NCT 03428360

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

Protocol Date: 02 March 2020

CLINICAL STUDY PROTOCOL

Protocol Number: 42-1703

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

IND Number:	129068
Name of Product:	Diazepam Buccal Film (formerly referred to as Diazepam Buccal Soluble Film)
Phase of Development:	3
Indication:	Treatment and management of selected, refractory subjects with epilepsy who are on stable regimens of antiepileptic drugs and who require intermittent use of diazepam to control bouts of increased seizure activity
Sponsor:	Gary Slatko, MD Senior Vice President, Chief Medical Officer Aquestive Therapeutics (Formerly known as MonoSol Rx) 30 Technology Drive Warren, NJ 07059 USA Tel: 908-941-1900 Fax: 908-561-1209
Protocol Version:	Amendment 2
Amendment 2 Date:	02 March 2020
Original Protocol Date:	31 July 2017
Amendment 1 Date:	11 September 2018

PROTOCOL AMENDMENT: SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Original	31 July 2017
Amendment 1	11 September 2018

Protocol 42-1703 Amendment 2

Date of Amendment: 02 March 2020

Amendment Summary

The Protocol 42-1703 is being amended to: 1) update Diazepam Buccal Soluble Film to Diazepam Buccal Film for consistency with current nomenclature; 2) include updated Instructions for Use of the Investigative Product; 3) include plans for the end-date of the study; 4) include modifications to the weight-adjusted regimen for children who may enter this study after participating Pediatric Epilepsy Monitoring Unit (EMU) study 160325 and who have taken study drug in the past and 5) incorporate edits based on the protocol clarification letter dated 11 September 2018.

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.
Appendix A	New Instructions for Use of Diazepam Buccal Film	The Instructions for Use of Diazepam Buccal Film were updated in January 2020.
Section 1 Synopsis	Section added to the Study Design Screening description: The last Screening Visit is 28 February 2020. Study Design Schema updated to include projected end-dates. Baseline Visit (Study Day 1): Sentence added: The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020. Study Final/Completion/Early Withdrawal Visit Sentence added: The last subject Study Completion Visit/Visit 5 is projected for 02 September 2020. Last Subject Last Telephone Contact : Section added and reads: The last subject follow-up telephone contact will occur in October 2020.	The planned end date for this study is 09 October 2020. The last screening visit is 28 February 2020. The last enrollment visit will occur no later than 06 March 2020. Thus, the last planned Visit 5 will be 02 September 2020 and the last planned follow up telephone contact will be completed by 09 October 2020. Subjects who are ongoing at the enrollment end-date, who are benefitting from the use of DBF, and who would like to stay on study, will be allowed to continue until study end.

Section	Revision	Rationale
Section 1 Synopsis *Continued →*	Treatment Duration in the description of Study Final/Completion/Early Withdrawal Visit, text added: The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of visits. Enrollment end-date is 06 March 2020. However, all ongoing subjects at the enrollment end-date who are benefitting from the use of DBF and would like to stay on study, will be allowed to do so until study end. Last subject/last contact telephone call is projected for 09 October 2020.	*Study end dates continued →*
Section 6.1	Screening Period: Sentence added: The last Screening Visit is 28 February 2020. Baseline Visit (Study Day 1) Sentence added: The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020. New text added in the description of Study Design: The planned end date for this study is 09 October 2020. Thus, the last screening visit is 28 February 2020. The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020. The last planned Study Completion Visit/Visit 5 will be 02 September 2020 and the last planned follow-up telephone contact will be completed by 09 October 2020. Subjects who are ongoing on 28 February 2020, who are benefitting from the use of DBF, and who would like to stay on study, will be allowed to continue until study end. New text added in section describing the Final/Completion or Early Withdrawal Visit The last subject Study Completion Visit/Visit 5 is projected for 02 September 2020. New text added in section describing the Telephone contact 30-37 days after the Final/Completion Visit The last subject follow-up telephone contact will occur in October 2020.	
Figure 1; Section 6.1	Study Schema updated to include projected end-dates	
Section 9.2.6	Introductory sentence added to this section: The last subject Final/Completion Visit is projected for September 2020.	
Section 9.2.7	Introductory sentence added to this section: The last subject telephone follow-up contact is projected to occur in October 2020.	

Section	Revision	Rationale
Table 6	Footnotes added to the Schedule of Assessments: To the Visit 1/Screening column: Screening end date is 28 February 2020. To the Visit 2/Day 1 column: The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020 To the Visit 5 (Final Visit) column: The last planned Study Completion Visit/Visit 5 will be in September 2020. To the Follow-up/Telephone Contact Column: The last subject telephone contact will occur in October 2020.	*Study end dates continued →*
Section 4.6	Rationale included in this section for the use of the weight-based dose regimen in pediatric subjects from Study 160325 who roll over into the current Study 42-1703.	Population pharmacokinetic modeling has demonstrated that diazepam exposure following DBF (like Diastat rectal gel) is dependent on body size. For this reason, the DBF dose for subjects entering Study 42-1703 from the Study 160325 performed in pediatric subjects with epilepsy < 17 years and have received DBF as part of the Study 160325 will be determined using the weight-based dosing regimen employed in Study 160325. Subjects enrolled directly into Study 42-1703 and who are naive to DBF will be dosed according to the 42-1703 protocol dose regimen (Table 4). After receiving their first dose of DBF, these subjects will be re-evaluated by the Investigator and, according to Investigator's judgment, may be moved to Table 5 for dose determination. Subjects already enrolled and dosed in Study 42-1703 according to the 42-1703 protocol dose regimen (Table 4) may be moved to Table 5 for dose determination after re-evaluation by the Investigator and, according to Investigator's judgment. Subjects who enter Study 42-1703 from the pediatric Epilepsy Monitoring Unit Study 160325 will be dosed according
Section 6.1	Sentence add to the description of overall study design: Study drug dosing is determined first according to age group and then by body weight within age group (Table 4) for subjects who entered into the present study 42-1703 never having received DBF as study drug before and Table 5 for rollover subjects from the pediatric EMU study 160325).	
Section 8.1	Inclusion of Table 5 (Calculated Prescribed Dose of Study Drug for Subjects < 17 Years of Age Entering Study 42-1703 from Study 160325)	

Section	Revision	Rationale
		the dosing regimen in Table 5 after evaluation by the Investigator.
Revisions made to implement Protocol Clarification Letter dated 11 September 2018		
Section 1 Synopsis Study Design and Treatment Duration Section 6.1 Section 9.2.3 Section 9.2.6	Section 1 : Treatment Duration statement added: The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of visits. This policy is intended to continue for the period that the study remains open. Study Final/Completion/Early Withdrawal Visit The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of visits. This policy is intended to continue for the period that the study remains open.	The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of assessments. This policy is intended to continue for the period that the study remains open.
Section 6.1	Section 6.1 Description of Overall Study Design and Plan; sentence amended: The duration of the study per subject will be a minimum of 6 months. Final/Completion or Early Withdrawal Visit • For those subjects who have exceeded 6 months on study with at least 3 uses of DBF, the subject may complete the study at the 6-month visit (Visit 5) per the protocol, or the subject may continue as described below. • For those subjects who have at least 6 months on study with less than 3 uses of DBF, the subject may complete the study at the 6-month visit (Visit 5) per the protocol, or the subject may continue as described below. Extension of Study Beyond Month 6 The duration of treatment is being extended beyond 6 months under a similar schedule of visits. This policy is intended to continue for the period while the study remains open. At the discretion of the Principal Investigator and the subject, caregiver or guardian as applicable, a subject may continue in the study beyond the 6-month visit under a similar schedule of assessments, while the study is open. No Medical Monitor approval is required for subjects with 3 or more uses. The subject may continue in the study while the study remains open.	

Section	Revision	Rationale
Revisions made to implement Protocol Clarification Letter dated 11 September 2018		
Section 6.1 *Continued→*	In order to continue: • The subject should be using the Investigational Product. • The subject is receiving benefit from the Investigational Product. • The subject is tolerating the Investigational Product. • The subject wishes to continue in the study. For subjects who continue beyond Month 6 (Visit 5), subsequent visits will occur every 3 months (± 14 days) while the study remains open. If a subject has not had 3 uses of DBF at the 6-month visit (Visit 5), or any visit after that, the Investigator should strongly consider the likelihood of the subject using DBF and whether the subject should continue in the study. The Investigator may consult with the Medical Monitor, if needed, to assess on a case-by-case basis the likelihood of achieving 3 uses of DBF by continuing the subject on study. If the assessment concludes that achieving 3 uses of study drug is likely, the subject's participation can be extended with a similar schedule of assessments. If the assessment concludes that achieving 3 uses use of the study drug is not likely, the study will be considered complete for the subject. The sponsor may elect to end study participation for non-users prior to end of study.	The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of assessments. This policy is intended to continue for the period that the study remains open. *Continued→*
Section 9.2.3	Treatment Period Clinical Site Visits; text added: The Sponsor has elected to extend the duration of the study beyond 6 months under a similar schedule of visits. The policy is intended to continue for the period while the study remains open.	
Section 9.2.6	Final / Completion or Early Withdrawal Visit; sentence added: The 6-month visit will serve as the study Final/Completion site visit. The Sponsor has elected to extend the study beyond 6 months under a similar schedule of visits.	
Table 6 Schedule of Assessments	Note added to the table for 6-month visit (Visit 5): The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of visits. This policy is intended to continue for the period that the study remains open. See Section 6.1 Final/Completion or Early Withdrawal Visit for criteria and methods.	

Section	Revision	Rationale
Revisions made to implement Protocol Clarification Letter dated 11 September 2018		
Section 1 Synopsis Clinical laboratory tests; Site Visit at 3 Months and 6 Months After Study Day 1:	Clinical laboratory tests (hematology, serum chemistry, urinalysis, and urine and serum pregnancy tests for female subjects of childbearing potential): If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be at the Investigator's discretion	To clarify that urine and serum pregnancy testing will be performed for female subjects of childbearing potential. However, if the subject is unable to provide a urine sample or is incontinent, the option to perform only serum pregnancy tests at study visits will be at Investigator's discretion. The reason the urine pregnancy testing could not be completed should be documented in the source documents and Case Report Form.
Section 7.1 Inclusion Criterion #5	Footnote states: If the subject is unable to provide a urine sample, the option to use only serum pregnancy test will be according to Investigator judgment.	
Section 7.2 Exclusion criterion #7	*Changed to read*: Lactating female or positive urine and serum pregnancy test (β-hCG) at screening for female subjects of childbearing potential	
Section 9.2.1 Screening; Section 9.2.3; Section 9.2.6	Change in the assessment of urine and serum pregnancy test in female subjects 12 years of age to read: Urine and serum pregnancy test in female subjects of childbearing potential	
Table 6 Schedule of Assessments; Table 8 Laboratory Assessments	Table note added to clarify this process As with other missing/unobtainable protocol-mandated assessments, the site must document the reason why the urine sample could not be obtained from the subject (e.g., subject is incontinent, subject is incapable of supplying a urine sample on request, etc.) in the source documents and via the eCRF. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter	If a protocol-required urine sample cannot be obtained from the subject (at any study visit), the Investigator will ensure an accurate and thorough review is conducted by the Investigator with the subject and/or subject's caregiver/study partner/legally authorized representative. This review should include, as applicable, a Physical Exam, Review of Systems/Symptoms (ROS), Past Medical History, Concomitant Medications (including last known diazepam use), any new or ongoing AEs, sexual activity history, pregnancy/menstrual cycle status and illicit drug use. This is extremely important during the screening/eligibility visit as the urine sample is a key component/assessment in determining a host of inclusion and exclusion criteria.

Section	Revision	Rationale
Revisions made to implement Protocol Clarification Letter dated 11 September 2018		
Section 9.2.1, Section 9.2.2, Section 9.2.3, Section 9.2.6	Text added to clarify the process If a subject cannot provide a urine sample for drug screen or, if in the judgment of the Investigator, the subject's exposure to drugs of abuse is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed. If the subject cannot provide a urine sample for routine analysis, the site must document in the source documents the reason that the assessment is not completed. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter	As with other missing/unobtainable protocol-mandated assessments, the site must document the reason why the urine sample could not be obtained from the subject (e.g. subject is incontinent, subject is incapable of supplying a urine sample on request, etc.) in the source documents and via the eCRF. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter.
Table 8	*Addition to the table*: If a subject cannot provide a urine sample for drug screen, an accurate and thorough review should be conducted by the Investigator with the subject and/or subject's caregiver/study partner/Legally Authorized Representative. This review should include, as applicable, a Physical Exam, Review of Systems/Symptoms (ROS), Past Medical History, Concomitant Medications (including last known diazepam use), any new or ongoing adverse events, sexual activity history, pregnancy/menstrual cycle status and illicit drug use.	
Section 11.9 Laboratory Assessments	Text above include in text of this section along with additional instructions: As with other missing/unobtainable protocol-mandated assessments, the site must document the reason why the urine sample could not be obtained from the subject (e.g., subject is incontinent, subject is incapable of supplying a urine sample on request, etc.) in the source documents and via the eCRF. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter	

Section	Revision	Rationale
Revisions made to implement Protocol Clarification Letter dated 11 September 2018		
Section 1 Synopsis Site Visit at 3 Months and 6 Months After Study Day 1 Description of age-appropriate scales Section 6.1 Treatment Period Clinical Site Visits Section 9.2.1 Screening Assessments Section 9.2.2 Baseline Assessments Section 9.2.3 Treatment Period Clinical Site Visits Section 9.2.6 Final / Completion or Early Withdrawal Table 6 Schedule of Assessments Section 11.4 Quality of Life Assessments Section 11.5 Columbia Suicide Severity Rating Scale Section 11.7 Gustatory Sense Assessment	Text added to clarify this process. The QoL and C-SSRS should be completed in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).	The Quality of Life (QoL) scale, Columbia-Suicide Severity Rating Scale and Gustatory assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
Table 6 Schedule of Assessments; Table 8 Laboratory Assessments Section 9.2.1 Screening; Section 9.2.2; Section 9.2.3; Section 9.2.6;	Table note added to clarify this process: The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed. Text added: The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed.	The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed.

Section	Revision	Rationale
Revisions made to implement Protocol Clarification Letter dated 11 September 2018		
Section 1 Synopsis: Age-appropriate QoL scales	Text revised to clarify this process Age-appropriate QoL scales; PedsQL 3.0 Epilepsy Module PedsQL Parent Proxy Report (ages 2 to 4 years); Peds QL 3.0 Epilepsy Module Parent Proxy Report (ages 5 to 7 years) PedsQL 3.0 Epilepsy Module Parent Proxy Report (ages 8 to 10 years) QOLIE-AD-48 Version 1 (ages 11 to 17 years) QOLIE-31-P Version 2 (18 years and older)	To clarify the age ranges for each Quality of Life scale and to identify the person who completes the assessment.
Section 1 Synopsis: Age-appropriate QoL scales *Continued*	*Text added*: The QoL and C-SSRS should be completed in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).	
Table 7 Age-Defined Quality of Life Assessment Modules	Table modified to include who completes each assessment listed in Table 7 (parent/guardian/caregiver or the subject)	
Section 5.2.1 Primary Endpoints; Table 6 Schedule of Assessments; Section 9.2.1 Screening; Section 9.2.2 Baseline; Section 9.2.3 Treatment Period Clinical Site Visits; Section 9.2.6 Final/Completion or Early Withdrawal Visit; Section 12.4.1 Primary Safety Endpoints; Section 12.4.1.3 Vital Signs	Note added to include this clarification. If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.	To clarify that body temperature requires oral temperature; however, many subjects are unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed. For these subjects, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.

Section	Revision	Rationale
Revisions made to implement Protocol Clarification Letter dated 11 September 2018		
Table 6 Schedule of Assessments	Corrected to read: 12-lead ECG testing is performed at Screening, Baseline, and at all onsite visits including the Final Visit. When performed on days of blood draws, ECG should be completed prior to blood collection.	Correction of footnote
Appendix F Quality of Life in Epilepsy for Adolescents QOLIE-48 (VERSION 1.0)	Note added to reflect the correct date and the extra page has been deleted.	To clarify that the QOLIE AD 48 version should reflect the version date as 04 Jan 18 – NOT 03 Jan 18. Page 5 of 6 is included twice

PROTOCOL APPROVAL

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

MEDICAL APPROVAL

I have read and approve the content of this protocol.

