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NEURELIS, INC.

PROTOCOL

VALTOCO®

(DIAZEPAM NASAL SPRAY)

PROTOCOL NUMBER DIAZ.001.08



**AN OPEN-LABEL, SINGLE-DOSE, PHARMACOKINETICS STUDY OF VALTOCO®
WITH OPEN-LABEL SAFETY PERIOD IN PEDIATRIC SUBJECTS WITH EPILEPSY**

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NEURELIS INC.



CONFIDENTIAL

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine aminotransferase
ARS	acute repetitive seizures
ASD	antiseizure drug(s)
AST	aspartate aminotransferase
AUC	area under the curve
AUC ₍₀₋₆₎	area under the plasma concentration time-curve to 6 hours post dose
BLQ	below the limit of quantitation
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Nutrition
cGMP	current Good Manufacturing Practices
CI	confidence interval
C _{max}	maximum plasma concentration
CNS	central nervous system
CO ₂	carbon dioxide
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DZP	diazepam

ABBREVIATION	DEFINITION
λ_z	elimination rate constant
eCRF	electronic case report form
ECG	electrocardiogram
<i>E.coli</i>	<i>Escherichia coli</i>
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
EMU	Epilepsy Monitoring Unit
EPA	Environmental Protection Agency
FDA	US Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	geometric mean ratio
GRAS	generally recognized as safe
HbSAg	Hepatitis B surface antigen
HED	human equivalent dose
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	intramuscular
IP	investigational product

ABBREVIATION	DEFINITION
IRB/EC	Institutional Review Board/Ethics Committee
IV	intravenous
IWRS	Interactive Web Response System
kg	kilogram
L	liter
LC/MS/MS	liquid chromatography tandem mass spectrometry
LD ₅₀	lethal dose 50% or median lethal dose
LDH	lactate dehydrogenase
MRHD	maximum recommended human dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mL	milliliter
mm	millimeter
NOEL	no observable effect level
NONMEM	Non-Linear Mixed Effects Modeling Software, Icon Ltd
OECD	Organisation for Economic Co-operation and Development
PBMC	peripheral blood mononuclear cells
PI	principal investigator
PK	pharmacokinetics
QTcF	corrected QT interval, Fridericia's formula
RBC	red blood cell

ABBREVIATION	DEFINITION
SAE	serious adverse event
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
$t_{1/2}$	half-life
$t_{\max}$	time to maximum plasma concentration
UDS	unit dose sprayer
μL	microliter
US/USA	United States of America
Vd	volume of distribution
Vz/F	volume of distribution, diazepam only
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonisation Good Clinical Practice Guidelines E6 (ICH-GCP).

I will maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in [Section 10.0](#) of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the Medical Monitor for approval prior to enrollment of the subject in the study.

I will allow the Sponsor, Neurelis, Inc. (Neurelis) and its agents, as well as the United States (U.S.) Food and Drug Administration (FDA) and other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than one week).

This protocol contains information that is proprietary to Neurelis. The information contained herein is provided for the purpose of conducting a clinical trial for Neurelis.

The contents of this protocol may be disclosed to study personnel under my supervision and to my IRB/EC. The contents of this protocol will not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Neurelis.

Investigator's Signature

Date

PROTOCOL SYNOPSIS

Study Title	An Open-Label, Single-Dose, Pharmacokinetics Study of VALTOCO® with Open-Label Safety Period in Pediatric Subjects with Epilepsy (DIAZ.001.08)
Phase	Phase 1/2a (Pharmacokinetics in Pediatric Subjects with Epilepsy)
Study Drug	VALTOCO® (diazepam nasal spray)
Objectives	Primary objective: - To assess the pharmacokinetics (PK) of diazepam after a single intranasal dose of VALTOCO administered to subjects with epilepsy 2-5 years of age. The primary PK variables to determine bioavailability will be the maximum plasma concentration (C_{max}) and the area under the curve through 6 hours ($AUC_{(0-6)}$). Secondary objectives: - To assess the safety and tolerability of diazepam after intranasal administration of VALTOCO in the subject population. - To assess the long-term safety and tolerability of diazepam after repeated exposure to intranasal administration of VALTOCO in the subject population.
Study Design	This is a Phase 1/2a, open-label, single-dose, PK study of VALTOCO with open-label safety period in pediatric epilepsy subjects age 2 to 5 years. A single 5 mg, 10 mg, or 15 mg dose of intranasal VALTOCO will be administered based on the subject's body weight in a clinical setting followed by PK sampling. All subjects will be administered VALTOCO by a trained medical professional as per the Instructions for Use consistent with VALTOCO prescribing information. Appropriate entertainment is allowed to help the subject remain relaxed and distracted during study procedures. The study consists of a screening period, a baseline period, a single-dose period, an open-label safety period, a follow-up phone call and an optional extension period. At the screening visit and after signing informed consent, each subject will be assigned a screening number in the format xx-yyy, where xx represents the site number (e.g., 01 for site #1), and yyy represents the subject screening number, which will increase sequentially at each site (e.g., 001, 002). At the baseline visit and after all pre-dose assessments are completed, the system will automatically assign to each qualified subject a 'subject ID' in the format xx-yyy-z, where xx is the site number, yyy (e.g., 001, 002) represents the subject number and z=1, 2 or 3 represents the blood sampling sequence as listed below. The system will automatically rotate the sequence numbers as subjects are sequentially enrolled across all sites. A total of six (6) blood samples for PK evaluation will be collected from each subject at specific times depending on sequence: • [REDACTED] A range of ± 5 minutes will be allowed for time points from 15 to 60 minutes and ± 10 minutes for time points from 75 to 360 minutes. For all blood samples the actual time of collection will be recorded and entered into the electronic case report form (eCRF). In the single-dose period, VALTOCO will be administered during an interictal period to subjects with epilepsy 2 – 5 years of age. The pre-dose PK blood sample will be collected at baseline, after all pre-dose safety assessments are completed. Once the pre-dose PK sample has been collected, a single dose of VALTOCO will be administered and the PK collection

