to dosing and at approximately 0.25 hours (15 minutes), 0.5 hours (30 minutes), and 1 hour (60 minutes) after application of the film (±5 minutes for all time points); and
- At Follow-up.

Mucosal irritation and any injuries to the oral cavity (e.g., tongue or mucosa laceration, broken tooth, bleeding) will be recorded using criteria specified in a checklist in the CRF. Any de novo post dose mucosal irritation or other abnormalities will be reported as AEs and followed as described in Section 12.1.3.

11.10. Usability

To assess usability of DBF, oral cavity insertion, retention, and placement will also be evaluated for each administration. The following usability endpoints will be reported:

- Whether successful placement was achieved (Placement is judged to be successful when the film adheres to the center of the buccal mucosa of either the right or the left cheek, as shown in Appendix A).
- Location of film placement (right or left)
- Time of successful film placement.
- Number of attempts needed to successfully insert the film (An attempt is defined as inserting the finger with the film into the subject's mouth.)

- Whether any remnant of the film remained 15 minutes after placement. (If yes, the subject should be instructed to swallow the remaining film and 15 minutes will be the time of complete film disintegration/dissolution that is reported in the CRF.)
- Whether the subject spit or blew the film out of their mouth. If yes, whether an attempt was made to reinsert it.
- Whether any saliva exited the subject's mouth. If yes, time of exit and estimated total amount (in mL).
- Whether a check of the subject's hands at 15 minutes after film placement revealed that the film (or a part of the film) was removed by subject.

Where applicable, categorical explanations of the circumstances will be given (e.g., uncooperative or confused patient in a peri-ictal state).

11.11. Food and Fluid Intake

The date/time of the patient's last meal before DBF dose (both treatment periods) will be recorded. Food and water intake will be restricted for 1 hour after dosing. Food and water will be allowed *ad libitum* at all other times.

11.12. Physical Activity

Subjects will be required to abstain from strenuous activities for the duration of each study period.

12. ADVERSE EVENTS

The CRO, Syneos Health, has established standard operating procedures (SOPs) in conformity with regulatory requirements to ensure the timely, accurate, and complete reporting of safety information.

12.1. Adverse Event Recording and Follow-up

Subjects will be instructed to inform clinic personnel of any untoward medical symptoms and/or events that may arise during the course of the study.

At the treatment and follow-up visits, subjects will be questioned concerning symptoms that may have occurred after administration of the study drug. The incidence, seriousness, severity, duration, and relationship to study drug of all AEs will be recorded.

12.1.1. Seizures

Subjects should record all seizures from the time of consent through the Follow-up Visit in their personal seizure diary records, and/or in seizure diaries dispensed at Screening and verified prior to Treatment Period A or Treatment Period B and at the Follow-up Visit.

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

12.1.2. Serious Adverse Events

A serious adverse event (SAE) is one 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.

If the subject has a planned or ***elective*** hospitalization due to a pre-existing condition, this will not result in a reportable SAE as defined in the criteria listed above.

12.1.3. Evaluation of Severity of AEs

Severity of AEs will be evaluated as follows:

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.

12.1.4. 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.

12.1.5. Investigator Presence

The Investigator or physician designee will be present approximately 30 minutes prior to dosing until at least 2 hours post dose for each subject. The Investigator or physician designee will remain on call throughout the duration of each study subject's treatment visit. The Investigator will be responsible for ensuring that a study subject is sufficiently medically stable to be safely discharged from the clinical unit (EMU or GCRC) regardless of whether the subject has received study drug.

12.1.6. Follow-up of AEs

All AEs, whether serious or non-serious, will be monitored throughout the study and followed to resolution or for up to 2 weeks following completion of the study, after which the Investigator will decide the course of action.

12.2. Procedures for Reporting Adverse Events

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

All symptoms will be recorded by clinic 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 Version 20.0 of the 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 pregnancy test before study drug administration at each Treatment Visit. Any cases of pregnancy in female subjects or in female sexual partners of male subjects that become known after administration of study drug will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) 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 (or designee) 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 phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

All SAEs, whether or not the event is deemed drug-related, will be reported on the SAE Report Form by email or fax to the designated Clinical Research Organization, Syneos Health, within 24 hours of the Investigator or site staff becoming aware of the SAE.