Allen H. Heller MD MPH — March 3, 2020

Allen H. Heller MD MPH — Date

Principal, Pharma Study Design LLC

(Consultant to Aquestive Therapeutics)

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 — March 3, 2020

Gary Slatko MD — Date

Senior Vice President, Chief Medical Officer

Aquestive Therapeutics

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Aquestive Therapeutics.
- Not to implement any changes to the protocol without written agreement from Aquestive Therapeutics and prior review and written approval from the Institutional Review Board (IRB) except where necessary to eliminate an immediate hazard to subjects.
- That I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Aquestive Therapeutics including, but not limited to, the current Investigator's Brochure (IB).
- That I am aware of, and will comply with, good clinical practice (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Aquestive Therapeutics study drug and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: _____

Name (print): _____

Site Number: _____

CONTACT LIST

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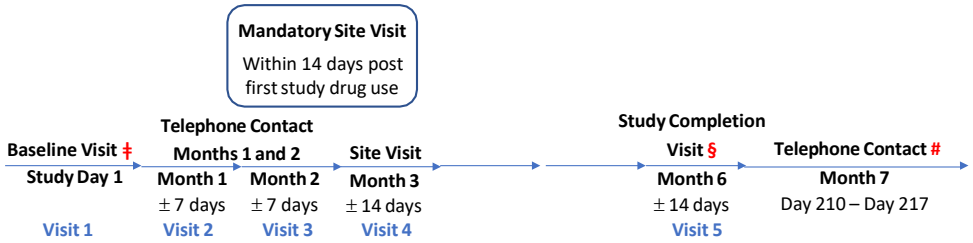
CRO Safety (Pharmacovigilance) Reporting:	Syneos Health Global Safety & Pharmacovigilance Telephone Hotline: 1-888-750-8020 Facsimile: 1-866-856-1649
Clinical Laboratory:	Covance Central Laboratory Services 8211 Scicor Drive Indianapolis, IN 46214 USA Telephone: 1-888-268-2623 or 1-317-217-1200

1. SYNOPSIS

Title of Study	An Open-Label, Safety and Tolerability Study of Chronic Intermittent Use of Diazepam Buccal Soluble Film (DBSF) in Pediatric, Adolescent, and Adult Subjects with Epilepsy
Protocol Number	42-1703
Investigator/Study Sites	Approximately 20 United States (US) study sites are projected
Phase of Development	3
Objectives:	Primary objective • To assess the safety and tolerability of DBF (study drug) administered a minimum of 3 times to subjects with epilepsy for the treatment of seizures over a minimum 6-month period. Secondary objectives • To evaluate the usability of study drug as assessed by the ability of caregivers/subjects to administer study drug based on the Instructions for Use (IFU) • To evaluate the Quality of Life (QoL) of the subjects during the study drug treatment period as assessed by use of age-appropriate epilepsy scales over a minimum 6-month period.
Study Design	This is a Phase 3 multicenter, open-label, long-term safety and tolerability study conducted in male and female pediatric (2 to 12 years old), adolescent (13 to 16 years old), and adult subjects (17 to 65 years old) with a clinical diagnosis of epilepsy who have bouts of increased seizure activity (e.g., Acute Repetitive Seizures [ARS], frequent breakthrough seizures, seizure clusters, or cluster seizures) and who are on chronic intermittent use of a rescue medication (e.g., Diastat® AcuDial™ or other benzodiazepine). Subjects who have completed the Phase 2 studies 160325 (Pediatric) or 160326 (Adult) which enrolled subjects with a similar diagnosis may screen for enrollment into this Phase 3 study when they come in for the follow-up visit after the last treatment period in the Phase 2 study (rollover subjects). These rollover subjects will be screened for enrollment using inclusion/exclusion criteria of this protocol (42-1703). The Screening visit for the Phase 3 study can be conducted on the day of the follow-up visit for the Phase 2 study. Subjects who initially consented and enrolled in the study under version 1 of the protocol dated 31 July 2017 may come in at their next scheduled site visit, reconsent under the amended protocol and be dispensed a new container of DBF based upon the revised mg/kg dosing. The subjects do not need to come in for unscheduled visit.

	Screening: Screening for enrollment eligibility can occur within 1 to 28 days prior to study entry. Before the performance of any study-related procedure, written informed consent will be obtained from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the Institutional Review Board (IRB). As a part of screening, potential subjects and caregivers will be advised that electronic diaries will be used by subjects and/or caregivers to document seizures, use of study drug, adverse events (AEs), and changes in concomitant medication to determine their ability/willingness to comply with this procedure. Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor. The last Screening Visit is 28 February 2020. The duration of the study per subject will be a minimum of 6 months:



‡ Date for last Baseline Visit/Study Day 1 no later than 06 March 2020.
§ Planned date for last Study Completion Visit/Visit 5 is 02 September 2020.
# Planned date for last Telephone Contact is 09 October 2020.

Subjects who are ongoing on 28 February 2020, who are benefitting from the use of DBSF, and who would like to stay on study, will be allowed to continue until study end.

	Baseline Visit (Study Day 1)-Conducted after completion of screening and confirmation of eligibility for study enrollment-based compliance with protocol Inclusion and Exclusion criteria: The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020. Training will be performed by the study team on study drug administration and the use of the electronic study diary. The training will be reinforced at all subsequent study visits/contacts. Study drug dosing will be administered away from the study site by the subject, with the assistance of a caregiver as appropriate. Administration and usability of study drug will be recorded at home in the electronic diary after each use of study drug. The electronic diary will also be used at home to capture seizure history and changes in health and medications. Subjects/caregivers will be instructed to call the site when the first seizure prompts study drug administration. A study site visit will occur within 14 days after this first use.

	Site Visit Following the First Seizure Prompting Study Drug Administration: A study site visit will be conducted within 14 days after the first study drug dosing. The subject or caregiver (if needed) will document the seizure and study drug administration in the electronic study diary AND call the study site after the first use of study drug. Based on subject diagnosis and history (Inclusion Criteria), it is expected that subjects will have a minimum of 3 uses of the study drug within the 6 months treatment period. **Telephone Contact at 1 Month and 2 Months After Study Day 1:** The study site staff will telephone the subjects at approximately 1 and 2 months ± 7 days after the baseline visit to check on the subject's health and seizure status, reinforce training on study drug administration and diary documentation, determine if study drug was used, and to address concerns. **Site Visit at 3 Months and 6 Months After Study Day 1:** A study site visit will be conducted every 3 months ± 14 days over the minimum 6-month course of treatment. At the Month 3 visit, the subjects (and their caregivers as appropriate) will have a review of the number of study drug uses, study drug usability assessment, seizure-control status, use of the study diary, AEs, concomitant medications, and subject/caregiver training. Subjects will undergo assessment of oral mucosal health, gustatory assessment, vital signs, physical and neurological examination, collection of blood and urine samples for clinical laboratory testing, 12-lead ECG, age-appropriate Quality of Life (QoL) and Columbia Suicide Severity Rating Scale (C-SSRS) assessments. The QoL and C-SSRS should be completed in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.). For all age groups, height and weight will be measured and body mass index (BMI; kg/m^2) recorded. Urine and serum pregnancy testing will be performed at for female subjects of childbearing potential. If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be at the Investigator's discretion. The reason that urine pregnancy screen could not be completed should be documented in the source documents and the Case Report Form.

	Study Final/Completion/Early Withdrawal Visit. A Final Visit after the end of the study drug treatment period or early withdrawal will occur for the subject to undergo final study assessments, return unused study drug, and return the study diary. The last subject Study Completion Visit/Visit 5 is projected for 02 September 2020. The subjects will have a review of AEs in relation to study drug treatment and severity, concomitant medication review, assessment of vital signs, body height and weight, physical and neurological status, C-SSRS assessment, 12-lead ECG, and assessments of tolerability, usability, and seizure-control status. The unused study drug will be returned, and study diary will be collected. Urine and serum pregnancy testing will be performed for female subjects of childbearing capacity. If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be at the Investigator's discretion. **Telephone contact 30-37 days after the Final Visit:** For subjects completing the study at 6 months, the 6-month visit serves as the Final/Completion Visit. The Investigator or designee will conduct a follow-up phone call with the subject at 30-37 days after the Final Visit to check on subject status and collect AE information. **Last Subject Last Telephone Contact:** The last subject follow-up telephone contact will occur in October 2020.
Selection of Subjects	Approximately 120 subjects are expected to be screened in order to have a minimum of 100 eligible subjects (50 adult and 50 pediatric/adolescent) enrolled. The enrollment should include at least 20 subjects in the 6 to 11-year-old group and 20 subjects in the 12 to 16-year-old group. Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor. *Inclusion Criteria*: Subjects must meet all the following criteria in order to be included in the study: 1. Female or male between 2 and 65 years of age, inclusive 2. Written informed consent to participate in the study from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the Institutional Review Board (IRB) prior to the performance of any study-related procedure 3. Caregiver, if needed for subject, provides written informed consent and is able to administer study drug in the event of a seizure.

	4. Subject has an established diagnosis of epilepsy with motor seizures with clear alteration of awareness, and while on a regimen of anti-epileptic medication(s), still experiences bouts of seizures (frequent break through seizures, e.g., ARS or seizure clusters) and who, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control at least 1 time a month on average. Subject must be on at least 1 concomitant anti-epileptic drug (AED) at screening. The study is open to subjects who, in the opinion of the Investigator, would benefit from the study drug. Concomitant prescription for a benzodiazepine for rescue (including diazepam) at screening or ongoing, or concomitant use of a benzodiazepine ongoing as a part of the subject's daily antiepileptic drug regimen does not exclude a subject from eligibility. Subjects are to be encouraged to use study drug when a benzodiazepine rescue treatment is needed. However, treatment decisions are to be guided in all cases according to the Investigator's judgment as to the optimal treatment in the interest of the subject's care and welfare. Participation in this study is never a basis for the withholding of any treatment considered to be indicated in the interest of the subject. 5. Female subjects have negative serum and urine pregnancy test at screening.[a] Female subjects of childbearing potential (not surgically sterile or less than 2 years postmenopausal) must have a partner who is sterile, agrees to abstinence, be practicing double barrier contraception or using a Food and Drug Administration (FDA) approved contraceptive (e.g., licensed hormonal or barrier methods) for greater than 2 months prior to screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days after the study. [a] If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be at the Investigator's discretion. 6. No clinically significant abnormal findings on the ECG (QTcF [Fridericia's Correction Formula] ≤ 450 msec for males and QTcF ≤ 470 msec for females). 7. Subject and caregiver (if applicable) must be willing to comply with all study visits and all required study procedures (including the use of the electronic diary). NOTE: Nonverbal and cognitively impaired subjects are eligible to participate in the study.

	Exclusion Criteria: Subjects meeting any of the following criteria are ineligible to participate in this study: 1. A history of clinically significant gastrointestinal, renal/genitourinary, hepatic, hematologic, dermatologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other clinically significant abnormalities, such as physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the Investigator require further investigation or treatment or which may interfere with study procedures or safety or other medical conditions (e.g., cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the Investigator could affect the subject's safety or interfere with the study assessments or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject. 2. Subject has had a significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening. 3. Subject has a recent history of suicide attempt (defined as an active, interrupted, or aborted attempt with the past five years) or reports suicidal ideation in the past six months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS performed at the Screening Visit. . NOTE: If a subject cannot complete the assessment, the site must document this. 4. A history of allergic or adverse responses to diazepam or any other benzodiazepine. 5. Participation in another clinical trial other than Aquestive Therapeutics Phase 2 studies 160325 and 160326 within 30 days prior to screening. Participation in an observational (non-interventional) study is not an exclusion provided there are no scheduling conflicts with this study. 6. Received any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before assignment to study drug treatment. 7. Lactating female or positive urine and serum pregnancy test (β-hCG) at screening for female subjects ≥ 12 years of age.[a] [a] If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be at the Investigator's discretion.

	8. In subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion), positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C, or a positive test result for drugs of abuse or alcohol, except marijuana use for medicinal indications. When marijuana is or was used for medicinal indications in the opinion of the Investigator, it is not considered as drug abuse and the subject can be enrolled in states where marijuana is legal, even if the marijuana metabolites are positive in the urine. NOTE: In such a case, the marijuana product will be recorded as a concomitant medication.
Planned Sample Size:	Approximately 120 subjects with epilepsy will be screened in order to have a minimum of 100 eligible subjects (50 adult and 50 pediatric/adolescent) enrolled in the 6-month (24-week) study period. The enrollment should include at least 20 subjects in the 6 to 11-year-old group and 20 subjects in the 12 to 16-year-old group.
Investigational Therapy:	Study drug dosing is determined according to age group and body weight within age group during each study site visit where subjects are dispensed 5, 7.5, 10. 12.5, 15, or 17.5 mg study drug. Dosing occurs away from the study site by the subject or caregiver. Investigators can make dosing adjustments after the first administration and at subsequent visits. The Investigator may choose to adjust the dose upward or downward by 1 dose level depending on clinical response to study drug. For all age groups, the height and weight will be measured and recorded at all study visits. Subjects with body weights in the range 112 to 134 kg (247 to 295 pounds) may participate in the study at the discretion of the investigator.
Treatment Duration:	• *Screening Period*: A minimum of 1 and a maximum of 28 days prior to enrollment Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor. • *Baseline Visit*/*Study Day 1*: Conducted after completion of screening. • *Study Drug Treatment Period*: Upon completion of the Baseline visit, the subject enters a 6-month minimum period of potential study drug treatment. – Study site visits occur every 3 months (± 14 days) after the Baseline Visit (Study Day 1/Visit 2) for a minimum of 6 months. – Subjects/caregivers will be instructed to call the site after the first seizure for which study drug is administered. A study site visit will occur within 14 days after this first use.

	– The study site staff will telephone the subjects at approximately 1 and again at 2 months after the date of the Baseline Visit (Study Day 1/Visit 2) to check on the subject's health and seizure status, reinforce training on study drug administration and diary documentation, determine if study drug was used, and to address concerns. • *Study Final/Completion/Early Withdrawal Visit*: A Final Visit at Month 6 of the study drug treatment period or early withdrawal will occur for the subject to undergo final study assessments, return unused study drug, and return the study diary. If a subject has experienced 3 uses of study drug, study participation will be complete. For those subjects who have not experienced 3 uses of study drug, the Investigator and the Medical Monitor will assess on a case-by-case basis the likelihood of achieving 3 uses of study drug by continuing the subject on study for an additional 3 months. If the assessment concludes use of the study drug is not likely, the study will be considered complete for the subject. The sponsor may elect to end study participation for non-users prior to end of study. • For subjects completing the study at 6 months, the 6-month visit serves as the Final Visit. The Investigator or designee will conduct a follow-up phone call with the subject at 30-37 days after the Final Visit to check on subject status and collect any reporting information should any SAE have occurred. The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of visits. This policy is intended to continue for the period that the study remains open. Enrollment end-date is 06 March 2020. However, all ongoing subjects at the enrollment end-date who are benefitting from the use of DBF and would like to stay on study, will be allowed to do so until study end. Last subject/last contact telephone call is projected for 09 October 2020.
Criteria for Evaluation:	*Safety Assessments*: At each study visit, the following assessments will be completed: • Documentation and assessment of AEs over the time elapsed between visits (serious and non-serious to include time of onset and resolution, severity, relationship to study treatment) • Concomitant medications review • Vital signs (blood pressure, heart rate, respiration rate, oral temperature) • Body height and weight • Symptom-driven physical and neurological examination except at screening and baseline (Day 1) when a complete physical and neurological examination is required

	• C-SSRS: if a subject cannot complete the questionnaire, the site must document this.
	• Clinical laboratory tests (hematology, serum chemistry, urinalysis, and urine and serum pregnancy tests for female subjects of childbearing potential) If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be at the Investigator's discretion. If a protocol-required urine sample cannot be obtained from the subject (at any study visit), the site must document the reason why the urine sample could not be obtained from the subject (e.g., subject is incontinent, subject is incapable of supplying a urine sample on request, etc.) in the source documents and via the eCRF. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter • Review of electronic diary which will capture the occurrence of seizures, use of study drug, usability assessment, study drug placement (left or right) for each seizure cluster treated, AE information, and any changes in medication. This information can be review directly in the subject's electronic diary or via the Engage Portal database.
	Tolerability Assessments: At each study site visit: • Oral examination for assessment of oral mucosa • Gustatory sense assessment in subjects 12 years of age and older by trained Investigator or other trained site personnel using the labeled Magnitude Scale (gLMS) and commercially available test strips from Burghart Messtechnik • Age-appropriate QoL scales; PedsQL 3.0 Epilepsy Module PedsQL Parent Proxy Report (ages 2 to 4 years); Peds QL 3.0 Epilepsy Module Parent Proxy Report (ages 5 to 7 years) PedsQL 3.0 Epilepsy Module Parent Proxy Report (ages 8 to 10 years) QOLIE-AD-48 Version 1 (ages 11 to 17 years) QOLIE-31-P Version 2 (18 years and older) Non-verbal and cognitively impaired subjects are eligible to participate in the study. If a subject cannot complete the assessment (ie, non-verbal subjects), the site must document this. The QoL and C-SSRS should be completed in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason

	that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
	Administration and Usability Assessments At each study site visit, the study team will review the Usability Assessments documented in the electronic diary. • Review diary for documentation of study drug use – Handling and administration of study drug, based on the Instructions for Use – Successful buccal insertion of study drug o Successful placement and adherence of the study drug against the buccal mucosa (inner cheek) – Oral cavity placement and retention o Study drug swallowed prior to sticking to inner cheek o Study drug spit out or blown out by subject after administration *Training* At each study site visit: • Use of electronic diary reinforced • Retraining of subjects/caregivers: when to administer study drug, how to open study drug package, and how to administer study drug based on the supplied Instructions for use
Analysis Population:	Safety Population: includes all subjects who receive at least 1 dose of study drug
Study Endpoints:	*Primary endpoints* • Treatment-emergent adverse event (TEAE) assessment including relationship to study drug and severity • C-SSRS assessment; if a subject cannot complete the assessment, the site must document this. • Vital signs (blood pressure, heart rate, respiration rate, oral temperature) • Laboratory analyses (hematology, serum chemistry, urinalysis) • Pathological change in oral mucosa as measured by an oral examination • Gustatory sense changes in subjects 12 years and older as measured by the general Labeled Magnitude Scale (gLMS) using commercially available Burghart Messtechnik taste test strips *Secondary endpoints*

	• Quality of Life (QoL) assessments by use of age-appropriate epilepsy scales; if a subject cannot complete the assessment, the site must document this.
	• Assessment of usability by subject and/or caregiver – Handling and administration of study drug, based on the Instructions for Use – Successful buccal insertion of study drug o Successful placement and adherence of the study drug against the buccal mucosa (inner cheek) – Oral cavity placement and retention o Study drug swallowed prior to sticking to inner cheek o Study drug spit out or blown out by subject after administration • 12-lead ECGs • Use of concomitant medications • Physical and neurological examinations • Body height and weight; BMI (kg/m^2)
Statistical Methods and Planned Analyses:	All analyses will be descriptive, and no formal statistical testing will be performed. All summaries will be done for all subjects combined as well as by age group (pediatric, adolescent, adult). Pediatric and adolescent might be combined as one group for summary purpose. An interim analysis is planned to obtain a snapshot of targeted Tables, Figures, and Listings and summary of the preliminary safety information. The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 9.3 or higher (SAS Institute, Cary, NC). All data will be listed and summary tables provided. Summary statistics will be presented by age group and overall. For continuous variables, data will be summarized with number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). For categorical variables, data will be tabulated with the number and proportion (percentage) of subjects for each category.

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NOTE: The term "patient" is used in this protocol when text is around individuals with epilepsy in the general public. The term "subject" is used when text is around individuals with epilepsy in this and other clinical trials.