	will continue for up to 6 hours after dosing to determine the diazepam plasma concentration versus time profile. The process will continue until at least 30 PK subjects have completed the single-dose period with at least one post-dose PK sample collected. The sponsor has the option to enroll additional subjects if any do not complete the full 360 minutes of PK sampling. Subjects who discontinue for any reason prior to dosing and/or obtaining at least 120 minutes of blood samples for PK assessment may be replaced at the discretion of the Sponsor. If a subject discontinues after dosing but prior to completing the PK assessment, they may continue in the open-label safety portion of the study. [REDACTED] Subjects may be discharged after the 6-hour post-dose assessments are complete provided that there are no clinically meaningful signs of sedation. For the open-label safety portion of this study, subjects will be supplied with VALTOCO to use as rescue medication as needed for the frequent breakthrough seizures or acute repetitive seizures (ARS) (as per VALTOCO prescribing information). Subjects and caregivers will be provided an electronic diary on their own device to record any usage of VALTOCO for seizures including, but not limited to, the date of use, time of seizure onset, time of dosing, and time of seizure resolution (Appendix F). Up to two reminder messages will be sent to the caregiver if the electronic diary is not completed daily. Subjects will return to the site on Day 30 (± 4 days) and Day 90 (± 4 days) for safety evaluations and to be provided with additional supply of study medication, and on Day 180 (± 4 days) for safety evaluations. A phone call will be conducted on Day 60, Day 120 and Day 150 (± 4 days) to determine if any adverse events (AEs) have occurred and to follow-up on any ongoing AEs. [REDACTED] Seven days (± 4 days) after the last study visit, a follow-up phone call will be conducted to determine if any AEs have occurred and to follow-up on any AEs ongoing since last communication with the subject. Safety assessments include: AEs, physical examination, vital signs, laboratory examinations, and nasal irritation assessments. Site personnel will be trained in the conduct of nasal irritation assessments based on a standardized scale (Appendix G). Additional assessments including seizure severity questionnaire and caregiver assessment will also be conducted at clinic visits by trained study personnel (Appendix H and Appendix I). All study drugs received, dispensed, and returned must be accounted for in the study Drug Accountability Log. At all study visits, caregivers should bring unused drug supply.
Sample Size	Approximately 30 subjects age 2 to 5 years are to be enrolled

Study Population	Subjects between the age of 2 to 5 years with a clinical diagnosis of epilepsy who, in the opinion of the Investigator, may need a benzodiazepine intervention for seizure control and have used rescue medication at least once in the past three months.
Main Inclusion Criteria	Subjects must meet all of the following Inclusion criteria to be enrolled in this study: 1. Male or female subjects between the ages of 2 and 5 years, inclusive at time of enrollment. 2. Written informed consent by legal guardian to participate in the study. 3. Subject has a clinical diagnosis of epilepsy and, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control. 4. Subjects having either partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness, for which rescue medications have been used at least once in the last 3 months or in the opinion of the Investigator, may need a benzodiazepine intervention for seizure control 1 – 2 times every 3 months on average. 5. In the opinion of the Investigator, no clinically significant abnormal findings that could impact the subject safety or the validity of study results in the medical history, on the physical examination, electrocardiogram (ECG) (corrected QT interval [QTcF] <440 msec), or in clinical laboratory results during screening including baseline (pre-dose visit) or within past 30 days of screening visit. 6. Caregivers must agree to comply with all required study procedures.
Main Exclusion Criteria	Subjects must NOT meet any of the following Exclusion criteria to be eligible for enrollment: 1. Subjects whose body weight are < 6 kg or > 33 kg at time of enrollment. 2. Subject is undergoing intracranial electroencephalogram (EEG) monitoring. 3. In the opinion of the Investigator, a history of clinically significant medical history that would jeopardize the safety of the subject or impact the validity of the study results (such as significant gastrointestinal, renal, nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration). 4. Subject has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening. 5. Subjects who donated blood or plasma within 30 days of the first dose of study drug. 6. Participation in a clinical trial within 30 days prior to the first dose of study drug. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study. 7. Inadequate or difficult venous access that may jeopardize the quality or timing of the PK samples. 8. Changes to the dose of phenobarbital or primidone within 30 days of the anticipated dosing visit (i.e., baseline). Adjustments to phenobarbital or primidone dose are permitted after PK collection is complete. 9. Treatment with warfarin or dabigatran or other blood thinners within 30 days of the anticipated dosing visit (i.e., baseline). 10. Treatment with any diazepam containing products within 14 days of the anticipated dosing visit (i.e., baseline). 11. Use of nasal decongestants or nasal steroids within 7 days prior to the screening visit or the baseline PK visit.
Restrictions	1. Treatment with any known strong or moderate inhibitors or inducers of metabolizing enzymes (e.g., CYP-P450 enzymes or MAO), including herbal medicines, within fourteen (14) days prior to the first dose of VALTOCO, or during the study, is prohibited without approval from the Medical Monitor.
Dosage and Administration	The dose of 5 mg, 10 mg or 15 mg of VALTOCO will be selected according to the subject's weight (rounded to the nearest kg) based on the following:

on of Study Drug	For Children Age 2-5 Years (0.5 mg/kg based on Diastat label): • 6 kg to 11 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril. • 12 kg to 22 kg body weight will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril. • 23 kg to 33 kg will receive a 15 mg dose (75 mg/mL, 2 x 100 µL) administered as two 7.5 mg sprays with one spray in each nostril (the left nostril will be sprayed first followed by the right nostril). The IWRS system will display dose level at enrollment based on subject's body weight.
Safety Analysis	AEs will be collected and reviewed to evaluate the safety and tolerability of diazepam nasal solution. Other safety assessments include complete physical examination, vital signs, laboratories (hematology, serum chemistry, and urinalysis), and 12-lead ECGs. AE collection will begin after baseline assessments are complete, following treatment with VALTOCO, and continue until the follow-up visit. AEs may be either spontaneously reported or elicited during questioning and examination of a subject. AE information will be elicited at study visits by indirect questioning using a non-leading question. Legal guardians/caregivers will receive a follow-up phone call approximately 7 days (± 4 days) after the last study visit to determine if any AE has occurred and to follow-up on any treatment-emergent AEs (TEAEs) ongoing since last communication with the subject. For subjects that continue on in the optional Extension Period, the reporting period for AEs will continue up to the final study visit. Safety data will be summarized, and descriptive statistics will be provided for actual values and change from baseline values for complete physical examination, vital signs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis). The incidence and severity of TEAEs reported during the study and their relationship to study drug will be tabulated. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by body system. The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort.
Pharmacokinetics Sample Collection	Prior to and following the single dose administration of VALTOCO®, a total of six (6) blood samples (3 mL each) for PK evaluation will be collected from each subject at specific times depending on the blood sampling sequence number assigned: • [REDACTED] ■ [REDACTED] ■ [REDACTED]

	A range of ± 5 minutes will be allowed for time points from 15 to 60 minutes and ± 10 minutes for time points from 75 to 360 minutes. For all blood samples the actual time of collection will be recorded and entered into the eCRF. The diazepam concentrations in the single-dose period will be analyzed using model-independent methods to calculate PK parameters such as C_{max}, time to C_{max} (t_{max}), and $AUC_{(0-6)}$. Other PK parameters may be calculated, if needed. PK parameters will be determined using actual times of sample collection relative to the administration of VALTOCO. Concentrations below the limit of quantitation (BLQ) before the first quantifiable concentration will be assigned a value of zero; other BLQ concentrations at any other time points will be reported as missing.
Statistical Analysis	PK Analysis: Individual subject diazepam plasma concentrations, actual sampling times, and PK parameters will be listed by analyte and treatment. Descriptive statistics will be calculated by analyte and treatment for plasma concentrations and PK parameters. Individual subject and mean plasma concentrations will be displayed on linear and semi-logarithmic axes. C_{max}, t_{max}, and $AUC_{(0-6)}$ will be determined and normalized to the 10 mg dose before analysis. Confidence intervals (CI) (90%) will be constructed for the geometric mean ratios (GMR) of the two parameters (C_{max} and $AUC_{(0-6)}$) using the log-transformed data. In addition, plasma concentration data from this study will be fitted to a previously developed population model for diazepam PK after administration of VALTOCO in children (6-12 years) and adult subjects using NONMEM software (V 7.3, Icon Ltd). The relationship between diazepam PK parameters and age will be evaluated. Additional covariates that may explain variability in exposure may be investigated in this analysis. Exposure parameters in the 2-5 years population will be compared to exposure with other pediatric age groups and in adults, if feasible. Details about these analyses will be described in a separate population PK analysis plan, and the results from this analysis will be reported elsewhere. Safety Analysis: All safety analyses will be performed in all subjects who took at least one dose of study medication. The incidence and severity of TEAEs reported during the study and their relationship to study drug will be tabulated. TEAEs will be coded using the latest version of MedDRA and will be presented by body system. Descriptive statistics will be provided for actual values and change from baseline values for complete physical examination, vital signs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).
Study Duration	It is planned that each subject will participate in the open-label safety period of the study for approximately 208 days, which comprises a 21-day screening period, a single-dose treatment period, a 180-day open-label safety period, and a follow-up phone call 7 days from last study visit. [REDACTED]
Study Centers	Approximately 12 study centers will enroll subjects.

1.0 INTRODUCTION

Epilepsy is a significant health problem affecting 50 million people worldwide, including 2.7 million Americans. Epilepsy has a bimodal distribution, with peaks in infancy/early childhood and in the elderly. About one third of all patients with epilepsy remain drug resistant despite numerous approved chronic oral therapies with a broad range of mechanisms of action. Epilepsy negatively impacts quality of life and increases morbidity and mortality. In the United States (US), 25,000 to 50,000 deaths each year are attributed to seizures and related causes.