The safety address where SAE report forms and other SAE related documents should be sent is:

Fax No. +1 866 856 1649

Email In case of emergency or fax failure the report can also be submitted by email to saereceipt.international@syneoshealth.com

If notification cannot be made via these means due to technical delivery problems, initial notification may be made by phone, using the Syneos Health GSPV "SAE Hotline" number. A telephone call to the SAE Hotline does not substitute for the site's responsibility to submit a written SAE Report Form to Syneos Health. SAEs reported via the Hotline number must be followed with the SAE report the same day.

Hotline No.: +1 888-750-8020

In the event of any fatal or life-threatening SAE, the Investigator must also inform a Medical Monitor at Syneos Health by telephone or email:

Dr. Marcel Reichert Senior Medical Director Medical Management and Scientific Services Clinical Solutions, Syneos Health, USA Mobile +1 650-554-1706 Fax ++1 650-550-1706 marcel.reichert@syneoshealth.com	Dr. Bruce Rubin Medical Director, CNS Medical Management and Scientific Services Clinical Solutions, Syneos Health, Regionally Based – Florida USA Tel: +1 984-459-4470 Mobile: +1 305-213-7639 bruce.rubin@syneoshealth.com

The Investigator will be responsible for notifying the IRB. The Sponsor will be responsible for notifying the regulatory agencies, as appropriate.

13. BIOANALYTICAL ANALYSIS

13.1. Analytical Procedures

Data management, quality review and reporting of study data pertaining to laboratory analysis of study data will be the responsibility of the following facility:

Syneos Health
2500, rue Einstein
Québec City, Québec G1P 0A2 Canada
Tel.: 1-418-527-4000

13.2. Samples to be Assayed

Samples from all subjects dosed in this bioavailability/observational study will be analyzed.

13.3. Analyte(s) in Biological Matrix

Plasma samples will be assayed for diazepam and desmethyldiazepam using a validated analytical method according to the principles of Good Laboratory Practice.

14. PHARMACOKINETIC AND STATISTICAL ANALYSIS

14.1. Pharmacokinetic Analysis Data Set

The data from the following subjects will be included in the final PK and statistical analysis:

- Subjects who complete at least one treatment period.
- Subjects who have missed samples but for whom it has been predicted prior to the start of bioanalytical analysis that reliable estimates of the PK parameters should be possible.

Data from subjects who were dismissed/withdrawn (for any reason other than non-compliance) or who withdrew will be evaluated by a Syneos Health PK specialist and/or the Sponsor for inclusion in the PK and statistical analysis. If reliable estimation of PK parameters is judged possible, the data will be included in the analysis. If removed from the analysis, the data will be presented separately.

Any decision for excluding data from the final data set will be provided with a detailed explanation and will be properly recorded and dated.

The final data set will be defined prior to sample analysis.

14.2. Data Analyzed

Pharmacokinetic and statistical analysis will be performed by Syneos Health/third party as determined by the Sponsor.

Pharmacokinetic and statistical analysis will be performed on all data from all subjects in the final data set (Intent-to-Treat population). The actual time of blood samples collection will be used for PK and statistical analysis.

The PK and/or statistical analyses outlined in this protocol may be altered with appropriate justification.

A final Statistical Analysis Plan will be issued prior to database lock.

14.2.1. Pharmacokinetic Analysis

The following PK parameters will be estimated (where possible) for diazepam and included in the PK and statistical analysis for the subjects in the final data set:

C_{max}	The maximal observed plasma concentration
T_{max}	Time when the maximal plasma concentration is observed

For PK and statistical analyses, drug concentrations below the lower limit of quantitation (BLQ) of an assay will be considered as zero except when they occur between two non-BLQ concentrations where they will be considered as missing during PK calculations and estimations.

Missed samples and non-reportable concentrations (e.g., quantity not sufficient) from the analytical laboratory will be treated as missing in the PK analysis.

14.2.2. Statistical Analysis

Summary statistics will be reported for pharmacokinetic, safety, and usability endpoints. No formal statistical tests will be performed to compare Period A vs. Period B on pharmacokinetic, safety, or usability endpoints. All analyses will be descriptive and exploratory.