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ARS	Acute Repetitive Seizures
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	Area Under the Curve
BMI	Body mass index (kg/m^2)
BP	Blood pressure
BUN	Blood Urea Nitrogen
CRA	Clinical Research Associate
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	Confidence Interval
C_{max}	Maximum concentration
CNS	Central Nervous System
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
DBF	Diazepam Soluble Buccal Film
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMU	Epilepsy Monitoring Unit
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
$GABA_A$	GABA receptors of the A-type
GCP	Good Clinical Practice
GI	Gastrointestinal
HCG	Human chorionic gonadotropin

Abbreviation	Definition
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFU	Instructions For Use
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
max	maximum
NDA	New Drug Application
NIH	National Institutes of Health
PI	Principal Investigator
PK	Pharmacokinetic
QOL	Quality of Life
RBC	Red blood cell
RLD	Reference Listed Drug
RR	Respiratory rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard deviation
TEAE	Treatment Emergent Adverse Event
T_{max}	Time of maximum concentration

Abbreviation	Definition
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential
US	United States

4. INTRODUCTION

4.1. Background on Treatment and Management of Individuals with Refractory Epilepsy

Acute repetitive seizures (ARS) comprising 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 anywhere from minutes to hours.[1] When these seizures occur outside a hospital, the patient is often transported to an acute care facility for treatment to prevent prolonged seizures.[2] 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.[3,4,5]

In these cases, the primary goals of the treatment are seizure cessation and prevention of seizure recurrence.[1] 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.[6]

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 (US), a portion of the population does not benefit from this treatment partly because the rectal route of administration is inappropriate or unacceptable.[7] 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.

4.2. Diazepam

Diazepam is a long-acting "classical" benzodiazepine that enhances the effect of γ-aminobutyric acid (GABA) at the (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.[8] It can be taken by mouth, inserted into the rectum, injected into muscle, or injected intravenously. When given intravenously, effects begin in one to five minutes. When diazepam is taken orally, effects may be delayed as long as 40 minutes.[9]

Intravenous diazepam is a first-line treatment for status epilepticus.[9] Diazepam gel has been demonstrated superior to placebo gel in reducing the risk of continuing seizures. Diazepam is rarely used for the long-term treatment of epilepsy because tolerance to its anticonvulsant effects develops over time with continuous treatment.[9] However, diazepam is effective when used intermittently for the prevention of repeated seizures. Like other benzodiazepines, diazepam administration may cause sedation, anxiolysis, and amnesia.[9]

4.2.1. 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 [10]. 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.

4.2.2. 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) [11]. 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 [12].

4.2.3. 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%).

4.3. Diastat® AcuDial™

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.[13] 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.[14,15] 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.[16]

4.4. Diazepam Buccal Film (DBF)

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

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

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

4.5. Background on Diazepam Buccal Film (DBF)

Diastat® AcuDial™ rectal gel is prescribed for increased seizure activity as defined by a marked increase in seizure activity, sometimes heralded by non-convulsive symptoms

that are characteristic for each subject and deemed by the prescriber to be the kind of seizure for which a benzodiazepine would be administered (Diastat® AcuDial™ rectal gel Prescribing Information). Diastat® AcuDial™ rectal gel has been marketed in the US since 1997 and currently is the only FDA approved drug in the US for this indication.

Though the Diastat® AcuDial™ rectal gel formulation is considered safe and effective, the route of administration is less than ideal. The mechanics of administering a rectal gel can be a difficult, time-consuming, and embarrassing experience for both subject and care-givers alike. For example, the subject or caregiver must first remove articles of clothing and then place the subject in an appropriate position. The Diastat® AcuDial™ rectal gel syringe tip is inserted into the rectum to a specific depth and the gel expressed into the rectal vault. However, improper technique can lead to subject injury, and leakage of gel from the rectum can result in incomplete dosing. Additionally, some subjects have a negative view of the rectal route of administration, and this may reduce compliance to treatment.[13] Each of these factors has a potential influence on subject morbidity. Persistent seizure activity is associated with less favorable outcomes across a spectrum of precipitating conditions.[14,15] 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.[15]

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

4.5.1. Nonclinical Studies

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 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. 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.

Metabolism and Elimination: It has been reported in the literature that diazepam is extensively metabolized to one major active metabolite (desmethyldiazepam) and two minor active metabolites, 3-hydroxydiazepam (temazepam) and 3-hydroxy-N-diazepam (oxazepam). With steady state dosing, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation

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

4.5.2. Clinical Studies

As of 18 July 2018, 6 DBF studies in healthy volunteers have been completed: two bioavailability/bioequivalence studies (Study numbers 1899 and 1900), a dose-proportionality study (Study number 162013), a fasting pivotal bioavailability study in comparison with Diastat® gel (Study number 162021) and two food effect studies (high and moderate fat) in healthy subjects (Study numbers 162022 and 172018).

4.5.2.1. Safety in Clinical Studies

It is anticipated that the adverse event (AE) profile from systemic exposure observed with study drug will resemble the already well-known profile for diazepam in general and the reference therapy, Diastat® AcuDial™ rectal gel, in particular. Diazepam rectal gel AE data were collected from double-blind, placebo-controlled studies and open label studies with 573 subjects exposed to diazepam rectal gel.[11] The majority of AEs were mild to moderate in severity and transient. The most frequent AE reported with diazepam rectal gel in the two double-blind, placebo-controlled studies was somnolence (23%). Less frequent AEs were headache (≤5%), diarrhea (≤4%), ataxia (≤3%), dizziness (≤3%), euphoria (≤3%), incoordination (≤3%), rash (≤3%), vasodilatation (≤2%), and asthma (≤2%).

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

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

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

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

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

An increased frequency of AEs following dosing in a fasted state was observed in the two food effect studies.

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

4.5.2.2. Pharmacokinetics in Clinical Studies

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

[redacted]

[redacted]

Table 1

[redacted]

[redacted]

Table 2

[redacted]

Section 4.5.2.2.4.1 Section 4.5.2.2.4.2

[redacted]

[redacted]

[redacted]

Table 4

Section 8.1

[redacted]

[redacted] Table 5 [redacted]

4.7. Clinical Risks/Benefits of Study Drug

4.7.1. Managing Clinical Risks/Benefits in the Current Study

The available data indicate that study drug is dose proportional over the studied dose-range, while Diastat® AcuDial™ is less than dose proportional with respect to C_{max}. The data suggest that study drug and Diastat® AcuDial™ are approximately bioequivalent at the 5 mg dose, and that C_{max} values for study drug exceed C_{max} from Diastat® AcuDial™ as the dose increases beyond 5 mg.

In this study, dose is based on age and weight category (Section 4.5.2.2 and Section 8.3). Note that subjects are to be weighed at screening and at each study visit, and dose dispensed will be adjusted depending on age and weight category at that visit (Section 8.3). Study drug dosing is determined first according to age group and then by body weight within age group. The Investigator may make adjustments as medically indicated. For all age groups, the height, weight, and body mass index (BMI; kg/m^2) will be measured and recorded at all study visits. The rationale for the dose regimen for DBF is explained in Section 4.6.

The subjects in this study will be administering study drug themselves or with the help of a caregiver, (trained by the study site staff in study drug administration and documentation) in the same setting as they typically use the diazepam rectal gel or other rescue medication, without the presence of study staff. The study design includes study site visits to monitor safety and tolerability, assess subject/caregiver use of study drug through review of subject/caregiver diaries, ensure adequate supply of study drug dose, and reinforce subject/caregiver training on the use of study drug, with a focus on safety and correct study conduct. Since the dosing is weight based, the subjects' drug inventory will be reviewed at each study visit and reissued with the correct dosage, based on body weight.

4.7.2. Overdosage Information Derived from Diastat® AcuDial™ Prescribing Information

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. Subjects 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 subjects treated with benzodiazepines. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, should be consulted prior to use.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

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

5.1.2. Secondary Objectives

- To evaluate the usability of study drug as assessed by the ability of caregivers/subjects to administer study drug based on the Instructions for Use (IFU).
- To evaluate the Quality of Life (QoL) of the subjects during the treatment period as assessed by use of age-appropriate epilepsy scales over a minimum 6-month period.

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

5.2. Study Endpoints

5.2.1. Primary Endpoints

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

- TEAE assessment, including relationship to treatment with study drug and severity.
- Columbia Suicide Severity Rating Scale (C-SSRS) assessment: If a subject cannot complete the assessment, the site must document this.
- Vital signs (blood pressure, heart rate, respiration rate, oral temperature)

  If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.
- Laboratory analyses (hematology, serum chemistry, and urinalysis)
- Pathological change in oral mucosa as measured by an oral examination
- Gustatory sense changes as measured by the general Labeled Magnitude Scale (gLMS) using commercially available Burghart Messtechnik test strips in cognitively appropriate subjects 12 years of age and older

5.2.2. Secondary Endpoints

Secondary endpoints are:

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

6. INVESTIGATIONAL PLAN

6.1. Description of Overall Study Design and Plan

This Phase 3, multicenter, open-label, long-term safety and tolerability study of chronic, intermittent use of DBF (study drug).

The study population will be male and female children (2 to 12 years old), adolescents (13 to 16 years old), and adults (17 to 65 years old) with a clinical diagnosis of epilepsy and with bouts of increased seizure activity, ARS, frequent breakthrough seizures, seizure clusters, or cluster seizures and who are on chronic, intermittent use of a rescue medication (e.g., Diastat® AcuDial™ or other benzodiazepine).

It is expected that approximately 120 subjects (~60 children and adolescents and ~60 adults) will be screened and approximately 100 subjects (50 children and adolescents and 50 adults) are expected to enroll. The enrollment should include at least 20 subjects in the 6- to 11-year-old group and 20 subjects in the 12- to 16-year-old group.

Subjects who initially consented and enrolled in the study under version 1 of the protocol dated 31 July 2017 may come in at their next scheduled site visit, reconsent under the amended protocol and be dispensed a new container of DBF based upon the revised mg/kg dosing in Table 4. The subjects do not need to come in for unscheduled visit.

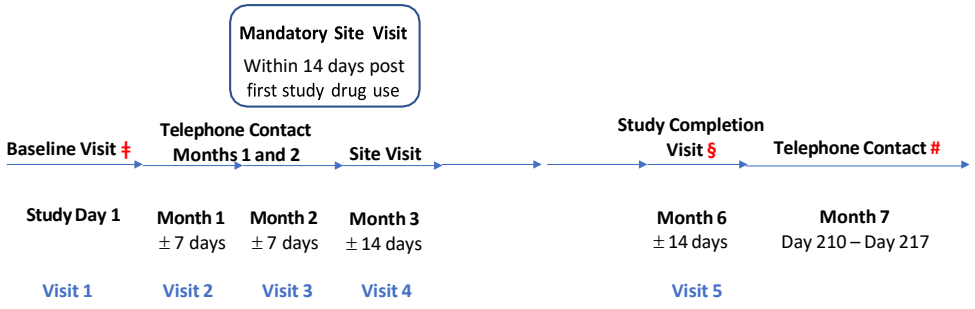
In addition to direct enrollment of subjects from screening, subjects who have completed the Phase 2 clinical trials (Study 160325 [Pediatric] and Study 160326 [Adult]) may screen and enroll (i.e., rollover subjects) into this Phase 3 long-term safety study when they come for their follow-up visit in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

The duration of the study per subject will be a minimum of 6 months (Figure 1). Subject study visits will occur at Baseline, within 14 days after the first seizure prompting study drug administration, and approximately every 3 months (± 14 days) over the course of the study. All visits are calculated from the time of the Baseline Visit/Study Day 1.

The planned end date for this study is 09 October 2020. Thus, the last screening visit is 28 February 2020.

The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020. The last planned Study Completion Visit/Visit 5 will be 02 September 2020 and the last planned follow-up telephone contact will be completed by 09 October 2020. Subjects who are ongoing on 28 February 2020, who are benefitting from the use of DBF, and who would like to stay on study, will be allowed to continue until study end.

Figure 1: Study Schema



‡ Date for last Baseline Visit/Study Day 1 no later than 06 March 2020.
§ Planned date for last Study Completion Visit/Visit 5 is 02 September 2020.
# Planned date for last Telephone Contact is 09 October 2020.

Subjects who are ongoing on 28 February 2020, who are benefitting from the use of DBSF, and who would like to stay on study, will be allowed to continue until study end.

The study site visits will be conducted to assess protocol-defined safety variables (Section 5.2).

Administration and usability of study drug will be recorded at home in the electronic diary after each use of study drug. The electronic diary will also be used at home to capture seizure history and changes in health and medications.

The study drug dose will be tailored to the subject's age and body weight, as described in Section 8.1, and adjusted throughout the study period if changes in body weight call for dose modification. For all age groups, the height and weight will be recorded at all study visits. Study drug dosing is determined first according to age group and then by body weight within age group. Subjects with weights in the range 112 to 134 kg (247 to 295 pounds) may be allowed to participate in the study at the discretion of the Investigator.

Table 4 provides the calculated prescribed DBF dose for DBF naive subjects (i.e., those who entered into the present study 42-1703 never having received DBF as study drug before). The Investigator is encouraged to use Table 5 for dose determination after subjects have received their first dose of DBF based on subject response to the study drug dose and the Investigator's judgment. Subjects already enrolled in the present study 42-1703 and dosed according to the guidelines in Table 4 can also be moved to dosing according to Table 5 after evaluation of subject response to the study drug dose and the Investigator's judgment. Table 5 will be used for dose-determination for subjects who enter the present study 42-1703 from the pediatric EMU study 160325 after Investigator review and evaluation of the subject's dose and response in the EMU study.

Study drug will be administered away from the study site, by the subject or, if applicable. by a caregiver, both trained in study drug administration and documentation using the electronic diary. This is expected to be in the home most often but could also occur in a non-clinical environment outside of the home. The subject and/or caregiver will be:

- able to recognize the occurrence of a qualifying event that for the individual subject is characteristic and is deemed by the investigator to be a kind for which benzodiazepine would ordinarily be administered acutely

- trained by the study team to administer the study drug following the Instructions For Use (IFU; Appendix B)

Investigators will be allowed to make adjustments to subjects' anti-epileptic drug regimens throughout the study, with the aim to control seizures, and reduce increased bouts of seizure frequency, as will be expected in the general practice of medicine.

Screening Period: The last Screening Visit is 28 February 2020. Screening for enrollment eligibility can occur within 1 to 28 days prior to study entry. Before the performance of any study-related procedure, written informed consent will be obtained from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the Institutional Review Board (IRB).

As a part of screening, potential subjects and caregivers will be advised that electronic diaries will be used by subjects and/or caregivers to document seizures, use of study drug, AEs, changes in concomitant medication to determine their ability/willingness to use the electronic diary during treatment. Training on the use of the diary will not be performed until the baseline visit.

Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor.

Baseline Visit (Study Day 1) – conducted after completion of screening and confirmation of eligibility for study enrollment determined by compliance with protocol Inclusion (Section 7.1) and Exclusion (Section 7.2) criteria. During the baseline visit at the study site, the subjects will undergo baseline assessments and subjects/caregivers will receive training in study drug administration and use of electronic diary, and receive their study drug supply with documentation materials (IFU [Appendix B]).

The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020.

Subjects/caregivers will be instructed to call the site when the first seizure prompts study drug administration. A study site visit will occur within 14 days after this first use.

See Section 9.2.2 for the detailed list of procedures scheduled for Study Day 1.

Treatment Period Clinical Site Visits: Upon completion of the Baseline visit, the subject enters a 6-month minimum period of study drug treatment with an expectation that the subject will use the study drug at least 3 times over the 6-month period.

The study site visits will be conducted within 14 days after the first study drug dosing and then approximately every 3 months (± 14 days) after the Baseline Visit (Study Day 1/Visit 2).

See Section 9.2.3 for a detailed list of procedures scheduled for the site visit following the first seizure prompting study drug administration.

Subjects will bring their diary and their supply of study drug to each study site visit. Subjects' height and weight (without shoes and with empty pockets) will be obtained at each site visit for determination of study drug dose (Section 8). The subject diary will be reviewed, and subject/caregiver training will be reinforced (Section 9.2.2). Review of

study diary use will include the number of study drug uses, study drug usability assessment, seizure-control status, AEs, and concomitant medications.

Subjects will undergo assessment of oral mucosal health, gustatory assessment, vital signs, physical and neurological examination, collection of blood and urine samples for clinical laboratory testing, 12-lead ECG, age-appropriate Quality of Life (QoL) and Columbia Suicide Severity Rating Scale (C-SSRS) assessments.

The QoL and C-SSRS should be completed in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

See Section 9.2.3 for a detailed list of procedures scheduled for the planned visits during the treatment period.

Scheduled Telephone Contact at 1 Month and 2 Months After Study Day 1: The study site staff will telephone the subjects at approximately 1 and 2 months ± 7 days after the baseline visit to check on the subject's health and seizure status, determine if study drug was used reinforce training on study drug administration and diary documentation, and to address concerns.

See Section 9.2.5 for a detailed list of procedures scheduled for the planned telephone contacts at Month 1 and Month 2.

Final/Completion or Early Withdrawal Visit

The last subject Study Completion Visit/Visit 5 is projected for 02 September 2020.

- For those subjects who have exceeded 6 months on study with at least 3 uses of DBF, the subject may complete the study at the 6-month visit (Visit 5) per the protocol, or the subject may continue as described below.
- For those subjects who have at least 6 months on study with less than 3 uses of DBF, the subject may complete the study at the 6-month visit (Visit 5) per the protocol, or the subject may continue as described below.

Subjects who prematurely withdraw from the study for any reason should undergo a final visit as well. If the Early Withdrawal Visit is not done, the reason(s) will be recorded in the eCRF. Assessments/procedures performed at the final visit are the same as those performed during Treatment Period Clinical Site Visits. In addition:

- Unused study drug will be returned, and the electronic study diary will be collected. For subjects completing the study at 6 months, the 6-month visit serves as the Final/Completion Visit.

See Section 9.2.6 for a detailed list of procedures scheduled for the final study visit.

Telephone contact 30-37 days after the Final/Completion Visit:

The last subject follow-up telephone contact will occur in October 2020.