Seizure emergencies include acute repetitive seizures (ARS, also known as a seizure cluster), which are defined as intermittent increases of seizure activity while on stable regimens of antiseizure drugs (ASDs). Pediatric patients with epilepsy are often prone to seizure clusters, especially patients with severe early onset developmental and epileptic encephalopathies. Seizure clusters during childhood often portend a poor neurological outcome. The intravenous (IV) formulation of diazepam has been used for over 50 years in the treatment of seizure emergencies, including status epilepticus. The current options for treatment of ARS using diazepam include VALTOCO® for patients with epilepsy 6 years of age and older and a rectal gel formulation of diazepam, Diastat® for patients with epilepsy 2 years of age and older (1).

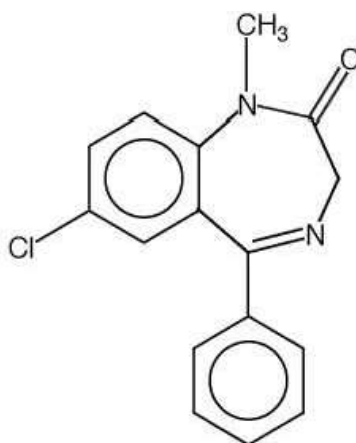
VALTOCO® was approved in 2020 for marketing by the US Food and Drug Administration (FDA) and is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, ARS) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.

Diastat rectal gel was approved by the FDA in 1997 and is intended for rectal administration in the management of selected, refractory patients with epilepsy, on stable regimens of ASDs, who require intermittent use of diazepam to control bouts of increased seizure activity and is approved for use in patients 2 years of age and older. Experience in clinical trials and post-marketing surveillance has demonstrated an excellent safety profile for Diastat with few significant side effects reported. Despite the safety and effectiveness of Diastat, the use is limited by social and legal restrictions related to the route of administration. Additionally, rectal administration of diazepam results in a highly variable dose due to inconsistent absorption and the potential of bowel movements which may necessitate an additional dose if part of the initial dose is expelled. Due to this route of administration, the use of Diastat has been limited primarily to the pediatric population, ages 2-12 years.

Diazepam, illustrated in [Figure 1](#), is a benzodiazepine anticonvulsant with the chemical name

7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one. It is a white or almost white crystalline compound, insoluble in water. The empirical formula is C₁₆H₁₃ClN₂O and the molecular weight is 284.75.

Figure 1: Diazepam



Clinical studies of patients with epilepsy 6 years of age and older were conducted to support the safety and tolerability of VALTOCO for the treatment of ARS. A total of 326 patients 6 years of age and older received VALTOCO, of whom 20 received VALTOCO for between 6 to less than 12 months, and 134 received VALTOCO for 12 months or more.

In a pharmacokinetic (PK) study in healthy adult subjects, the highest plasma diazepam concentration after nasal administration of VALTOCO was reached in 1.5 hours. The estimated volume of distribution of diazepam at steady state is 0.8 to 1.0 L/kg. The absolute bioavailability of VALTOCO relative to IV diazepam was 97%. The mean elimination half-life of diazepam following administration of a 10 mg dose of VALTOCO was about 49.2 hours. In another PK study in healthy adult subjects, diazepam plasma exposures (maximum plasma concentration [$C_{\max}$] and area under the curve [AUC]) increased approximately proportional to dose from 5 mg to 20 mg.

In a relative bioavailability study in healthy adult subjects, diazepam exposure ($C_{\max}$ and AUCs) was evaluated following administration of 15 mg and 20 mg of VALTOCO nasal spray and diazepam rectal gel. The diazepam PK parameters were 2 to 4-fold less variable for VALTOCO and within the range of those seen with diazepam rectal gel.

In a PK study in subjects with epilepsy, PK parameters were similar between seizure versus non-seizure states.

In a Phase 3 study evaluating long-term safety and tolerability of repeated intermittent at-home use in epilepsy subjects, VALTOCO demonstrated a good safety profile overall for the intended indication.

1.1. Nonclinical Assessments

Given the clinical history of diazepam, the pharmacology, toxicology, and general safety are well understood. Since it was first approved for marketing more than 40 years ago, a large amount of the relevant data on the safety and efficacy of diazepam is derived from clinical use. The following section provides a brief overview of the literature and public information on the nonclinical safety of diazepam for the benefit of the investigator.

Neurelis has conducted animal PK studies to assess the bioavailability and tolerability of the VALTOCO formulations intended for use in clinical studies. These studies were conducted in rats, rabbits, and dogs. No unexpected or adverse clinical observations were noted in these studies.

1.1.1. Pharmacology

Diazepam has anticonvulsant properties unique to some benzodiazepines and is one of the only products that is specifically approved for the treatment of ARS. Benzodiazepines act via the gamma-aminobutyric acid (GABA) receptor and significantly inhibit depolarization-sensitive calcium uptake in rat nerve cell preparations (2). Diazepam inhibits acetylcholine release in mouse hippocampal synaptosomes, which was determined by measuring sodium-dependent high affinity choline uptake in mouse brain cells *in vitro*, after pretreatment of the mice with diazepam *in vivo*. This may play a role in explaining diazepam's anticonvulsant properties (3). Diazepam binds with high affinity to glial cells in animal cell cultures (4). Diazepam at high doses has been found to decrease histamine turnover in mouse brain via direct action at the benzodiazepine GABA receptor complex (5). Diazepam also decreases prolactin release in rats (6). Diazepam has no effect on GABA levels and no effect on glutamate decarboxylase activity but has a slight effect on GABA transaminase activity (7).