Summary statistics of **pharmacokinetic data** will include intra-subject comparisons of C_{max} and T_{max} for diazepam.

Summary statistics will be presented by age category and weight category, and data will be explored for the potential influence of concomitant medications. No efficacy analysis will be performed.

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

14.2.3. Safety Endpoints

Frequency of the following **safety endpoints** will be reported:

- Type, incidence, and severity of AEs
- TEAEs related to study drug
- TEAEs leading to discontinuation
- SAEs
- Columbia Suicide Severity Rating scale (age-appropriate versions)

- Vital signs (oxygen saturation, blood pressure, heart rate, respiratory rate, and temperature)
- Physical/neurological examination at Screening and at the Follow-up Visit.
- 12-lead ECG
- Clinical laboratory tests (hematology, serum chemistry, and urinalysis)
- Oral mucosa inspection

For purposes of the analysis, it is intended that seizures reported as AEs as described in Section 12.1.1 will be handled as unrelated to the study drug.

14.2.4. Usability Endpoints

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

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

14.3. Statistical Analyses

No formal statistical tests will be performed to compare Period A vs. Period B on pharmacokinetic, safety, or usability endpoints

Additional statistical and alternate tests will be performed if necessary. The PK and statistical analysis will be performed using an appropriate Statistical Analysis System (SAS®) Version.

15. ETHICAL CONSIDERATIONS

15.1. Basic Principles

This research will be carried out in accordance with Good Clinical Practice (GCP) as set out by the International Council for Harmonization (ICH), the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312), the Belmont Report, Directive 2001/20/EC (Europe), The Tri-Council Policy Statement and the principles enunciated in the most recent version of the World Medical Association Declaration of Helsinki.

15.2. Informed Consent

Informed consent will be performed by the site PI and/or their IRB-approved designee.

As noted in Section 8.1.2 and Section 9.1, written informed consent will be obtained from the parent(s) or legally authorized representative of each potential subject before any study-specific procedures or assessments are performed and after the aims, methods, anticipated benefits, and potential hazards are explained. The willingness of the parent(s) or legally authorized representative to have the subject participate in the study will be documented in writing in a consent form, approved by the IRB, which will be signed by the subject's parent(s) or legally authorized representative and the Investigator or designee, with the date of signature indicated. The Investigator will keep the original consent forms, and copies will be given to the subject's parent(s) or legally authorized representative. Verbal and/or written assent will be obtained from the subject as required by the IRB. It will also be explained to the parent(s) or legally authorized representative and the subject that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study will be given to the parent(s) or legally authorized representative and, if appropriate, to the subject, in a language they can understand. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study.

15.3. Revisions and/or Amendments to the Protocol

Revisions and/or amendments to the protocol must be documented and approved by the Principal Investigator and Sponsor. If the revision/amendment will affect subject safety and/or study design, then the amendment will be re-submitted to the IRB for approval. Administrative changes (i.e., change of analytical facility, typographical errors, discrepancies, clarifications) will also be submitted to the IRB, but may not require approval. A copy of the IRB's approval documents will be included in the final report.

For revisions or amendments to the protocol that substantially alter the study design after initiation of the study, the Principal Investigator and Sponsor will decide whether a revised Informed Consent Form (ICF) will be needed for continued participation.

It is the Sponsor's responsibility to submit, or to assign responsibility to submit, all revisions and amendments to the appropriate regulatory authorities when necessary.

15.4. Delegation of Investigator Tasks

The Investigator may delegate tasks as appropriate to individuals who are qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task, as described in the FDA Guidance for Industry on Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009.

16. REFERENCES

Bateman LM, Li C-S, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. Brain. 2008;131:3239-3245.

Bergen DC. Do seizures harm the brain? *Epilepsy Curr*. 2006;6(4):117-118.

Calcaterra NE, Barrow JC. Classics in chemical neuroscience: diazepam (valium). *ACS Chem Neurosci*. 2014;5(4):253-260.

Cereghino JJ. Identification and treatment of acute repetitive seizures in children and adults. *Curr Treat Options Neurol*. 2007;9(4):249-255.