For subjects completing the study at 6 months, the Investigator or designee will conduct a follow-up phone call with the subject at 30-37 days after the Final Visit to check on subject status and collect reporting information, should any AE/serious adverse event (SAE) have occurred.

See Section 9.2.7 for a detailed list of procedures scheduled for the telephone contact performed 30-37 days after the Final/Completion visit for subjects completing the 6-month visit.

Extension of Study Beyond Month 6:

The duration of treatment is being extended beyond 6 months under a similar schedule of visits. This policy is intended to continue for the period while the study remains open.

At the discretion of the Principal Investigator and the subject, caregiver or guardian as applicable, a subject may continue in the study beyond the 6-month visit under a similar schedule of assessments, while the study is open. No Medical Monitor approval is required for subjects with 3 or more uses. The subject may continue in the study while the study remains open.

In order to continue:

- The subject is using the Investigational Product
- The subject is receiving benefit from the Investigational Product
- The subject is tolerating the Investigational Product
- The subject wishes to continue in the study

If a subject has had 3 or more uses of DBF, subjects may complete the study at the 6-month visit (Visit 5) per protocol or the subject may continue as described above.

If a subject has not had 3 uses of DBF at the 6-month visit (Visit 5), or any visit after that, the Investigator should strongly consider the likelihood of the subject using DBF and whether the subject should continue in the study. The Investigator may consult with the Medical Monitor, if needed, to assess on a case-by-case basis the likelihood of achieving 3 uses of DBF by continuing the subject on study. If the assessment concludes that achieving 3 uses of study drug is likely, the subject's participation can be extended with a similar schedule of assessments. If the assessment concludes that achieving 3 uses use of the study drug is not likely, the study will be considered complete for the subject.

6.2. Rationale for Study Design

The subjects in this study will be administering study drug themselves or with the help of a caregiver (trained by study site staff in study drug administration and documentation) in the same setting as they typically use the diazepam rectal gel or other rescue mediation, without the presence of study staff. The study design includes study site visits to monitor safety and tolerability, assess subject/caregiver use of study drug through review of electronic diaries, ensure adequate supply of study drug dose, and reinforce subject/caregiver training on the use of study drug, with a focus on safety and correct study conduct. Since dosing is weight-based, the subject's drug inventory will be

reviewed at each study visit and investigative product (IP) will be dispensed with the correct dosage, based on age and body weight.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

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

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

7.1. Inclusion Criteria

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

1. Female or male between the ages of 2 and 65 years, inclusive
2. Written informed consent to participate in the study from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the Institutional Review Board (IRB) prior to the performance of any study-related procedure
3. Caregiver, if needed for subject, provides written informed consent and is able to administer study drug in the event of a seizure
4. Subject has an established diagnosis of epilepsy with motor seizures with clear alteration of awareness, and while on a regimen of anti-epileptic medication(s), still experiences bouts of seizures (frequent break through seizures, e.g., ARS or seizure clusters) and who, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control at least 1 time a month on average. Subject must be on at least 1 concomitant anti-epileptic drug (AED) at screening.

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

5. Female subjects have negative serum and urine pregnancy test at screening[1]. Female subjects of childbearing potential (not surgically sterile or less than 2 years postmenopausal) must have a partner who is sterile, agrees to abstinence, be practicing double barrier contraception or using an FDA-approved contraceptive (e.g., licensed hormonal or barrier methods) for greater than 2 months prior to screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days after the final study visit.
6. No clinically significant abnormal findings on the ECG (QTcF [Fridericia's Correction Formula] ≤ 450 msec for males and QTcF ≤ 470 msec for females)
7. Subject and caregiver (if applicable) must be willing to comply with all study visits and all required study procedures (including the use of electronic diary). NOTE: Non-verbal and cognitively impaired subjects are eligible to participate in the study.

7.2. Exclusion Criteria

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

1. A history of clinically significant gastrointestinal, renal/genitourinary, hepatic, hematologic, dermatologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease, or any other clinically significant abnormalities, such as physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the Investigator require further investigation or treatment or which may interfere with study procedures or safety or other medical conditions (e.g., cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the Investigator could affect the subject's safety or interfere with the study assessments or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject.
2. Subject has had a significant traumatic injury, major surgery, or open biopsy within 30 days prior to screening
3. Subject has a recent history of suicide attempt (defined as an active, interrupted, or aborted attempt with the past five years) or reports suicidal ideation in the past six months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS performed at the Screening Visit.
   NOTE: If a subject cannot complete the assessment, the site must document this.
4. A history of allergic or adverse responses to diazepam or any other benzodiazepine.
5. Participation in another clinical trial other than Aquestive Therapeutics Phase 2 studies 160325 and 160326 within 30 days prior to screening. Participation in an observational (non-interventional) study is not an exclusion provided there are no scheduling conflicts with this study.

[1] If the subject is unable to provide a urine sample, the option to use only serum pregnancy test will be according to Investigator judgment.

6. Received any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before assignment to study drug treatment.
7. Lactating female or positive urine and serum pregnancy test (β-hCG) at screening for female subjects of childbearing potential.[1]
8. In subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion), positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis C, or a positive test result for drugs of abuse or alcohol, except marijuana use for medicinal indications. When marijuana is or was used for medicinal indications in the opinion of the Investigator, it is not considered as drug abuse and the subject can be enrolled in states where marijuana is legal, even if the marijuana metabolites are positive in the urine. NOTE: In such a case, the marijuana product will be recorded as a concomitant medication.

7.3. Withdrawal, Removal, and Replacement of Subjects

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- progressive disease
- unacceptable toxicity or AE
- intercurrent illness: a condition, a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment with study drug and necessitated the subject's termination from the study
- general or specific changes in the subject's condition that renders him/her ineligible for further treatment with study drug according to the inclusion/exclusion criteria
- subject or caregiver withdrawal of consent: At any time, a subject's participation in the study may terminate at his/her request or on the basis of the Investigator's clinical judgment. The reason for subject withdrawal will be noted on the electronic case report form (eCRF)
- protocol deviation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits), and the deviation in the judgment of the Principal Investigator and/or the Sponsor warrants premature termination from the study.
- lost to follow-up: The subject stopped coming for visits, and study personnel were unable to contact the subject. After two documented telephone contacts and a certified letter, the subject will be withdrawn as lost to follow-up.

[1] If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be according to Investigator judgment.

This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her site for any reason including safety or low enrollment.

7.4. Follow-up for Drug Discontinuation/Subject Withdrawal from Study

If a subject discontinues study treatment with study drug and is withdrawn from the study for any reason, the study site must promptly notify the clinical research associate (CRA). The date and the reason for study discontinuation must be recorded on the eCRF. Subjects who withdraw prematurely are to be scheduled and attend an Early Withdrawal Visit, if possible, and complete all assessments.

In the event that a subject discontinues prematurely from the study due to a TEAE or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a subject is withdrawn from the study, the subject may not re-enter the study.

8. TREATMENTS

8.1. Details of Study Treatment

Basic information about the study treatment with study drug is provided in Table 3.

Table 3: Details of Investigative Product

	Preparations to be Administered
	Test Product (Generic)
Trade Name	diazepam
Manufacturer	Aquestive Therapeutics (formerly known as MonoSol Rx LLC)
Dose(s)	5, 7.5, 10, 12.5, 15, 17.5 mg (age and weight based)[a]
Route	buccal mucosa
Formulation	buccal mucosa soluble film
Buccal Soluble Film Strength	5, 7.5, 10, 12.5, 15, 17.5 mg (fasting or fed condition)

[a] Where there is overlap in body weight with age, the age-adjustment takes precedence. Investigator may make adjustments as medically indicated.

The DBF dose will be determined according to age and weight category in a manner analogous to the Diastat® AcuDial™ label [11] (Table 4). The rationale for the dose regimen of the test product is provided in Section 4.5.2.2.

The dose levels specified in Table 4 are intended as the starting dose for subjects who have not received diazepam administered as DBF in the past. The Investigator may choose to adjust the dose upward or downward by 1 dose level depending on clinical response to study drug. The Investigator is encouraged to use Table 5 for dose determination after subjects have received their first dose of DBF based on subject response to the study drug dose and the Investigator's judgment.

Subjects who initially consented and enrolled in the study under version 1 of the protocol dated 31 July 2017 may come in at their next scheduled site visit, reconsent under the amended protocol and be dispensed a new container of DBF based upon the revised mg/kg dosing in Table 4. The subjects do not need to come in for unscheduled visit. . These subjects already enrolled in the present study 42-1703 and dosed according to the guidelines in Table 4 can also be moved to dosing according to Table 5 after evaluation of subject response to the study drug dose and the Investigator's judgment.

For subjects entering this study after participating in the Pediatric EMU Study 160325, who have taken DBF in the past, the Investigator will begin dosing according to dosing regimen derived from population pharmacokinetic modeling provided in Table 5 after Investigator review and evaluation of the subject's dose and response in the EMU study.

See also the rationale for the modified pediatric dose regimen for these subjects entering Study 42-1703 from Study 160325 in Section 4.6.

Table 4: Calculated Prescribed Dose of Study Drug for Subjects Who Have Not Received Diazepam Administered as DBF in the Past

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

[a] Dose of study drug expected to provide C_{max} equal to C_{max} for Diastat® dose.

[b] Where there is overlap in body weight with age, the age-adjustment takes precedence. Investigator may make adjustments as medically indicated.

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

Table 5: Calculated Prescribed Dose of Study Drug for Subjects < 17 Years of Age Entering Study 42-1703 from Study 160325

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	17.5

8.1.1. Controlled Substance Documentation

The study drug DBF 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 at the study sites must be kept in a secure, double-locked, substantially constructed enclosure with restricted access.

Prior to shipment of study drug to the study site, 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.

8.1.2. Description of Study Drug

The study drug, DBF, contains the active ingredient diazepam incorporated into a polymer-based film matrix utilizing Aquestive Therapeutics PharmFilm® technology. For the purposes of this study, with a population ranging in age from 2 to 65 years, 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 study drug doses up to 20 mg were tested in a pilot clinical study (Study 1900). The inactive ingredient composition, the film dimensions, and the manufacturing process selected for study drug are based on the information gained from the development of the study drug 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 study drug is a green rectangular film.

The primary package used for study drug 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 study drug film.

8.2. Labelling, Maintenance and Retention of Study Drug

It is the responsibility of the Sponsor to ensure that all drug supplies provided for the study are manufactured under current Good Manufacturing Practices (cGMP) 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 Drug Enforcement Agency Controlled Substance certificate.

The study drugs will be sent to the Site Pharmacy already packed in individual unit-dose packages. Each unit-dose pouch will be labeled in English containing the Sponsor name (MonoSol Rx [now Aquestive Therapeutics])[1], Protocol Number, Drug Name, Strength, Kit Identification Number, Subject Number, Lot Number, Route of Administration, Quantity of Dosage Units and a statement “Caution: New Drug – Limited by Federal Law to investigational use and the kit label will include at minimum Sponsor Name and Address, Drug Name, Strength, Quantity of Pouches, Route of Administration, Lot

[1] Some labels will retain the original name MonoSol Rx.

Number, Kit Identification Number, Protocol Number, Subject Number, Investigator Name, Directions for Use, Storage Conditions, and a statement 'Keep out of reach of children'.

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 Interactive Web Response System (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 numbers assigned to the subject. Only these kits will be removed from inventory. At study visit 2 (Baseline visit) a starter kit containing 6 doses of one strength of study drug will be dispensed to each subject.

At each subsequent study visit, a 3-month supply of study drug will be dispensed to each subject. Doses will be in individual labeled pouches inside a labeled container. Each container will hold either 15 or 23 pouches of the same dose of DBF. The decision of which quantity container is to be dispensed will be based on investigator estimation of whether or not the subject will need a 2nd dose of study drug for a seizure episode. Each subject will receive a new container with either 15 or 23 pouches at each visit. The subject should bring back the container with empty (used) and unused pouches at their next study visit. The container will not be re-dispensed.

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

8.3. Dosage Schedule

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

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

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

If a subject has experienced 3 uses of study drug, study participation will be complete at Month 6. For those subjects who have not experienced 3 uses of study drug, the Investigator and the Medical Monitor will assess on a case-by-case basis the likelihood of achieving 3 uses of study drug by continuing the subject on study for an additional 3

months. If the assessment concludes use of the study drug is not likely, the study will be considered complete for the subject. The sponsor may elect to end study participation for non-users prior to end of study.

8.4. Study Treatment Assignment

Subjects will be assigned to treatment with study drug with the use of IWRS. There will be no subject randomization; however, each study drug kit will have a kit number which will be documented. The Investigator may adjust the study drug dose as medically appropriate, in accordance with guidelines provided in Section 8.1.

8.5. Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain records of study treatment with study drug delivered to the study site, the inventory at the site, the distribution to and use by each subject, and the return of materials to the clinical supply vendor for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, in clinic temperature log, and unique code numbers assigned to the product and study subjects.

At each visit after initiation of treatment with study drug, site staff will record compliance of subjects with their assigned regimen. Subjects will be instructed to bring their diaries and study drug containers with unused/partially used/empty pouches back for inspection at each study visit. Subjects are to be reminded of the importance of compliance with their assigned regimen, with an emphasis on taking their study drug timed to occur during a qualifying seizure when it is safe to do so and maintaining the prescribed minimum interval between doses.

Investigators will maintain records that document adequately that the subjects were provided with the correct study drug treatment kits and will reconcile the products received from the drug dispensing center. Study drug will not be returned to the clinical supplies vendor until accountability has been fully monitored.

Unused medication must be returned at each visit, as compliance will be assessed by soluble film counts. Noncompliance is defined:

- taking more than 2 doses for a single episode
- treating a second episode in less than 5 days
- treating more than 5 episodes per month
- unaccounted for doses

Discontinuation for noncompliance is at the Investigator's discretion and is to be noted on the eCRF.

Study drugs may be administered by a caregiver (including group home or school personnel) trained to assist with study drug administration.

8.6. Prior and Concomitant Illnesses and Medications

8.6.1. Prior and Concomitant Illnesses

Investigators should document all surgeries and prior significant illnesses that the subject has experienced prior to screening. Additional illnesses present at the time when informed consent is given and up to the time of first dosing are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF. For subjects completing the Aquestive Therapeutics Phase 2 studies, this information will be collected.

8.6.2. Prior and Concomitant Medications

All medications and other treatments taken by the subject during the study, including those treatments initiated prior to the start of the study, must be recorded on the eCRF.

Medications taken by or administered to the subject for 30 days before screening will be recorded in the eCRF. After the baseline visit, concomitant medication will be reviewed on a case by case basis to determine further participation in the study. Any treatment or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

Subjects who test positive for tetrahydrocannabinol (THC) at screening can continue with screening if the Principal Investigator is able to affirm 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(s), and hence the marijuana product shall be recorded as a concomitant medication. This is applicable in states where medical marijuana use is legal.

9. STUDY PROCEDURES

Table 6 outlines the timing of procedures and assessments to be performed throughout the study. All site visits and telephone contacts are calculated from the time of the Baseline Visit/Study Day 1 with the exception of the Final/Completion/Early Withdrawal Visit which is calculated from the time of the 6-month visit.

See Section 11 for additional details of study procedures.

NOTE: The schedule of procedures and assessments in this table assumes the subjects has experienced 3 uses of study drug over the minimum 6-month study period. For those subjects who have not experienced 3 uses of study drug, the Investigator and the Medical Monitor will assess on a case-by-case basis the likelihood of achieving 3 uses of study drug by continuing the subject on study for an additional 3 months. Thus, for these subjects who continue on study, the Day 180 (Month 6) visit would entail all procedures and assessments performed at the Day 90 (Month 3) visit including:

- review training subject/caregiver on timing of study drug administration and use of electronic diary
- review of study drug administration (IFU)
- providing a new supply of study drug

If the assessment concludes use of the study drug is not likely, the Sponsor may elect to end study participation for non-users prior to end of study

Table 6: Schedule of Assessments

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

Study Period	**Screening[a]**	**Baseline[b]**	**Study Drug Treatment[c] (Study drug dosing administered away from the study site)**				**Follow-up**
Visit	**Visit 1¶**	**Visit 2†**	**Visit 3**	**Telephone Contact**	**Visit 4**	**Visit 5 (Final)#**	**Telephone Contact ǂ**
Study Day	**Day -1 to -28**	**Day 1**	**within 14 days post first study drug dose**	**Day 30, Day 60**	**Day 90**	**Day 180**	**Month 7 (Day 210 – Day 217)**
Collect Samples for Complete Blood Count, Blood Chemistry, Urinalysis, Urine Drug Screen, Breath Alcohol Tests[p] ††	×	×	×		×	×	
Gustatory Sense Assessment [q] ¶¶		×	×		×	×	
Review Instances of At Home Study Drug Use with Subject [r]			×	x	×	x	
Quality of Life by age appropriate epilepsy scales[s] ¶¶	×	×	×		×	×	
Collect/Review Caregiver/Subject Diary[t]			×		×	×	
Supply Study Drug		×	×		×	×[u]	
Collect/Count Study Drug			×		×	×	
Adverse Events Evaluation[u]	×[u]	×[u]	×	×	×	×	×
Study Site will telephone subjects[v]				×			×

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale: ECG = electrocardiogram; IFU = Instructions for Use; NIH = National Institutes of Health; SAE=serious adverse event; WOCBP=women of childbearing potential.

¶ Screening end date is 28 February 2020.

† The last Baseline Visit/Study Day 1 will occur no later than 06 March 2020.

The last planned Study Completion Visit/Visit 5 will be in September 2020.

ǂ The last subject telephone follow-up contact will occur in October 2020. The Sponsor has elected to extend the duration of treatment beyond 6 months under a similar schedule of visits. This policy is intended to continue for the period that the study remains open. See Section 6.1 Final/Completion or Early Withdrawal Visit for criteria and methods.

¶¶ The QoL, C-SSRS, and Gustatory assessments should be completed in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

††The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed. If a subject cannot provide a urine sample for drug screen, the same policy applies. If a subject cannot provide a urine sample or, if in the judgment of the Investigator, the subject's exposure to drugs of abuse is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed. If the subject cannot provide a urine sample for routine analysis, the site must document in the source documents the reason that the assessment is not completed. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter.