Pharmacokinetic studies in animals and man have indicated that oral diazepam has a relatively rapid absorption from the gastrointestinal tract under fasted conditions. Peak blood levels are reached within 1-2 hours after administration. The half-life of diazepam is 6-8 hours with a slower decline thereafter, possibly due to tissue storage (8, 9).

Limited data are available on nonclinical evaluations of diazepam in safety pharmacology studies for central nervous system (CNS) effects. However, diazepam has been extensively studied in humans and its effects on the CNS are well established clinically. Diazepam is a benzodiazepine with CNS depressant properties and a somewhat flatter dose-response slope than other sedative-hypnotic drugs. In laboratory animals, diazepam produces, in varying doses, taming, disinhibitory, sedative, anticonvulsant, muscle relaxant, ataxic, and hypnotic effects.

Diazepam is relatively devoid of autonomic effects and does not significantly reduce locomotor activity at low doses, nor depress amphetamine-induced excitation. In high doses, it activates the drug metabolizing enzymes in the liver. Diazepam also possesses dependence liability and may produce withdrawal symptoms but has a wide margin of safety against poisoning.

Diazepam has a slight depressive effect on cardiovascular function but is widely considered to have less cardiovascular liability than any other benzodiazepines.

1.1.2. Toxicology of VALTOCO and Diazepam

1.1.2.1. Single Dose Toxicity Studies

The acute toxicity of diazepam is considered to be very low relative to other benzodiazepine compounds or other psychotropic drugs. Generally, after very large acute doses (more than 450 times the typical human dose), respiratory depression and failure are the primary causes of death in animals. Acute toxicology studies have been reported in the rat, dog, and mouse (10). Based on these studies a median lethal dose (LD₅₀) for diazepam has been established for each species.

LD ₅₀ (oral) rat:	1200 mg/kg
LD ₅₀ (oral) dog:	1000 mg/kg
LD ₅₀ (oral) mouse:	700 mg/kg

1.1.2.2. Repeated-Dose Toxicology Studies

The toxicology of diazepam is well understood in the literature and based on literature for approved marketed products.

During animal PK studies, a total of 12 intranasal formulations of diazepam with Intravail A3 concentrations up to 0.50% were evaluated in rabbits. These studies included evaluation of clinical signs and symptoms of toxicology, as well as nasal irritation. During these studies with intranasal doses up to 10 mg/animal, no unexpected clinical signs of toxicity were observed, with the only notable effect being sedation, an expected pharmacological effect of diazepam. Gross pathology and histopathology evaluations of nasal mucosa from animals after sacrifice did not reveal signs of nasal irritation or other findings that were abnormal as compared to controls.

Thus, no significant toxicity or nasal irritation (of selected formulations within the two studies) was observed with any of the VALTOCO formulations tested in the rabbit.

Intranasal doses of VALTOCO non-aqueous solution were well tolerated in rats up to 1 mg/day (a 10 µL dose volume of 100 mg diazepam per mL) and dogs dosed with 20 mg/day (a 200 µL dose volume of 100 mg diazepam per mL). After intranasal administration of VALTOCO formulations to rabbits in single dose PK and tolerability studies, and to rats and dogs in non-Good Laboratory Practices (GLP) intranasal toxicity studies for 28 days, there were no significant signs of clinical effects to indicate acute irritation and after sacrifice there were no dose-limiting clinical observations or toxicologically important events. All dose levels were well tolerated with only minimal histopathological changes. A full summary of the repeat-dose toxicology studies is provided in the VALTOCO Investigator's Brochure.

The anticipated safety of the VALTOCO formulations is expected to be similar to diazepam dosed by rectal gel administration. Based on animal studies there does not appear to be any significant acute or chronic irritation of the nasal mucosa.

1.1.2.3. Genotoxicity and Carcinogenicity Studies

Diazepam has been reported to have mutagenic activity in the *Salmonella typhimurium* tester strain TA100 in the Ames test (11). Little or no effect was seen in an assay for chromosomal aberrations, performed in Chinese hamster cells *in vitro* (12).

Studies by de la Iglesia *et al.* (13) have demonstrated no increase in tumor frequency after feeding diazepam, 75 mg/kg/day, to rats and mice for 104 and 80 weeks, respectively.

1.1.2.4. Reproductive and Developmental Studies

Diazepam has been shown to be teratogenic in mice and hamsters when given orally at single doses of 100 mg/kg or greater (approximately eight times the maximum recommended human dose [MRHD = 1 mg/kg/day] or greater on a mg/kg basis). Cleft palate and exencephaly are the most common and consistently reported malformations produced in these species by administration of high, maternally-toxic doses of diazepam during organogenesis. Rodent studies have indicated that prenatal exposure to diazepam doses similar to those used clinically can produce long term changes in cellular immune responses, brain neurochemistry, and behavior (1).

1.1.3. Pharmacology and Toxicology of Intravail A3

The toxicokinetics and metabolism of alkylglycosides, such as Intravail A3 (dodecylmaltoside), have been studied in detail under Organisation for Economic Co-operation and Development (OECD) Guidelines for Testing of Chemicals. Orally and nasally administered alkylglycosides are hydrolyzed to glucose and the corresponding long chain alcohol. No toxic metabolites are formed at any stage in the metabolic process. Dodecyl maltoside is a component (up to approximately 25%) of a mixture of alkylglycosides that are the subject of an application for Generally Recognized as Safe (GRAS) status designation by the US FDA Center for Food Safety and Nutrition (CFSAN) and the US Environmental Protection Agency (EPA) based on their use as detergents or surfactants, as a component of compounds in food industry, and agricultural usages. With their use in these contexts, there is no established limitation on the oral or topical exposure allowed for humans.