Dean L. Diazepam Therapy and CYP2C19 Genotype In: Pratt V, McLeod H, Dean L, editors. *Medical Genetics Summaries [Internet]*. Bethesda MD: National Center for Biotechnology Information (US); 2016. Accessed 22 May 2017. Available from: https://www.ncbi.nlm.nih.gov/books/NBK379740

DelRosso LM, Hoque R, Mitchell C, Ly NP. Severe postictal hypoxemia-associated seizure in a 12-year-old child. J Clin Sleep Med.2016;12(12):1691–1693

Diastat® AcuDial™ rectal gel prescribing information. December 2016. Accessed 2 May 2017. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=A84A73A7-8E3A-4985-8BE0-04B3028F5E49

Fisgin T, Gurer Y, Tezic T, Senbil N, Zorlu P, Okuyaz C, Akgun D. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study. *J Child Neurol*. 2002;17(2):123-126.

Glauser TA. Designing practical evidence-based treatment plans for children with prolonged seizures and status epilepticus. *J Child Neurol*. 2007;22(5 Suppl):38S-46S.

Haut SR. Seizure clustering. *Epilepsy & Behavior*. 2006;8(1):50-55.

Kapur J, Macdonald RL. Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. *J Neurosci*. 1997;17(19):7532-7540.

Lowenstein DH, Alldredge BK. Status epilepticus. *N Engl J Med*. 1998;338(14):970-976.

Matheson AJ, Lowe MN, Palmer KJ, Wilde MI. Management of Acute Repetitive Seizures. *Disease Management and Health Outcomes*. 2000;8(6):355-368.

Riss J, Cloyd J, Gates J, Collins S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. *Acta Neurol Scand*. 2008;118(2):69-86.

Sankar R, Rho JM. Do seizures affect the developing brain? Lessons from the laboratory. *J Child Neurol*. 2007;22(5 Suppl):21S-29S.

Singh K, Katz ES, Zarowski M, Loddenkemper T, Llewellyn N, Manganaro S, et al. Cardiopulmonary complications during pediatric seizures: A prelude to understanding SUDEP. Epilepsia. 2013;54(6):1083-1091.

Tan KR, Rudolph U, Lüscher C. Hooked on benzodiazepines: GABAA receptor subtypes and addiction. *Trends Neurosci*. 2011;34(4):188-197.

Tatum WO. Adult patient perceptions of emergency rectal medications for refractory seizures. *Epilepsy Behav*. 2002;3(6):535-538.

Waterhouse EJ, Garnett LK, Towne AR, Morton LD, Barnes T, Ko D, DeLorenzo RJ. Prospective population-based study of intermittent and continuous convulsive status epilepticus in Richmond, Virginia. *Epilepsia*. 1999;40(6):752-758.

Appendix A

Placement Diagram for Aquestive Therapeutics Diazepam Buccal Film (DBF)

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

The DBF film is to be centered against the inner aspect of the right or left cheek, as illustrated by the Figure below. 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.

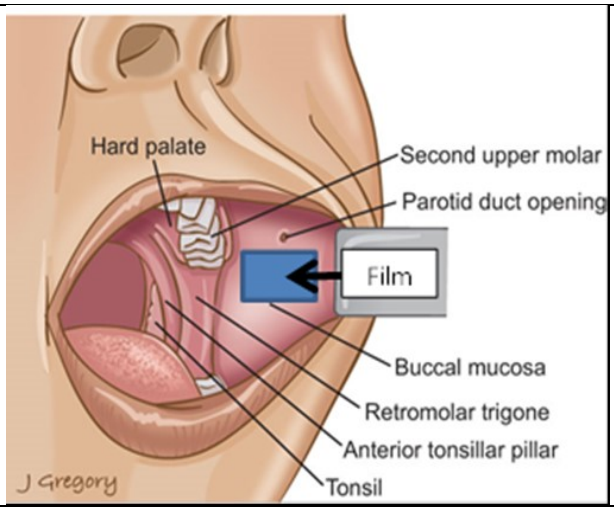


Figure: Test Drug: Placement of Aquestive Therapeutics Buccal Film against the buccal mucosa of the mouth.

Subjects are not required to lie on their side after administration; AE reports in PK studies in healthy adults indicate an increased incidence of somnolence when the subject lies on their side.