[a] Screening evaluation is to be conducted for all direct enrolling subjects within 28 days before the baseline visit. Rollover subjects may consent and undergo screening during their final visit of their Phase 2 trial, thus eliminating an additional screening visit. Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor.

[b] The Baseline visit includes a battery of assessments, as well as training in study drug administration and documentation and supply of study drug and study logs.

[c] Study site visits will be conducted at Baseline, within 14 days after the first study drug dose, and approximately every 3 months until completion 6 months or Discontinuation. The study site staff will telephone the subjects at approximately 1 and 2 months ± 7 days after baseline to check on status, reinforce training on study drug administration and diary documentation, and address any concerns.

[d] Before the performance of any study-related procedure, written informed consent will be obtained from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the Institutional Review Board (IRB).

[e] Age, weight, height, gender, ethnicity and race at screening; Body weight and height will be measured at every site visit. Study drug dosage based on age and body weight. Duration of epilepsy history is documented.

[f] Training of subject/caregiver (as applicable) on the use of the electronic diary; use of the diary will be reviewed at each visit/contact to ensure subjects/caregivers understand and are comfortable with using the electronic diary.

[g] Review/record medical history.

[h] Vital signs include body temperature, respiration rate, heart rate, systolic and diastolic blood pressure measurements. All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm (if possible) for the duration of the study. If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.

i Body height and weight is obtained for all subjects at screening to document body mass index (kg/m^2). Body weight (without shoes and with empty pockets) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at all study site visits to calculate weight-based study drug dosage.

[j] Complete physical examination: head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological and musculoskeletal systems.

[k] Symptom-driven Physical and Neurological examinations will be conducted at the First/Day 1 visit, at the Final/Completion or Early Withdrawal visit, and as clinically indicated during the study.

[l] C-SSRS; If a subject cannot complete the assessment, the site must document this.

[m] Oral mucosal health assessment will be performed by the Investigator or trained Study nurse at all study site visits. In addition, any mucosal or tongue lacerations encountered during the study are recorded in the diary.

[n] 12-lead ECG testing is performed at Screening, Baseline, and at all onsite visits including the Final Visit. When performed on days of blood draws, ECG should be completed prior to blood collection.

[o] Serum and/or urine pregnancy test for females of childbearing potential. If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be at the Investigator's discretion. The reason that urine pregnancy testing could not be completed should be documented in the source documents and CRF. Females with positive pregnancy tests cannot be dosed.

[p] Hematology testing includes Full and differential blood count, hematocrit, hemoglobin, RBC morphology, mean corpuscular volume, platelet count, RBC count and WBC with differential. Albumin, ALT, AST ALP, BUN, creatinine, creatine kinase, Na, K, Cl, Ca, glucose, protein, total protein, total bilirubin, uric acid will be performed. For urinalysis, dipstick is acceptable. Microscopic analyses if clinically indicated.

[q] Gustatory sense assessment will be administered to cognitively-appropriate subjects 12 years and older at all site visits. The general Labeled Magnitude Scale (gLMS) will remain as the evaluation scale for gustation (taste) testing; however, commercially available test strips from Burghart Messtechnik will replace the liquid taste solutions described as part of the NIH Toolbox Regional Taste Intensity Test.

[r] Study drug will be self-administered or with the assistance of a caregiver, as applicable. The dosing is administered remote from the study site, usually in the home setting, according to the IFU (see Appendix B)

[s] Quality of life will be assessed at all study site visits by age appropriate epilepsy scales (Section 11.4). If a subject cannot complete the assessment, the site must document this.

[t] Use of an electronic diary will be reviewed with the subject/caregiver (as applicable) to determine their ability/willingness to use the electronic diary during treatment.

[u] Adverse events should be recorded. At the screening visit, this applies only to rollover subjects from the Phase 2 studies. For all other subjects, adverse events observed/reported after provision of informed consent/assent are recorded. Subjects must be followed for AEs for 30 days after the last study drug treatment administration or until all drug related toxicities have resolved, whichever is later.

[v] The study site staff will telephone the subjects at approximately 1 and 2 months ± 7 days after the baseline visit to check on the subject's health and seizure status, reinforce training on study drug administration and diary documentation, and to address concerns. The investigator or designee will conduct a follow-up phone call with the subject at 30-37 days after the Final Visit to check on subject status and collect reporting information, should any SAE have occurred.

9.1. Subject Informed Consent

Before the performance of any study-related procedure, written informed consent will be obtained from the subject or subject's legally authorized representative and oral and/or written assent will be obtained from the subject as required by the IRB.

Subjects who initially consented and enrolled in the study under version 1 of the protocol dated 31 July 2017 may come in at their next scheduled site visit, reconsent under the amended protocol and be dispensed a new container of DBF based upon the revised mg/kg dosing in Table 4. The subjects do not need to come in for unscheduled visit.

9.2. Procedures by Study Visit or Period

Assessments are to be performed as outlined in the following by-visit subsections.

9.2.1. Screening

The Screening visit (Visit 1) will occur within 1 to 28 days prior to Study Day 1.

Subjects who have completed the Phase 2 studies 160325 (Pediatric) or 160326 (Adult) which enrolled subjects with a similar diagnosis may screen for enrollment into this Phase 3 study when they come in for the follow-up visit after the last treatment period in the Phase 2 study (rollover subjects). These rollover subjects will be assessed for enrollment using inclusion/exclusion criteria of this protocol (42-1703). In addition to the Follow-up clinical laboratory assessments for the Phase 2 studies, clinical laboratory screen for this Phase 3 study includes HIV, HBsAg, and hepatitis C in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion).

The following procedures will be performed:

- Obtain written informed consent/assent (Section 9.1)
- Record medical/medication history and demographic information based on the interview with the potential subject
- For rollover subjects from the Phase 2 studies described above, AEs will be documented/assessed (Section 11.10).
- Obtain vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], oral temperature). All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm (if possible) for the duration of the study.

  If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.
- Obtain height and body weight (without shoes and with empty pockets)
- Obtain a 12-lead ECG; ECG should be completed prior to any blood collection.

- Perform a complete physical and neurological examination, including examination of the oral cavity to verify there are no significant lesions, recent prophylactic procedures, mouth jewelry, dentures, braces, or piercings in the mouth or tongue that in the opinion of the Investigator would likely interfere with successful completion of the dosing procedure.
- Advise potential subjects and caregivers that electronic diaries will be used by subjects and/or caregivers to document seizures, use of study drug, adverse events (AEs), changes in concomitant medication to determine their ability/willingness to comply with this procedure.
- C-SSRS; Baseline Screening

  C-SSRS should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
- Quality of Life (QoL) assessment by use of age-appropriate epilepsy scales (Appendix C through Appendix G). If a subject cannot complete the assessment, the site must document this along with the reason.

  QoL assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
- Collect blood and urine samples for hematology, chemistry, urinalysis and screening for drugs of abuse. Perform breath alcohol test. Urine and serum pregnancy test in female subjects of childbearing potential. A complete listing of all tests to be performed is provided in Section 11.9.
  If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be according to Investigator judgment.

  The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed.

  If a subject cannot provide a urine sample for drug screen or, if in the judgment of the Investigator, the subject's exposure to drugs of abuse is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not

completed. If the subject cannot provide a urine sample for routine analysis, the site must document in the source documents the reason that the assessment is not completed. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter.

- Principal Investigator's/Sub-Investigator's review of Inclusion/Exclusion criteria (Section 7.1 and Section 7.2) and all screening results/data to assess eligibility.

NOTE: Subjects may be re-screened during the study per Investigator judgment after consultation with and approval by the Medical Monitor.

9.2.2. Baseline (Study Day 1)

The baseline period begins after the subject has successfully completed screening, within to 28 days after the screening visit. This is Day 1 for the subject in the study. The following procedures will be performed:

- Review of Inclusion/Exclusion criteria
- Review medical/medication history
- Obtain vital signs (BP, HR, RR, oral temperature). All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm (if possible) for the duration of the study.

  If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.
- Obtain height and body weight (without shoes and with empty pockets)
- Collect blood and urine samples for hematology, chemistry, urinalysis and screening for drugs of abuse. Perform breath alcohol test; urine and serum pregnancy test in female subjects of childbearing potential. A complete listing of all tests to be performed is provided in Section 11.9.
  If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be according to Investigator judgment.

  The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed.

If a subject cannot provide a urine sample for drug screen or, if in the judgment of the Investigator, the subject's exposure to drugs of abuse is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed. If the subject cannot provide a urine sample for routine analysis, the site must document in the source documents the reason that the assessment is not completed. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter.

- Perform symptom-driven physical examination, including examination of the oral cavity to verify there are no significant lesions, recent prophylactic procedures, mouth jewelry, dentures, braces, or piercings in the mouth or tongue that in the opinion of the Investigator would likely interfere with successful completion of the dosing procedure.
- Perform limited neurological examination.
- Gustatory sense assessment using the general labeled Magnitude Scale and commercially available Burghart Messtechnik taste test strips in cognitively-appropriate subjects 12 years and older.

  Gustatory sense assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
- C-SSRS, since last visit. If a subject cannot complete the assessment, the site must document this along with the reason on the eCRF.

  C-SSRS assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
- Perform 12-lead ECG; ECG should be completed prior to any blood collection.
- Quality of Life (QoL) assessment by use of age-appropriate epilepsy scales (Appendix C through Appendix G). If a subject cannot complete the assessment, the site must document this along with the reason.

  QoL assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source

documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

- Review and record AEs
- A starter kit containing 6 doses of one strength of study drug will be dispensed to each subject. The DBF dose will be determined according to age and weight category in a manner analogous to the Diastat® AcuDial™ label [11] (Table 4).
- Subjects/caregivers will be instructed to call the site when the first seizure prompts study drug administration. A study site visit will occur within 14 days after the first study drug dosing.
- Training of subjects/caregivers on drug administration and documentation in the electronic diary ensuring that subjects/caregivers understand:
    1. The guidelines on when to use study drug
    2. How to store study drug and how to obtain additional study drug if needed before the next scheduled visit
    3. How to administer study drug including review of Instructions for Use (IFU)
    4. Where to record information in the electronic diary
        a. Record assigned seizure type A, B, C, and D in the "Seizure Type Diary"
        b. Record seizures in the "Seizure Calendar" section of the diary; recording seizure type, number, and date
        c. Seizures other than those defined at baseline can be recorded in the "Change in Health" section
        d. Record each attempt to use study drug in the "Study Drug Administration and Usability" section
        e. Record study drug placement and disposition after application in the "Study Drug Administration and Usability" section
        f. Log of AEs and changes in health will be recorded in the "Change in Health" section. Any buccal mucosa or tongue lacerations encountered during the study will be recorded in the "Change in Health" section.
        g. Changes/additions to concomitant medications will be recorded in the "New Medications" section.

Electronic diaries will be preprogrammed to transmit subject-entered data to the electronic diary database (Engage Portal) whenever the diary is connected to WiFi. Study center staff will monitor the electronic diary Engage Portal to ensure that subjects are recording medication use (following the Baseline/Day 1 visit), and that the data are being transmitted to the data base. Study center staff will follow up with subjects/caregivers as necessary to counsel them on completion of the electronic diaries. Study center staff will review the data entries with the subjects/caregivers at the study visits and ask

subjects/caregivers to fill in any missing study drug administration and usability questionnaires to the best of their recollection, if necessary.

9.2.3. Treatment Period Clinical Site Visits

Upon completion of the Baseline visit, the subject enters a 6-month minimum period of potential study drug treatment with an expectation that the subject will use the study drug at least 3 times over the 6-month period. Study site visits occur every 3 months (± 14 days) after the Baseline Visit (Study Day 1/Visit 2) for a minimum of 6 months.

The study visits will be conducted within 14 days after the first study drug dosing and then approximately every 3 months for a minimum of 6 months. The Sponsor has elected to extend the study beyond 6 months under a similar schedule of visits. The policy is intended to continue for the period while the study remains open.

The following procedures will be performed at the study during the study drug treatment period. Additional details with frequency are listed in Table 6, Schedule of Assessments:

- Review and record concomitant medications
- Obtain vital signs (BP, HR, RR, oral temperature). All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm (if possible) for the duration of the study.

  If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.
- Obtain height and body weight (without shoes and with empty pockets)
- Collect blood and urine samples for hematology, chemistry, urinalysis and screening for drugs of abuse. Perform breath alcohol test. Urine and serum pregnancy test in females of childbearing potential. A complete listing of all tests to be performed is provided in Section 11.9.
  If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be according to Investigator judgment.

  The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed.

  If a subject cannot provide a urine sample for drug screen or, if in the judgment of the Investigator, the subject's exposure to drugs of abuse is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not

completed. If the subject cannot provide a urine sample for routine analysis, the site must document in the source documents the reason that the assessment is not completed. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter.

- Perform symptom-driven physical examination, including examination of the oral cavity to verify there are no significant lesions, recent prophylactic procedures, mouth jewelry, dentures, braces, or piercings in the mouth or tongue that in the opinion of the Investigator would likely interfere with successful completion of the dosing procedure.
- Perform limited neurological examination.
- C-SSRS, since last visit. If a subject cannot complete the assessment, the site must document this along with the reason on the eCRF.

  C-SSRS assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
- Perform 12-lead ECG; ECG should be completed prior to any blood collection.
- Obtain age-appropriate QoL assessment; Appendix C (PedsQL™ Epilepsy Module Parent Report for Toddlers (Ages 2-4); Appendix E (PedsQL™ Epilepsy Module Parent Report for Children (Ages 8-10); Appendix F (Quality of Life in Epilepsy for Adolescents QOLIE-48).

  QoL assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).
- Oral mucosal health assessment will be performed by the Investigator or other trained site personnel. In addition, any mucosal or tongue lacerations encountered during the study are recorded in the diary.
- Gustatory sense assessment by a trained Investigator, sub-investigator, or study nurse using commercially available test strips from Burghart Messtechnik in cognitively appropriate subjects 12 years of age and older.

  Gustatory sense assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject

to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

- Review subject/caregiver diary for drug administration and usability and provide training as described in Section 9.2.1.
- Dispense a new 3-month supply of study drug based on body weight and supportive documentation as needed. NOTE: where there is an overlap in age and weight criteria, the age-adjustment takes precedence (Table 4). Investigator may make adjustments as medically indicated (Section 8.1).
- Review and record AEs

9.2.4. Treatment Period (Remote Study Drug Administration)

The study drug Treatment Period is for a minimum of 6 months after baseline (Day 1). The subjects will administer the study drug as needed with help of their caregiver, if applicable, to treat their recurring seizures as they would have with Diastat® AcuDial™, or other prescribed benzodiazepine. The subject or caregiver will document all procedures as trained (Section 9.2.2). Subjects and/or caregivers will perform the following:

- Monitor and record seizures, using seizure calendar in electronic diary
- Dose with study drug and record use in electronic diary
- Complete diary documentation as instructed at the Baseline/Day 1 visit (Section 9.2.2)
- Record any AEs in the electronic diary
- Record any changes in concomitant medication in the electronic diary
- Store study drug in a safe place with limited access (Section 0)
- Bring unused study drug, empty pouches, and electronic diary to all study site visits

9.2.4.1. Food and Fluid Intake

Food and water will be allowed ad libitum at all times, except during the study drug application. Per dosing instructions, the subject should refrain from eating or drinking during study drug dosing until full dissolution of study drug has been confirmed by visual inspection.

9.2.4.2. Dosing

Dosing will occur away from the study site. The subject or caregiver will administer the study drug as described in the IFU. The actual time of study drug film placement will be documented in the study diary.

A second dose, when required, may be given within 4 to 12 hours after the first dose, as previously discussed between the investigator and subject/caregiver. No more than 5

episodes per month or one episode every 5 days should be treated with study drug or with any other product containing diazepam (e.g., Diastat® AcuDial™) except as instructed by a physician.

The DBF dose will be determined according to age and weight category in a manner analogous to the Diastat® AcuDial™ label [11] (Table 4). The rationale for the dose regimen of the test product is provided in Section 4.5.2.2.

The adjustment of study drug dose by body weight and dispensing of study drug is done at each study visit with use of IWRS assigning the appropriate kit number. Where there is overlap in body weight with age, the age-adjustment takes precedence. The Investigator may also make adjustments as medically indicated.

9.2.5. Treatment Period Scheduled Telephone Contact with Subjects

Study site staff will telephone subjects approximately 1 and 2 months ± 7 days after the Baseline Visit (Study Day 1/Visit 2) to query the subject/caregiver regarding study drug administration, diary use, seizures, AEs, changes in concomitant medication, to reinforce training, and to address concerns.

If subject has had qualifying seizures for which study drug was not taken, the site should determine if the subject chose to use a different rescue (eg, Diastat ® in lieu of study drug and the reasons why and brought back in for a study visit). The site should discuss with the medical monitor the appropriateness of the subject's inclusion in the study.

If the subject has not had any qualifying seizures within this timeframe, the site should discuss with the Medical Monitor the appropriateness of the subject's inclusion in the study.

9.2.6. Final / Completion or Early Withdrawal Visit

The 6-month visit will serve as the study Final/Completion site visit . The Sponsor has elected to extend the study beyond 6 months under a similar schedule of visits.

The last subject Final/Completion Visit is projected for September 2020.

Prior to the subject's return for the 6-month visit, site personnel will review the subject's status with respect to use of study drug. If a subject has experienced 3 uses of study drug, study participation will be complete. For those subjects who have not experienced 3 uses of study drug, the Investigator and the Medical Monitor will assess on a case-by-case basis the likelihood of achieving 3 uses of study drug by continuing the subject on study for an additional 3 months. If considered likely, the subject's participation can be extended for another 90 days with a similar schedule of assessments. If the assessment concludes use of the study drug is not likely, the study will be considered complete for the subject. The sponsor may elect to end study participation for non-users prior to end of study.

Subjects who prematurely withdraw from the study for any reason should undergo a Final Visit as well. If the Early Withdrawal Visit is not done, the reason(s) will be recorded in the eCRF.

The following procedures will be performed. Additional details are listed in Table 6, Schedule of Assessments.