Twenty (20) GLP nonclinical studies of the pharmacology and toxicology of Intravail A3 have been conducted by a number of investigators, as a single agent and in combination with pharmacologically active ingredients in *in vitro* studies and in rats, Guinea pigs, rabbits, dogs, and monkeys. Conclusions from the rat and rabbit studies include findings of a regenerative response typically seen following local irritation of nasal mucosa, which may be attributed to the use of pipettes for dosing (most likely the result of whole droplet instillation), according to Charles Rivers pathologists. In contrast, nasal spray actuators were used for dosing in the dog

and monkey toxicology studies (for delivery as a mist or fine plume representative of human administration), and these findings were not observed. The pathologist concluded the effects were mild and reversible and should be considered of minimal risk for clinical trials.

Spack *et al.* (14) evaluated Intravail A3 for its potential to cause genotoxicity in preclinical studies for use as a mucosal surface permeation enhancer of AG284, a protein peptide complex for the treatment of multiple sclerosis. Intravail A3 was tested in the bacterial reverse mutation assay using *S.typhimurium* and *Escherichia coli* (*E.coli*) tester strains. The maximum dose tested was 25 mg/plate. No positive response was observed and hence Intravail A3 was deemed not mutagenic at 0.5 mg/mL. Intravail A3 was also tested in the chromosomal aberration assay using *in vitro* mammalian cytogenetic tests with human blood peripheral mononuclear cells (PBMCs). A dose range was established first and then its clastogenic potential was tested. The maximum concentration tested was 50 mg/mL. No statistically significant increases were observed in either the non-activated or S9 activated test systems relative to the control group. Therefore, based on these findings, Intravail A3 was not considered a mutagen or genotoxic agent.

[REDACTED]

Table 1: Intravail A3 Safety Margins Based on Current VALTOCO Formulation

[REDACTED]

1.2. Clinical Experience (Diazepam and VALTOCO)

Diazepam has been in clinical trials and human use for over 50 years by multiple routes of administration including intranasal and IV dosage forms. In general, the product has a good safety profile and has not been associated with any chronic or serious side effects in humans. Diazepam has been extensively studied and its PK and metabolism in humans is well understood. When administered orally, intravenously, intramuscularly or rectally, diazepam is extensively and rapidly absorbed, with bioavailability varying from 80 to 100 % and time to maximum plasma concentration (t_{max}) ranging from minutes (IV) to several hours (oral).

The safety of diazepam by the intranasal route of administration is also supported by the IV formulation as the IV administration exhibits the most rapid $t_{\max}$ and highest maximum plasma concentration ($C_{\max}$). Doses of IV diazepam are safe up to 30 mg administered as a 20- to 30-minute infusion time in adults, according to the FDA product labeling. Given the bioavailability demonstrated for VALTOCO (97%) (15, 16) in the absolute bioavailability study in comparison to IV diazepam, it is considered that a dose of up to 20 mg of diazepam given by intranasal administration would not cause a safety concern even if completely and rapidly absorbed.

For diazepam, the US product labeling states that the usual recommended dose in older children and adults ranges from 2 to 20 mg by intramuscular (IM) or IV administration, depending on the indication and its severity. In some conditions (e.g., tetanus), larger doses may be required. For seizure emergencies, such as status epilepticus and severe recurrent convulsive seizures, IV doses of up to 30 mg diazepam administered over a 20- to 30-minute time period is approved for adults according to US FDA labeling.

1.2.1. Clinical Trials with VALTOCO

1.2.1.1. Study DIAZ.001.01

Study DIAZ.001.01 was an open-label, randomized, three-treatment, three-period, six-sequence crossover study. The primary objective of this study was to assess the bioavailability and pharmacokinetics (PK) of diazepam after intranasal administration of suspension and solution formulations compared to IV administration to healthy volunteers under fasted conditions (16).

Diazepam was absorbed after intranasal administration of both proprietary formulations to humans, with higher exposure after administration as a solution (B) (absolute bioavailability 97%) than as a suspension (A) (absolute bioavailability 67%). With the exception of two subjects who had longer $t_{\max}$ for the intranasal solution, $t_{\max}$ was randomly distributed between the two intranasal treatments with comparable medians and ranges. The difference in exposure between the intranasal solution and intranasal suspension is therefore due to the extent rather than to the rate of absorption.

In this study, both diazepam nasal spray formulations were well-tolerated; the overall frequency of adverse event (AE) occurrence following intranasal diazepam (both formulations) was comparable to that following IV diazepam administration. Intranasal administration of diazepam did not appear to actuate the occurrence of epistaxis (or nasal irritation); more AEs of epistaxis were observed following IV diazepam than after administration of either intranasal formulation.

There were no AE reports of nasal pain by any subject in any treatment period. All AEs across all treatment groups were considered to be mild or moderate in severity; no subject withdrew from the study in response to an AE, and no subject experienced a serious adverse event (SAE).