- Review and record concomitant medications
- Obtain vital signs (BP, HR, RR, oral temperature). All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm (if possible) for the duration of the study.

  If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.
- Obtain height and body weight (without shoes and with empty pockets)
- Collect blood and urine samples for hematology, chemistry, urinalysis and screening for drugs of abuse. Perform breath alcohol test. Urine and serum pregnancy test in females of childbearing potential. A complete listing of all tests to be performed is provided in Section 11.9.
  If the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be according to Investigator judgment.

  The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed.

  If a subject cannot provide a urine sample for drug screen or, if in the judgment of the Investigator, the subject's exposure to drugs of abuse is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed. If the subject cannot provide a urine sample for routine analysis, the site must document in the source documents the reason that the assessment is not completed. Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter.
- Perform symptom-driven physical examination, including examination of the oral cavity to verify there are no significant lesions, recent prophylactic procedures, mouth jewelry, dentures, braces, or piercings in the mouth or tongue that in the opinion of the Investigator would likely interfere with successful completion of the dosing procedure.

- Perform gustatory sense assessment using the general labeled Magnitude Scale and commercially available Burghart Messtechnik taste test strips in cognitively-appropriate subjects 12 years and older.

  Gustatory sense assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

- Administer C-SSRS, since the last visit. If a subject cannot complete the assessment, the site must document this along with the reason on the eCRF.

  C-SSRS assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

- Perform 12-lead ECG; ECG should be completed prior to any blood collection.

- Obtain age-appropriate QoL assessment; Appendix C (PedsQL™ Epilepsy Module Parent Report for Toddlers (Ages 2-4); Appendix E (PedsQL™ Epilepsy Module Parent Report for Children (Ages 8-10); Appendix F (Quality of Life in Epilepsy for Adolescents QOLIE-48).

  QoL assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's (or parent's/guardian's/caregiver's) cognitive status does not allow the subject (or parent/guardian/caregiver) to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

- Review subject/caregiver diary for drug administration and usability and provide training as described in Section 9.2.1.

- Review and record AEs

- Review study drug

- Return unused drug

9.2.7. Telephone Contact 30-37 Days After the Final Visit

The last subject telephone follow-up contact is projected to occur in October 2020.

The Investigator or designee will conduct a follow-up phone call with the subject at 30-37 days after the Final Visit to check on subject status and collect AE information.

9.2.8. Unscheduled Visits

The Investigator may at his/her discretion arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up, or an AE considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

10. EFFICACY ASSESSMENTS

Not applicable.

11. SAFETY ASSESSMENTS

Safety assessments are performed at each study visit/contact, as specified in the Schedule of Assessments, Table 6.

11.1. Vital Signs

Vital signs (body temperature, respiration rate, heart rate, systolic and diastolic blood pressure measurements) will be measured, recorded, and evaluated at the visits indicated in the Schedule of Assessments. All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm (if possible) for the duration of the study.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range BP, RR or HR measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

11.2. Body Height and Weight

Body weight (without shoes, and empty pants pockets) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at all study site visits, to calculate weight-based study drug dosage.

11.3. Physical and Neurological Examinations

A complete physical examination (head, eyes, ears, nose, and throat [HEENT], heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at Screening Visit 1. Physical examinations will be performed by medically qualified site personnel. In addition, medical history will be recorded at screening, including smoking history, if applicable.

A symptom-driven physical examination to verify continued subject eligibility and to follow up any change in medical history will be performed at the visits indicated in the Schedule of Assessments. Symptom-driven limited physical and neurological examinations will be performed at First, Early Withdrawal / Completion Visit, and as clinically indicated at any study visit. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

11.4. Quality of Life Assessments

Age-appropriate QoL assessments will be performed at all study site visits (Table 7). QoL administration should be delayed if a subject has experienced a simple or complex seizure within the previous 4 hours, or a generalized tonic-clonic seizure within the previous 24 hours.

If a subject moves from one age range to the next while participating in the study, continued to use the same scale throughout the study. Do not switch to the next QoL module.

Table 7: Age-Defined Quality of Life Assessment Modules

Scale Name	Corresponding Age Ranges in This Study[a]	Who Completes the Assessment
PedsQL 3.0 Epilepsy Module PedsQL Parent Proxy Report (Ages 2-4 years)	2-4 years	Parent/Guardian/Caregiver
PedsQL 3.0 Epilepsy Module PedsQL Parent Proxy Report (Ages 5-7 years)	5-7 years	Parent/Guardian/Caregiver
PedsQL 3.0 Epilepsy Module PedsQL Parent Proxy Report (Ages 8-12 years)	8-12 years	Parent/Guardian/Caregiver
QOLIE-AD-48 (Version 1)	11-17 years	Self-assessment
QOLIE-31-P (Version 2)	18 years and older	Self-assessment

[a] Please note this column indicates the age range for each Scale to be applied in this study.

Non-verbal and cognitively impaired subjects are eligible to participate in the study. The Quality of Life assessments should be personally completed by the subject using non-verbal methods with assistance of site staff trained for these assessments. If the scales are not able to be completed, the site must document this.

Quality of Life assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

11.5. Columbia Suicide Severity Rating Scale

The C-SSRS, which assesses suicidal behavior and ideation, will be administered at each study visit. Qualified, trained staff will administer the C-SSRS, Baseline-Screening version at screening, and the C-SSRS, Since Last Visit version will be administered at Baseline and all subsequent visits. Subjects with Type 4 (active suicidal ideation with some intent to act, without specific plan) or Type 5 (active suicidal ideation with specific plan and intent) suicidal ideation during the study will be discontinued from the study and referred to a mental health professional.

The C-SSRS assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

11.6. Oral Mucosa Health Assessment

A checklist was developed to use in the assessment of the health of the oral mucosa with sporadic, yet chronic use of study drug. During site initiation, use of the oral mucosa examination checklist will be reviewed with the clinical investigators and other medically qualified study personnel.

The examiner will make an illumination-assisted visual inspection of the oral mucosa at Screening, and at all study site visits. 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 eCRF. Any de novo post-dose mucosal irritation or other abnormality will be reported as an AE of special interest and will be followed until resolution.

11.7. Gustatory Sense Assessment

A gustatory (sense of taste) assessment using commercially available taste test strips from Burghart Messtechnik, in subjects 12 years and older, will be conducted by trained Investigator or other trained site personnel.

The general Labeled Magnitude Scale (gLMS) will be used as the evaluation scale (ranging from “no sensation at all” to “strongest sensation of any kind”) using commercially available taste test strips from Burghart Messtechnik The taste strips are statistically well-correlated with the NIH Toolbox Regional Taste Intensity Test solutions.[17] The test takes approximately 6 minutes to administer. The subject must not eat or drink for 30 minutes prior to completing the taste test.

The assessment will be performed during all study site visits.

Gustatory sense assessment should be completed according to the schedule of assessments in appropriately aged subjects. These assessments may be omitted as applicable if a subject's cognitive status does not allow the subject to personally complete the assessment. The site must document in the source documents the reason that these assessments cannot be completed (e.g., unable to perform test due to incapacity, etc.).

11.8. Electrocardiograms

A 12-lead resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 6). When performed on days of blood draws, ECG should be completed prior to blood collection.

At Screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the subject from the study. An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated at Baseline and 6 months after dosing, and at the Study Final/Completion or Early Withdrawal Visit, and at any study site visit if clinically significant abnormalities are observed or artifacts are present.

11.9. Laboratory Assessments

Laboratory assessment samples listed below in Table 8 will be obtained at the visits indicated in the Schedule of Assessments (Table 6).

Table 8: Laboratory Assessments

Hematology	Serum Chemistry	Urine Analysis (dipstick)
Full and differential blood count	Albumin	pH
Hematocrit (Hct)	Alanine aminotransferase (ALT)	Protein
Hemoglobin (Hb)	Alkaline phosphatase (ALP)	Glucose
Red blood cell (RBC) morphology	Aspartate aminotransferase (AST)	Ketone bodies
Mean corpuscular volume (MCV)	Blood urea nitrogen (BUN) or Urea	Indicators of blood and WBCs Nitrites Specific gravity
Platelet count	Creatinine	
RBC count	Creatine kinase	
White blood cell (WBC) count with differential	Electrolytes (Na, K, Cl, Ca)	Urine human chorionic gonadotropin (HCG) in pre-menopausal females only Urobilinogen
	Glucose	
	Protein	
	Total bilirubin	
	Uric Acid	
Serology: At screening (in subjects 17 years of age and older) tests for HIV, HBsAg, and HCV. Test positive for any of these tests is exclusionary. These may be collected in subjects < 17 years of age at the Investigator's discretion.		
Pregnancy Tests: Both serum and urine pregnancy tests will be performed in all female subjects of childbearing potential; if the subject is unable to provide a urine sample, the option to use only the serum pregnancy test will be according to Investigator judgment.		
Breath Alcohol Test: The Alcohol Breath Test should be completed according to the schedule of assessments in subjects 17 years of age and older (and in subjects < 17 years of age at the Investigator's discretion). If a subject cannot complete the assessment or, if in the judgment of the Investigator, the subject's exposure to alcohol is limited as determined by the medical history, incapacity, etc., the site must document in the source documents the reason that the assessment is not completed.		
Urine Tests for Drugs of Abuse: amphetamines, phencyclidine, cocaine, opiates, benzodiazepines, tetrahydrocannabinol; if a subject cannot provide a urine sample for drug screen, an accurate and thorough review should be conducted by the Investigator with the subject and/or subject's caregiver/study partner/Legally Authorized Representative. This review should include, as applicable, a Physical Exam, Review of Systems/Symptoms (ROS), Past Medical History, Concomitant Medications (including last known diazepam use), any new or ongoing adverse events, sexual activity history, pregnancy/menstrual cycle status and illicit drug use.		

Blood and urine samples will be analyzed at a central laboratory facility. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of dipstick indicate abnormalities to be further investigated. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the subject's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant

should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

If/When a protocol-required urine sample cannot be obtained from the subject (at any study visit), the Investigator should in lieu ensure that an accurate and thorough review be conducted by the Investigator with the subject and/or subject's caregiver/study partner/Legally Authorized Representative. This review should include, as applicable, a Physical Exam, Review of Systems/Symptoms (ROS), Past Medical History, Concomitant Medications (including last known diazepam use), any new or ongoing adverse events, sexual activity history, pregnancy/menstrual cycle status and illicit drug use. This is extremely important during the screening/eligibility visit as the urine sample is a key component/assessment in determining a host of inclusion and exclusion criteria. As with other missing/unobtainable protocol-mandated assessments, the site must document the reason why the urine sample could not be obtained from the subject (e.g., subject is incontinent, subject is incapable of supplying a urine sample on request, etc.) in the source documents and via the eCRF.

Urine samples obtained using a urine collection bag are acceptable. Urine-soaked diapers, urine pads, etc. are not acceptable methods of obtaining a urine sample for this study. The Sponsor does not advocate use of a urinary catheter.

11.10. Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Symptoms present at screening in rollover subjects whose screening visit is also their final visit of the Phase 2 study will be recorded as AEs (Table 6). Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the subject enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the subject's medical history.

Additionally, anticipated AEs for this study population, listed below, must be reported by Investigators to the Sponsor but will not be expedited on an individual basis. Instead these AEs will be reviewed in aggregate every three months by Syneos Health responsible group or Data and Safety Monitoring Board (DSMB). This aggregate review may result in an expedited safety report.

11.10.1. Anticipated Adverse Events for this Study and Precautions

11.10.1.1. List of Anticipated Adverse Events for this Study

The most frequent adverse event reported to be related to Diastat®AcuDial™ in the two double-blind, placebo-controlled studies was somnolence (23%). Less frequent adverse

events were headache (≤ 5%), diarrhea (≤ 4%), ataxia (≤ 3%), dizziness (≤ 3%), euphoria (≤ 3%), incoordination (≤ 3%), rash (≤ 3%), vasodilatation (≤ 2%), and asthma (≤ 2%). The majority of adverse events were mild to moderate in severity and transient in nature.

Adverse events reported elsewhere were dose related and included fatigue, drowsiness, muscle weakness, ataxia, occasional dizziness, dysarthria, slurred speech, headache, paradoxical reactions, confusion, emotional poverty, decreased alertness, depression, and increased or decreased libido (Valium® package insert 2015).

In the pilot study drug bio-equivalence bio-availability studies, the most frequently reported adverse event was somnolence. In Study1899, there were 7 occurrences of somnolence in 7 subjects while taking 5 mg study drug and there were 10 occurrences of somnolence in 10 subjects while taking 5 mg Diastat®AcuDial™ rectal gel. In Study 1900, there were 12 occurrences of somnolence in 12 subjects while taking 20 mg study drug and there were 11 occurrences of somnolence in 11 subjects while taking 20 mg Diastat®AcuDial™ rectal gel.

11.10.1.2. Cautionary Statements

Due to the Central Nervous System (CNS) depressant effect of diazepam, any subject or subject taking it should be cautioned not to operate dangerous machinery or motor vehicles or engage in activities requiring mental alertness until they have returned to their baseline level of functioning. Additionally, there is the potential for a synergistic CNS depressant effect when diazepam is used simultaneously with alcohol or other CNS depressants including barbiturates, anxiolytics, sedatives, anti-depressants, hypnotics, anti-epileptic drugs, phenothiazines, skeletal muscle relaxants, anti-histamines, narcotic analgesics and anesthetics.

Although study drug will not be used on a chronic daily basis, as noted in the preceding sections, diazepam is a Schedule IV controlled substance and can produce drug dependence. Caution should be used in any subject with a history, however remote, of alcohol or drug abuse or dependence. Diazepam may interact with disulfiram, cimetidine, ketoconazole, fluvoxamine, fluoxetine, diltiazem or omeprazole resulting in increased plasma levels of diazepam. Subjects who have taken diazepam concomitantly with these medications or within 5 half-lives of the respective drug, should be observed closely for evidence of enhanced benzodiazepine response (e.g., increased or prolonged sedation (Valium® PI).

11.10.2. Collection and Documentation of Adverse Events

Subjects/caregivers will be instructed to report AEs at each study visit. All AEs are to be followed until resolution or until a stable clinical endpoint is reached. Any de novo post-dose mucosal irritation or other abnormality will be reported as an AE of special interest and will be followed until resolution (see Section 11.6).

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject gives informed consent until the Final Visit. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator. The Investigator or designee will conduct a follow-up phone call with the subject at 30-37 days after the Final Visit to check on subject status and collect reporting information, should any SAE have occurred.

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 9 and Table 10.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be recorded. If the intensity category changes over a number of days, then the changes should be recorded separately (with distinct onset dates).

Table 9: Classification of Adverse Events by Intensity

MILD	An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE	An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE	An event that prevents normal everyday activities

Table 10: Classification of Adverse Events by Relationship to Study Drug

Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to current 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 reasonable time sequence 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 adverse events which are judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be recorded. If the intensity category changes over a number of days, then the changes should be recorded separately (with distinct onset dates).

11.10.3. Serious Adverse Events and Reporting

11.10.3.1. Serious Adverse Events

An AE is considered "serious" if, in the view of either the Investigator or the Sponsor, it meets 1 or more of the following criteria:

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

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered serious adverse events (SAEs) if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE. Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.10.3.2. Reporting Serious Adverse Events

An SAE occurring during the study or 30 days of stopping the study drug treatment must be reported to the Syneos Pharmacovigilance Group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not considered related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made using the dedicated fax line or telephone line for the Syneos Pharmacovigilance Group:

Syneos Pharmacovigilance Fax Number:	+1-866-856-1649
Syneos Pharmacovigilance Telephone Number:	+1-888-750-8020

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

If the Investigator contacts the Syneos Pharmacovigilance Group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE electronic eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the Syneos Pharmacovigilance Group within 10 calendar days. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

11.10.4. Pregnancy

Female subjects of childbearing potential must not be pregnant or breast feeding and must have a negative pregnancy test at Screening. Following administration of study drug, any known cases of pregnancy in female subjects will be reported until the subject completes or withdraws from the study. The pregnancy will be reported immediately by 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.

11.10.5. Overdose

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug. Previous reports of diazepam overdose have shown that manifestations of diazepam overdose include somnolence, confusion, coma, and diminished reflexes. Respiration rate, pulse and blood pressure should be monitored, as in all cases of drug overdose, 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. Subjects treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with

flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. Caution should be observed in use of flumazenil in epileptic subjects treated with benzodiazepines. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, should be consulted prior to use.

12. STATISTICAL ANALYSIS

All analyses will be descriptive, and no formal statistical testing will be performed. All summaries will be done for all subjects combined, as well as by age group (pediatric, adolescent, adult). Pediatric and adolescent subjects might be combined as 1 group for summary purpose.

The statistical evaluation will be performed using the Statistical Analysis Software (SAS®) Version 9.3 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by age group and overall. For continuous variables, data will be summarized with the number of subjects (n), mean, standard deviation (SD), median, min, and max. For categorical variables, data will be tabulated with the number and proportion of subjects for each category.

A separate statistical analysis plan (SAP) will provide further details regarding the summary statistics to be provided. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

12.1. Determination of Sample Size

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

12.2. Analysis Population

Safety Population: all subjects administered at least 1 dose of study drug. The Safety Population is used for all data summaries.

12.3. Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized descriptively by age group and overall. Subject demographic baseline disease characteristics include age, race, gender, weight (kg), height (cm), BMI (kg/m^2), and duration of epilepsy.

12.4. Safety Analysis

12.4.1. Primary Safety Endpoints

12.4.1.1. Adverse Events

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 20.0, or later). The incidence of TEAEs (adverse events with onset dates on or after administration of study drug) will be included in incidence tables. Events with missing onset dates will be included as study drug treatment-emergent. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. SAEs and AEs causing discontinuation will be tabulated. All AEs will

be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Exploratory analysis of possible correlation between AEs and exposure might be performed, in addition to other variables such as age, gender, cognitive status, concomitant medications:

- Documentation and assessment of TEAEs (serious and non-serious; time, incidence and severity, relationship to study drug treatment) over the time elapsed between visits.
- Review of the caregiver/subject electronic diary which captures the occurrence of seizures and location of study drug placement for each cluster treated. In addition, the subject or caregiver documents any adverse effects
- Documentation and assessment of AEs (serious and non-serious; time, incidence and severity, relationship to study drug treatment) over the time elapsed between visits
- Assessment of safety measures at end of study vs baseline:
  - Vital signs (BP, HR, RR, oral temperature)

    If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.
  - Body height and weight
  - Electrocardiogram (12-lead ECG)
  - Clinical laboratory tests (hematology, serum chemistry, urinalysis)
  - Assessment of oral mucosa by oral examination
  - Physical and Neurological examination
  - C-SSRS
  - Age-defined QoL assessments
- Pathological change in oral mucosa as measured by an oral examination
- Gustatory changes as measured by the by the general Labeled Magnitude Scale (gLMS) using commercially available taste test strips from Burghart Messtechnik

Descriptive summaries will be provided for change in oral mucosa and gustation at each visit.

12.4.1.2. C-SSRS Assessment

Frequency and severity of suicidality using the C-SSRS will be summarized at each visit.

12.4.1.3. Vital Signs

Vital signs (BP, HR, RR, oral temperature) will be summarized for each visit. If a subject is unable to provide an oral temperature as they are unable to retain an oral thermometer in position with their mouth closed, a tympanic, axillary, or temporal (forehead) temperature may be taken. In this case, the method should be recorded in the source documents.

12.4.1.4. Laboratory Analyses

Clinical laboratory data will be summarized using descriptive statistics at each visit separately for hematology, serum chemistry, urinalysis and drug screen, see Table 8. For hematology and serum chemistry laboratory tests, numbers of subjects with values outside limits of the normal range at each visit will be summarized.

12.4.1.5. Oral Mucosa Examination

Pathological change in oral mucosa as measured by an illuminated oral examination will be summarized at each visit.

12.4.1.6. Gustatory Sense Assessment

Gustatory sense changes as measured by the general Labeled Magnitude Scale (gLMS) using commercially available taste test strips from Burghart Messtechnik will be summarized at each visit.

12.4.2. Secondary Safety Endpoints

12.4.2.1. Electrocardiograms

Summary tables will be provided for 12-lead ECG results obtained for all study visits.

12.4.2.2. Concomitant Medications

Summary tables will be provided for concomitant medications initiated after administration of study drug.

12.4.2.3. Other Safety Assessments

Summaries will be provided for other safety assessments for all study visits:

- physical and neurological examinations – descriptive summaries will be provided
- body height and weight and BMI (kg/m^2) – summary tables will be provided

12.4.3. Secondary Tolerability Endpoint

12.4.3.1. Quality of Life Assessment

Quality of Life assessment by age appropriate use of epilepsy scales will be summarized at all study visits for the 6-month period.

12.4.4. Secondary Usability Endpoint

12.4.4.1. Oral Cavity Insertion and Retention Assessment

Attempt is defined as the process of placing the study drug against the buccal mucosa in the oral cavity. Categorical explanations will be capture for attempt failures and will be presented in data listings.

Descriptive summaries will be provided for the following variables:

- Handling and administration of study drug, based on IFU
  - Ability to open packaging and remove study drug
  - Successful study drug buccal insertion
    - Successful insertion will be defined as the process of placing the study drug against the buccal mucosa
    - Categorical explanations will be captured for unsuccessful insertion
- Oral cavity placement and retention assessment
  - Study drug is swallowed prior to sticking to inner check
  - Study drug spit out or blown out by subject after administration

12.5. Interim Analysis

An interim analysis is planned to obtain a snapshot of targeted Tables, Figures, and Listings and summary of the preliminary safety information.

12.6. Data Monitoring Committee

Not applicable.

13. STUDY MANAGEMENT

13.1. Approval and Consent

13.1.1. Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with GCP guidelines.

13.1.2. Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted Investigational Review Board/Investigational Ethics Committee (IRB/IEC). Approval is required for the study protocol, investigational drug brochure, protocol amendments, Informed Consent Forms (ICFs), and subject information sheets.

13.1.3. Informed Consent

For each study subject, written informed consent will be obtained prior to any protocol related activities. As part of this procedure, the Principal Investigator (PI) or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the subject and/or the subject's parent(s) or legally authorized representative are aware of the potential risks, inconveniences, or adverse effects that may occur. The subject and/or the subject's parent(s) or legally authorized representative should be informed that the subject may withdraw from the study at any time, and the subject and/or the subject's parent(s) or legally authorized representative will receive all information that is required by local regulations and International Conference on Harmonization (ICH) guidelines. Verbal and/or written assent will be obtained from the subject as required by the IRB. The PI will provide the Sponsor or its representative with a copy of the IRB/IEC approved ICF prior to the start of the study.

13.2. Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not

transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by Syneos Health. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access.

Any changes made to data after collection will be made through the use of Data Clarification Forms. The eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

13.3. Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, diaries or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

13.4. Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study or 2 years after the last approval of a marketing application in an ICH region, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study subjects and/or the subject's parents or legally authorized representatives authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

13.5. Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

13.6. Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and

reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

13.7. Protocol Amendment and Protocol Deviation

13.7.1. Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

13.7.2. Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility.

13.8. Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR, and in compliance with GCP guidelines.

IRBs/IECs will review and approve this protocol and the ICF. All subjects are required to give written informed consent prior to participation in the study.

13.9. Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

13.10. Publication Policy / Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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15. APPENDICES

APPENDIX A. Placement Diagram for Aquestive Therapeutics Buccal Soluble Film

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

MonoSol Rx 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.

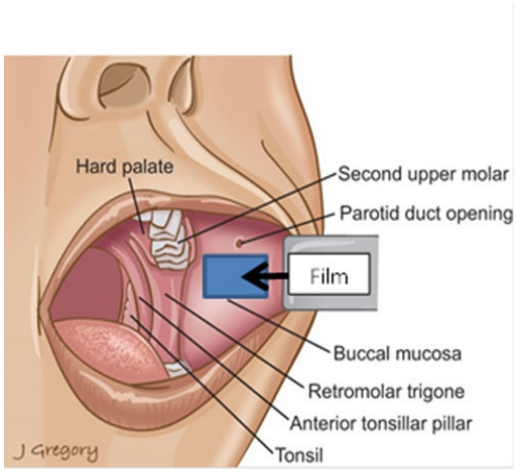


Figure: Test Drug: Placement of Aquestive Therapeutics Buccal Soluble Film against the buccal mucosa of the mouth.

Appendix B. Study Drug Instructions for Use

This Instructions for Use contains information on how to use diazepam buccal soluble film. This information does not take the place of talking to your healthcare provider (study investigator) about your medical condition or your treatment. Ask your healthcare provider (study investigator) if you have any questions about how to use diazepam buccal soluble film the right way.

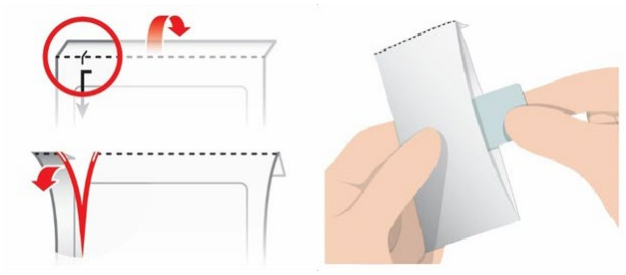
Important Information You Need to Know Before Using Diazepam Buccal Film:

- For buccal use (place film on inside of cheek)
- Before using diazepam buccal film, make sure your healthcare provider shows you the right way to use it. If treatment is unable to be given and there is concern, **call for emergency medical help right away**.

Preparing to Use Diazepam buccal film

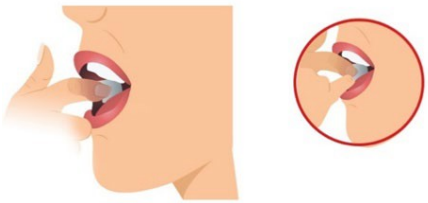
- Ensure hands are clean and dry before handling film so the film does not stick to your fingers.

Step 1. Open Pouch and Remove Film from Pouch



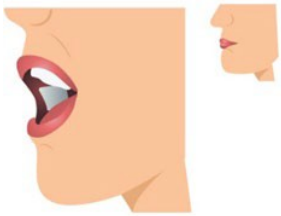
- Fold foil pouch along the side with vertical slit. While folded over, note where the vertical slit is and carefully tear down the side of the pouch at the slit to open pouch.
- Remove diazepam buccal soluble film from foil pouch.
  Each foil pouch contains one dose of diazepam buccal film.

Step 2. Place One Film on Inside of Cheek



- Stretch either cheek open with one hand and place one film flat against the cheek with your other hand. Do not rub film into cheek with your finger.
- Remove fingers from the cheek.
- If the film is spit or blown out immediately, attempt to give another dose using a new film.
- Do not give diazepam buccal film with liquids.

Step 3. Allow Film to Dissolve



- Diazepam buccal soluble film will stick to the inside of the cheek and begin to dissolve.
- The mouth can be closed or remain open while waiting.
- Saliva may be swallowed normally as the film dissolves.
- If the film is accidentally swallowed or chewed there is no need to give a replacement dose.

What to do after diazepam buccal soluble film has been used:

- Note time diazepam buccal soluble film was given in your electronic diary.
- Continue to observe the person.
- Your doctor may prescribe a second dose of diazepam buccal soluble film. If a second dose is needed, take it 4 hours to 12 hours after the first dose of diazepam buccal soluble film is taken.

Wash your hands after administering diazepam buccal soluble film.

Place the empty foil pouch back in the hard case or cardboard carton. Bring the case containing unused/partially used and empty pouches with you to your next study visit.

Call for emergency medical help if any of the following occur:

- There is an increase in seizure frequency that does not stop after using diazepam buccal soluble film as instructed by your healthcare provider.
- Seizure behavior is different from other episodes.
- The frequency or severity of the seizure is alarming.
- Either color or breathing is alarming.
- The person is having unusual or serious problems.

Please remember to fill out the electronic diary with each use of diazepam buccal soluble film.

How to store diazepam buccal soluble film

- Store at room temperature 68° to 77°F (20°C to 25°C); excursions permitted to 59°C to 86°F (15°C to 30°C)
- Keep diazepam buccal film in foil pouch until ready to use.
- Use immediately after opening foil pouch.
- **Keep diazepam buccal soluble film out of the reach of children.**

Disposing of diazepam buccal film

- Any films that were spit out or not used after opening should be flushed down the toilet or placed in the sink and rinsed with water until no longer visible.

Manufactured by:
Aquestive Therapeutics
30 Technology Dr.
Warren, NJ 07059

Revision Date: 01/2020

APPENDIX C. PedsQL™ Epilepsy Module Parent Report for Toddlers (AGES 2-4)

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

PedsQL – Epilepsy Module

PedsQL™
Epilepsy Module

Version 3.0

PARENT REPORT for TODDLERS (ages 2-4)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child.** Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

PedsQL – Epilepsy Module

*In the past **ONE month**, how much of a **problem** has your child had with…*

IMPACT	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble doing the same physical activities or sports as other kids	0	1	2	3	4
2. My child has trouble being as independent in daily tasks (e.g., dressing) as other kids his/her age	0	1	2	3	4
3. My child's activities are restricted due to epilepsy	0	1	2	3	4
4. My child has trouble taking his/her epilepsy medicine or doing other treatments (e.g., a special diet)	0	1	2	3	4
5. My child has trouble avoiding seizure triggers (e.g., flashing lights, being tired)	0	1	2	3	4
6. My child misses preschool/daycare or social activities because of epilepsy and/or its treatments	0	1	2	3	4

COGNITIVE FUNCTIONING	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble thinking quickly	0	1	2	3	4
2. My child has trouble remembering things	0	1	2	3	4
3. My child has trouble learning new things	0	1	2	3	4
4. My child needs extra help at preschool/daycare	0	1	2	3	4
5. My child has trouble understanding what he/she reads	0	1	2	3	4

SLEEP/FATIGUE	Never	Almost Never	Some-times	Often	Almost Always
1. My child feels tired during the day	0	1	2	3	4
2. My child has trouble sleeping (e.g., falling and staying asleep)	0	1	2	3	4

EXECUTIVE FUNCTIONING	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble sitting still	0	1	2	3	4
2. It is hard for my child to do what he/she is told	0	1	2	3	4
3. My child has trouble paying attention	0	1	2	3	4
4. My child has trouble finishing things he/she started	0	1	2	3	4

MOOD/BEHAVIOR	Never	Almost Never	Some-times	Often	Almost Always
1. My child feels grouchy	0	1	2	3	4
2. My child feels angry	0	1	2	3	4
3. My child feels sad or blue	0	1	2	3	4
4. My child feels afraid or scared	0	1	2	3	4
5. My child is easily frustrated	0	1	2	3	4

Aquestive_42-1703_PedsQL Parent (2-4)_English (US)_Version 1.0_03Jan2018 Page 2 of 2
Formatted from; PedsQL-3.0-Epilepsy-PT_AU3.0_eng-USori
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APPENDIX D. PedsQL™ Epilepsy Module Parent Report For Young Children (AGES 5-7)

Protocol 42-1703	Site Number	Subject ID	Visit	Examination Date
Aquestive				Day – Month – Year

PedsQL – Epilepsy Module

PedsQL™
Epilepsy Module

Version 3.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child.** Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

PedsQL – Epilepsy Module

*In the past **ONE month**, how much of a **problem** has your child had with…*

IMPACT	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble doing the same physical activities or sports as other kids	0	1	2	3	4
2. My child has trouble being as independent in daily tasks (e.g., dressing) as other kids his/her age	0	1	2	3	4
3. My child's activities are restricted due to epilepsy	0	1	2	3	4
4. My child has trouble taking his/her epilepsy medicine or doing other treatments (e.g. a special diet)	0	1	2	3	4
5. My child has trouble avoiding seizure triggers (e.g., flashing lights, being tired)	0	1	2	3	4
6. My child misses school or social activities because of epilepsy and/or its treatments	0	1	2	3	4
7. My child does not like being left alone in case he/she has a seizure	0	1	2	3	4
8. My child feels different from other kids or family members	0	1	2	3	4
9. My child feels embarrassed when a seizure happens	0	1	2	3	4

COGNITIVE FUNCTIONING	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble thinking quickly	0	1	2	3	4
2. My child has trouble remembering things	0	1	2	3	4
3. My child has trouble learning new things	0	1	2	3	4
4. My child needs extra help at school	0	1	2	3	4
5. My child has trouble understanding what he/she reads	0	1	2	3	4
6. My child has trouble keeping up with schoolwork	0	1	2	3	4

SLEEP/FATIGUE	Never	Almost Never	Some-times	Often	Almost Always
1. My child feels tired during the day	0	1	2	3	4
2. My child has trouble sleeping (e.g., falling and staying asleep)	0	1	2	3	4
3. My child needs more sleep than other kids	0	1	2	3	4

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

PedsQL – Epilepsy Module

*In the past **ONE month**, how much of a **problem** has your child had with…*

EXECUTIVE FUNCTIONING	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble sitting still	0	1	2	3	4
2. It is hard for my child to do what he/she is told	0	1	2	3	4
3. My child has trouble paying attention	0	1	2	3	4
4. My child has trouble finishing things he/she started	0	1	2	3	4
5. My child acts without thinking	0	1	2	3	4
6. My child has trouble staying organized	0	1	2	3	4

MOOD/BEHAVIOR	Never	Almost Never	Some-times	Often	Almost Always
1. My child feels grouchy	0	1	2	3	4
2. My child feels angry	0	1	2	3	4
3. My child feels sad or blue	0	1	2	3	4
4. My child feels afraid or scared	0	1	2	3	4
5. My child is easily frustrated	0	1	2	3	4

APPENDIX E. PedsQL™ Epilepsy Module Parent Report for Children (AGES 8-10)

Protocol 42-1703	Site Number	Subject ID	Visit	Examination Date
Aquestive				Day – Month – Year

PedsQL – Epilepsy Module

PedsQL™
Epilepsy Module

Version 3.0

PARENT REPORT for **CHILDREN** (ages **8-10**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child.** Please tell **us how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

PedsQL – Epilepsy Module

*In the past **ONE month**, how much of a **problem** has your child had with …*

IMPACT	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble doing the same physical activities or sports as other kids	0	1	2	3	4
2. My child has trouble being as independent as other kids his/her age in daily tasks (e.g., riding bikes)	0	1	2	3	4
3. My child's activities are restricted due to epilepsy	0	1	2	3	4
4. My child has trouble taking his/her epilepsy medicine or doing other treatments (e.g., a special diet)	0	1	2	3	4
5. My child has trouble avoiding seizure triggers (e.g., flashing lights, being tired)	0	1	2	3	4
6. My child misses school or social activities because of epilepsy and/or its treatments	0	1	2	3	4
7. My child does not like being left alone in case he/she has a seizure	0	1	2	3	4
8. My child feels different from other kids or family members	0	1	2	3	4
9. My child feels embarrassed when a seizure happens	0	1	2	3	4

COGNITIVE FUNCTIONING	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble thinking quickly	0	1	2	3	4
2. My child has trouble remembering things	0	1	2	3	4
3. My child has trouble learning new things	0	1	2	3	4
4. My child needs extra help at school	0	1	2	3	4
5. My child has trouble understanding what he/she reads	0	1	2	3	4
6. My child has trouble keeping up with schoolwork	0	1	2	3	4

SLEEP/FATIGUE	Never	Almost Never	Some-times	Often	Almost Always
1. My child feels tired during the day	0	1	2	3	4
2. My child has trouble sleeping (e.g., falling and staying asleep)	0	1	2	3	4
3. My child needs more sleep than other kids	0	1	2	3	4

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

PedsQL – Epilepsy Module

*In the past **ONE month**, how much of a **problem** has your child had with …*

EXECUTIVE FUNCTIONING	Never	Almost Never	Some-times	Often	Almost Always
1. My child has trouble sitting still	0	1	2	3	4
2. It is hard for my child to do what he/she is told	0	1	2	3	4
3. My child has trouble paying attention	0	1	2	3	4
4. My child has trouble finishing things he/she started	0	1	2	3	4
5. My child acts without thinking	0	1	2	3	4
6. My child has trouble staying organized	0	1	2	3	4

MOOD/BEHAVIOR	Never	Almost Never	Some-times	Often	Almost Always
1. My child feels grouchy	0	1	2	3	4
2. My child feels angry	0	1	2	3	4
3. My child feels sad or blue	0	1	2	3	4
4. My child feels afraid or scared	0	1	2	3	4
5. My child is easily frustrated	0	1	2	3	4

APPENDIX F. Quality of Life in Epilepsy for Adolescents QOLIE-48 (VERSION 1.0)

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Quality of Life in Epilepsy for Adolescents
QOLIE-AD-48 (Version 1.0)

HOW EPILEPSY AFFECTS MY LIFE
A Questionnaire For Young People Who Have Epilepsy

INSTRUCTIONS

This is a survey in two parts. The first part asks about your general health. The second part asks about the effects of your epilepsy and antiepileptic medications. **Please answer every question** by circling the appropriate number (1, 2, 3, 4, 5). If you are not sure about how to answer a question, please give the **best answer you can**. You may write notes in the margin to explain your feelings. Even if some questions look similar, answer every question. Please ask if you need help reading, understanding, or marking the form.