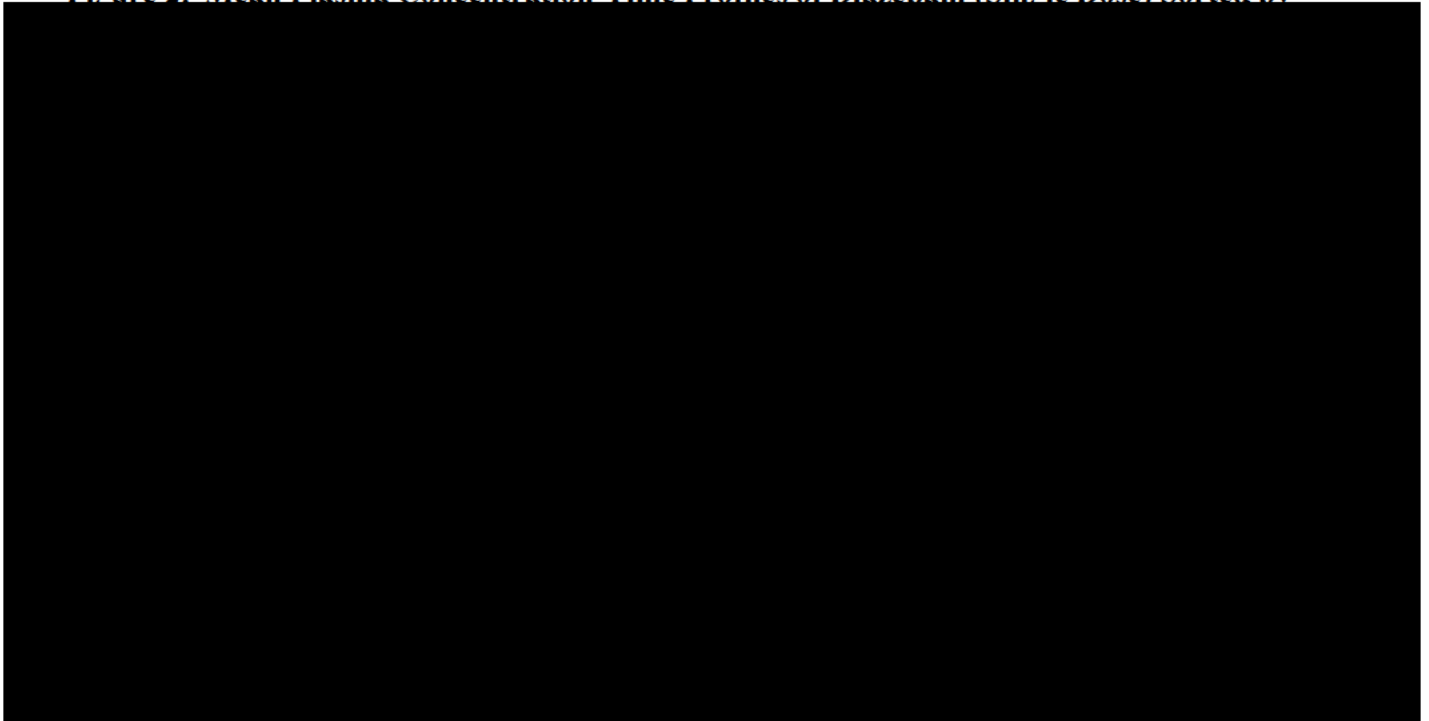
1.2.1.2. Study DIAZ.001.02

Study DIAZ.001.02 was an open-label, randomized, three single-dose, three-period, six-sequence crossover study, followed by a fourth two-dose period, that consisted of a screening period, baseline period, and an open-label treatment period (17). The purpose of the study was to evaluate the dose proportionality of VALTOCO.

Thirty-six (36) eligible subjects were randomized, after an overnight fast, into one of six sequences to receive single doses of 5, 10, and 20 mg of VALTOCO in the first three treatment periods (Treatments 1, 2, and 3) followed by two 10 mg doses of VALTOCO 4 hours apart (Treatment 4). Blood samples were collected for 240 hours after the single dose or the first dose of the two-dose treatment. Doses were administered as a 100 µL intranasal spray at drug concentrations of 50 mg/mL and 100 mg/mL.

The results from this study showed that single doses of VALTOCO ranging from 5 to 20 mg diazepam rapidly entered the systemic circulation with apparent dose proportionality (Figure 2) but it was inconclusive because of variability in the pharmacokinetic data. This variability was attributed to enrolled subjects with higher BMI. In fact, there appears to be a general trend of higher drug exposure (maximum serum concentration and area under the curve; $C_{\max}$ and AUC) in subjects with a lower body weight or BMI. This may be attributed to the high degree of lipophilicity of diazepam and the corresponding affinity for tissue absorption.

Figure 2: Mean Plasma Concentration-Time Profiles of Diazepam (Single Dose) Sorted by



[REDACTED]

Desmethyldiazepam (nordiazepam) was formed rapidly with measurable concentrations often being observed by the first blood draw, but maximum concentration was not reached until 96 hours (median) postdose ([Figure 3](#)).



The most commonly ($\geq 5\%$) reported TEAEs in all the VALTOCO nasal spray treated subjects were somnolence, reticulocyte count increase, blood glucose increase, hemoglobin decrease, abnormal urine analysis, alanine aminotransferase increase, blood pressure decrease and euphoric mood. There were no discontinuations due to adverse events.

1.2.1.3. Study DIAZ.001.03

Study DIAZ.001.03 was an open-label, randomized, single-dose, three-treatment, three-period, six-sequence crossover study that consisted of a screening period, baseline period, and an open-label treatment period (18). The purpose of this study was to assess the relative bioavailability and safety of diazepam from VALTOCO compared with Diastat (diazepam rectal gel) and oral Valium (diazepam tablets) in healthy volunteers.