PART 1: GENERAL HEALTH

1. In general, would you say your health is: *(Circle one number)*

Excellent	Very Good	Good	Fair	Poor
5	4	3	2	1

2. **Compared to 1 year ago,** how would you rate your health in general **now?**

Much better now	Somewhat better now	About the same now	Somewhat worse now	Much worse now
5	4	3	2	1

The following questions are about activities you might do during a TYPICAL DAY. We want you to answer how much **your health** limits you in these activities. *(Circle one number on each line)*

In the past 4 weeks, how often has your health limited:	Very often	Often times	Some-	Not often	Never
3. Heavy activities, such as running, participating in very active sports (such as gymnastics, roller-blading, skiing)?	1	2	3	4	5
4. Moderate activities (such as walking to school, bicycle riding)?	1	2	3	4	5
5. Light activities (such as carrying packages or a school bag full of books)?	1	2	3	4	5
6. Other daily activities (such as taking a bath/shower alone, going to and from school alone)?	1	2	3	4	5

Should read version date as 04 Jan 2018 instead of 03 Jan 2018.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date Day – Month – Year

The following questions are about your regular daily activities, such as chores at home, baby-sitting, attending school, being with friends and family, doing homework, or taking part in after-school activities and lessons. We want to know if you had any of the following difficulties with your regular activities as a result of any **physical problems (such as illness) or emotional problems (such as feeling sad or nervous)?**

In the past 4 weeks, how often have physical or emotional problems caused you to:	Very often	Often	Some-times	Not often	Never
7. Do fewer things than you would have liked to do?	1	2	3	4	5
8. Limit the ***kind*** of schoolwork, chores, sports, or other activities you did?	1	2	3	4	5
9. Have ***difficulty*** performing the schoolwork, chores, sports, or other activities you did (for example, it took extra effort)?	1	2	3	4	5

In the past 4 weeks, how often:	Very often	Often	Some-times	Not often	Never
10. Did you skip school for no reason?	1	2	3	4	5
11. Were you in trouble in school (with teachers or other staff)?	1	2	3	4	5
12. Were you in trouble out of school (with police, security guards, bus driver, etc)?	1	2	3	4	5

These questions are about how you FEEL and how things have been for you during the **past 4 weeks.** For each question, please indicate the one answer that comes closest to the way you have been feeling.

(Circle one number on each line) In the past 4 weeks, how often have you:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
13. Had trouble concentrating on an activity?	1	2	3	4	5
14. Had trouble concentrating on reading?	1	2	3	4	5

Should read version date as 04 Jan 2018 instead of 03 Jan 2018.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date Day – Month – Year

The following questions are about mental activities and language problems that may interfere with your normal schoolwork or living activities. *(Circle one number on each line)*

In the past 4 weeks, how often have you:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
15. Had difficulty thinking?	1	2	3	4	5
16. Had difficulty figuring out and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5
17. Had a problem with complicated projects that require organization or planning like computer games or difficult homework)?	1	2	3	4	5
18. Had trouble remembering things you read hours or days before?	1	2	3	4	5
19. Had trouble finding the correct word?	1	2	3	4	5
20. Had trouble understanding your teachers?	1	2	3	4	5
21. Had trouble understanding what you read?	1	2	3	4	5

The following questions ask about the support you get from others (including family and friends). *(Circle one number on each line)*

In the past 4 weeks, how often did you:	Very often	Often	Some-times	Not often	Never
22. Have someone available to help you if you needed and wanted help?	5	4	3	2	1
23. Have someone you could confide in or talk to about things that were troubling you?	5	4	3	2	1
24. Have someone you could talk to when you were confused and needed to sort things out?	5	4	3	2	1
25. Have someone who accepted you as you were, both your good points and bad points?	5	4	3	2	1

Should read version date as 04 Jan 2018 instead of 03 Jan 2018.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

PART 2: EFFECTS OF EPILEPSY AND ANTIEPILEPSY MEDICATIONS

The following questions ask about how your epilepsy or medications (antiepileptic drugs) have affected your life in the past 4 weeks. *(Circle one number on each line)*

In the past 4 weeks, how often did you:	Very Often	Often	Some-times	Not often	Never
26. Feel that **epilepsy or medications** limited your social activities (such as hanging out with friends, doing extra-curricular activities)compared with social activities of others your age?	**1**	2	3	4	5
27. Feel alone and isolated from others because of your epilepsy/seizures ?	**1**	2	3	4	5
28. Miss classes because of seizures or medications?	**1**	2	3	4	5
29. Use epilepsy or medication side effects as an excuse to avoid doing something you didn't really want to do?	**1**	2	3	4	**5**
30. Feel embarrassed or "different" because you had to take medications?	**1**	2	3	4	5

In the past 4 weeks, how often did you:	Very Often	Often	Some-times	Not often	Never
31. Feel that epilepsy or medications limited your school performance?	**1**	2	3	4	5
32. Feel you had limitations because of your seizures?	1	2	3	4	5
33. Feel that epilepsy or medications limited your independence?	1	2	3	4	5
34. Feel that epilepsy or medications limited your social life or dating?	1	2	3	4	5
35. Feel that epilepsy or medications limited your participation in sports or physical activities?	**1**	2	3	4	5

Should read version date as 04 Jan 2018 instead of 03 Jan 2018.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

The following question asks about possible side effects from antiepileptic drugs.
In the past 4 weeks, how did you feel:

	Very Bad	Bad	OK	Good	Very good
36. About how you looked (side effects such as weight gain, acne/pimples, hair change, etc.)?	1	2	3	4	5

In the past 4 weeks, how much were you bothered by:

	A Lot	Some	Not much	A little	Not at all
37. Limits set by parents/family because of your epilepsy or medications?	1	2	3	4	5

Next are some statements people with epilepsy sometimes make about themselves. For each statement, circle the answer that comes closest to the way **you** have felt about **yourself** in the **past 4 weeks.**

	Strongly agree	Agree	Disagree	Strongly disagree
38. I consider myself to be less than perfect because I have epilepsy.	1	2	3	4
39. If I applied for a job, and someone else also applied who didn't have epilepsy, the employer should hire the other person.	1	2	3	4
40. I can understand why someone wouldn't want to date me because I have epilepsy.	1	2	3	4
41. I don't blame people for being afraid of me because I have epilepsy.	1	2	3	4
41. I don't blame people for being afraid of me because I have epilepsy.	1	2	3	4
42. I don't blame people for taking my opinions less seriously than they would if I didn't have epilepsy.	1	2	3	4
43. I feel that my epilepsy makes me mentally unstable.	1	2	3	4

Should read version date as 04 Jan 2018 instead of 03 Jan 2018.

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date Day – Month – Year

The following questions ask about your attitudes toward epilepsy. Circle one number for how often in the **past 4 weeks** you have had these attitudes.

	Very bad	A little bad	Not sure	A little good	Very good
44. How good or bad has it been that you have epilepsy?	1	2	3	4	5
	Very Unfair	**A little unfair**	**Not sure**	**A little fair**	**Very fair**
45. How fair has it been that you have epilepsy?	1	2	3	4	5
	Very sad	**A little sad**	**Not sure**	**A little happy**	**Very happy**
46. How happy or sad has it been for you to have epilepsy?	1	2	3	4	5
	Very bad	**A little bad**	**Not sure**	**A little good**	**Very good**
47. How bad or good have you felt it is to have epilepsy?	1	2	3	4	5

In the past 4 weeks, how often did you:	Very often	Often	Some-times	Not often	Never
Worry about having another seizure?	1	2	3	4	5
Fear dying because of seizures?	1	2	3	4	5
Worry about hurting yourself during a seizure?	1	2	3	4	5

Please check all pages before stopping to be sure that you have answered all the questions.

Thank you for completing this questionnaire.

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Should read version date as 04 Jan 2018 instead of 03 Jan 2018.

APPENDIX G. Patient-Weighted Quality of Life in Epilepsy: QOLIE-31-P

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

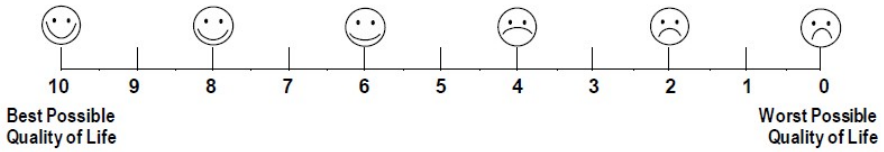
Patient-Weighted Quality Of Life In Epilepsy: QOLIE-31-P (Version 2.0, US - English)

INSTRUCTIONS:

This survey asks about your health and daily activities. **Answer every question** by circling the appropriate number (1, 2, 3…).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin. Please feel free to ask someone to assist you if you need help reading or marking the form.

1. Overall, how would you rate your quality of life?
(Circle one number on the scale below)



Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part A

These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
2. Did you feel full of pep?	1	2	3	4	5	6
3. Did you have a lot of energy?	1	2	3	4	5	6
4. Did you feel worn out?	1	2	3	4	5	6
5. Did you feel tired?	1	2	3	4	5	6

*Reviewing only questions in **Part A**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
6. How much do the above problems and worries about energy **distress** you overall?	1	2	3	4	5

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part B.

These questions are about how you have been FEELING during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…
(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
7. Have you been a very nervous person?	1	2	3	4	5	6
8. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9. Have you felt calm and peaceful?	1	2	3	4	5	6
10. Have you felt downhearted and blue?	1	2	3	4	5	6
11. Have you been a happy person?	1	2	3	4	5	6

*Reviewing only questions in **Part B**, consider the overall impact of these issues on your life **in the past 4 weeks.***

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
12. How much do the above problems and worries about emotions **distress** you overall?	1	2	3	4	5

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part C.

The following questions are about how you FEEL and about problems you may have with daily ACTIVITIES during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

The following question asks about how you FEEL and how things have been going for you.

The following question asks about how you FEEL and how things have been going for you.

How much of the time during the past 4 weeks…

(Circle one number)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
13. Has your health limited your social activities (such as visiting with friends or close relatives)?	1	2	3	4	5	6

The following questions ask about problems you may have with certain ACTIVITIES.

How much of the time during the past 4 weeks your epilepsy or antiepileptic medication has caused trouble with…

(Circle one number on each line)

	A great deal	A lot	Somewhat	Only a little	Not at all
14. Leisure activities (such as hobbies, going out)	1	2	3	4	5
15. Driving (or transportation)	1	2	3	4	5

	Not at all bothersome				Extremely bothersome
16. How much do your work limitations bother you?	1	2	3	4	5
17. How much do your social limitations bother you?	1	2	3	4	5

*Reviewing only questions in **Part C**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
18. How much do the above problems and worries about daily activities **distress** you overall?	1	2	3	4	5

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part D.

These questions are about thinking, reading, concentrating and memory problems you may have had during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
19. Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5	6

	Yes, a great deal	Yes, somewhat	Only A little	No, not at all
20. In the past 4 weeks, have you had any trouble with your memory?	1	2	3	4

In the past 4 weeks, how often have you had…

(Circle one number on each line)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
21. Trouble remembering things people tell you?	1	2	3	4	5	6
22. Trouble concentrating on reading?	1	2	3	4	5	6
23. Trouble concentrating on doing one thing at a time?	1	2	3	4	5	6

	Not at all bothersome				Extremely bothersome
24. How much do your memory difficulties bother you?	1	2	3	4	5

*Reviewing only questions in **Part D**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
25. How much do the above problems and worries about mental function **distress** you overall?	1	2	3	4	5

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part E.

These questions are about problems you may have related to your epilepsy or antiepileptic medication.

During the past 4 weeks…

(Circle one number on each line)

	Not at all bothersome				Extremely bothersome
26. How much do physical effects of antiepileptic medication bother you?	1	2	3	4	5
27. How much do mental effects of antiepileptic medication bother you?	1	2	3	4	5

	Very worried	Somewhat worried	Not very worried	Not worried at all
28. How worried are you that medications you are taking will be bad for you if taken for a long time?	1	2	3	4

*Reviewing only questions in **Part E**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
29. How much do the above problems and worries about the effects of medication **distress** you overall?	1	2	3	4	5

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part F.

These questions are about how you FEEL about your seizures during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

(Circle one number)	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
30. Have you worried about having another seizure?	1	2	3	4	5	6

	Very fearful	Somewhat fearful	Not very fearful	Not fearful at all
31. How fearful are you of having a seizure during the next month?	1	2	3	4

	Worry a lot	Occasionally worry	Don't worry at all
32. Do you worry about hurting yourself during a seizure?	1	2	3

	Very worried	Somewhat worried	Not very worried	Not at all worried
33. How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?	1	2	3	4

	Not at all bothersome				Extremely bothersome
34. How much do your seizures bother you?	1	2	3	4	5

*Reviewing only questions in **Part F**, consider the overall impact of these issues on your life **in the past 4 weeks**.*

(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
35. How much do the above problems and worries about <u>seizures</u> **distress** you overall?	1	2	3	4	5

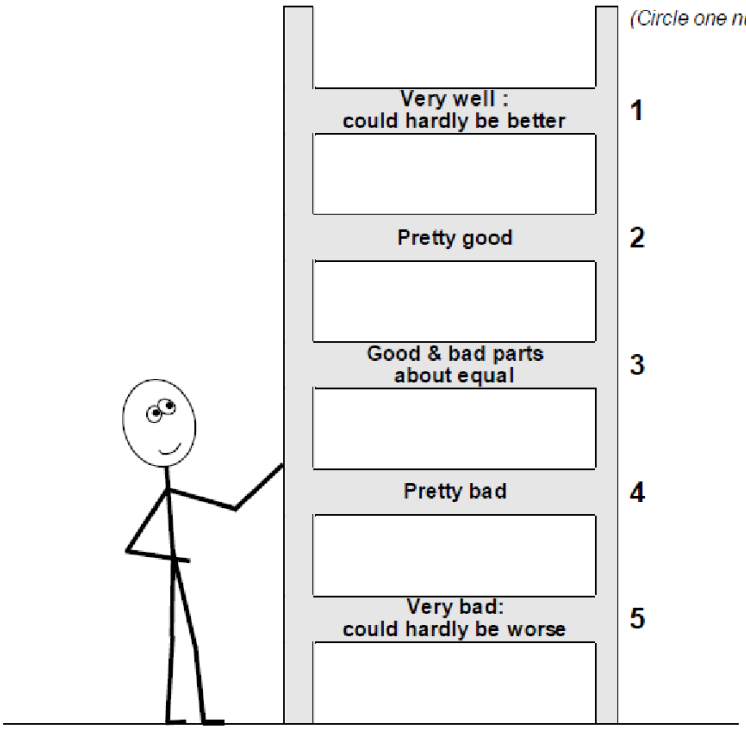
Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part G.

The following question asks about how you FEEL about your overall quality of life. Please indicate the one answer that comes closest to the way you have been feeling.

36. How has the **QUALITY OF YOUR LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?

(Circle one number)



*Reviewing only questions 1 and 36 in **Part G** (on page 1 and this page), consider the overall impact of your quality of life **in the past 4 weeks**.*

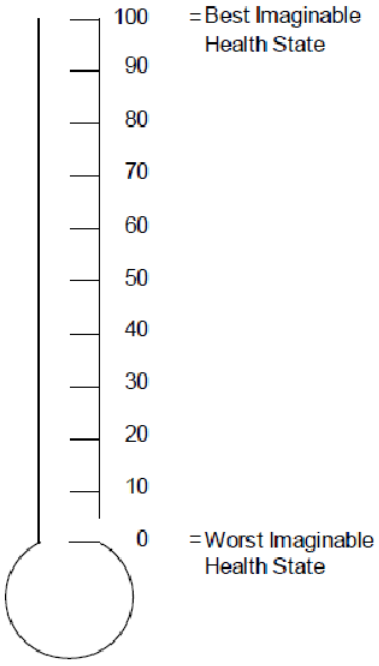
(Circle one number)

	Not at all	Somewhat	Moderately	A lot	Very much
37. How much does the state of your quality of life **distress** you overall?	1	2	3	4	5

Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part H.

38. How good or bad do you think your HEALTH is?
On the scale below, the best imaginable state of health is 100 and the worst imaginable state is zero (0). Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when you answer this question.**



Protocol 42-1703 Aquestive	Site Number	Subject ID	Visit	Examination Date
				Day – Month – Year

Part I.

*Considering **ALL** the questions you have answered, please **indicate the areas** related to your epilepsy that are most **IMPORTANT** to you **NOW.***

39. *Number the following topics from '1' to '7', with '1' corresponding to the very most important topic and '7' to the least important one. Please use each number only once.*

- ☐ **A.** Energy (tiredness)
- ☐ **B.** Emotions (mood)
- ☐ **C.** Daily activities (work, driving, social)
- ☐ **D.** Mental activity (thinking, concentrating, memory)
- ☐ **E.** Medication effects (physical, mental)
- ☐ **F.** Seizure worry (impact of seizures)
- ☐ **G.** Overall quality of life

Please check to be sure you have answered every question on every page.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE ABOUT LIVING WITH EPILEPSY.