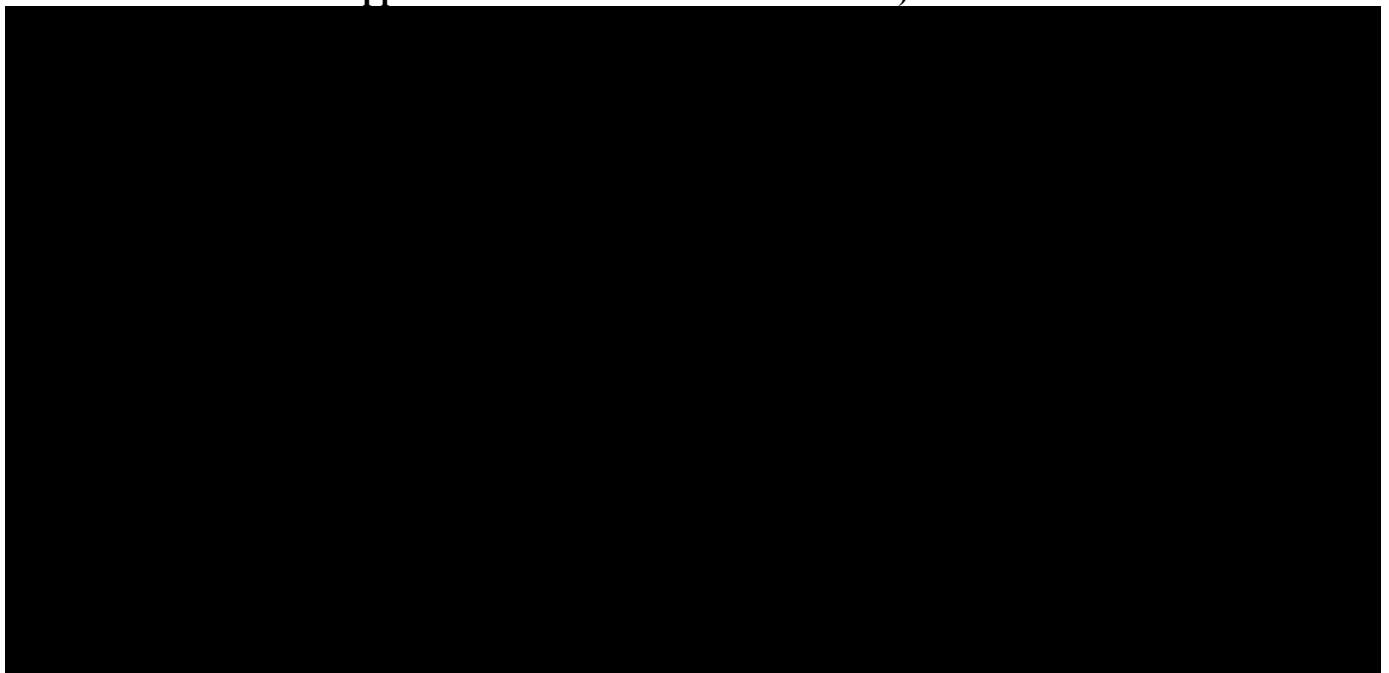
Forty-eight (48) eligible subjects were randomized after an overnight fast into one of six sequences that received a single dose of VALTOCO, Diastat, or oral Valium in three treatment periods (Treatment period 1, 2, and 3). Dosing in the Valium arm was 10 mg as an internal reference. VALTOCO and Diastat were dosed by weight categories with subjects 51 to 75 kg of weight receiving 15 mg of diazepam and 76 to 111 kg of weight receiving 20 mg of diazepam.

Blood samples were collected for 240 hours after dosing.

Variability in $C_{\max}$ and $AUC_{0-\infty}$ was lowest with the oral Valium formulation, followed by VALTOCO, with Diastat showing the greatest variability. In all three routes of administration, the high-weight subjects showed greater variability compared to the low-weight subjects.

Compared to Diastat, intranasal administration of VALTOCO resulted in comparable $AUC_{0-\infty}$ values at the 20 mg dose but was slightly lower than Diastat at the 15 mg dose (Figure 4). The slightly lower exposure at the 15 mg dose of VALTOCO relative to Diastat was possibly due to the variability of Diastat. Overall, the exposure for Diastat and VALTOCO were similar given the high rate of variability seen following Diastat administration.

Figure 4: Mean Plasma Concentration-Time Profiles of Diazepam, 15 and 20 mg VALTOCO Nasal Spray, and 15 and 20 mg Diazepam Rectal Gel (Geometric Mean with Upper and Lower 1 Geometric Deviation)



[Redacted text block]

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1.2.1.4. Study DIAZ.001.04

Study DIAZ.001.04 was a Phase 1, open-label, PK and safety study in epilepsy subjects under ictal or peri-ictal (involving motor activity and/or altered awareness) and normal conditions (19).

Two doses of intranasal VALTOCO were administered at either 5 mg, 10 mg, 15 mg, or 20 mg based on the subject's body weight. The study consisted of a screening period, a baseline period, and a post-dose follow-up period. VALTOCO was administered during the ictal or peri-ictal period and under normal non-seizing (interictal) conditions.

Fifty-seven (57) subjects, including 11 subjects age 6 to 11 years, 6 subjects age 12 to 16 years, and 40 subjects over 16 years were enrolled as part of this study with dosing during the ictal or peri-ictal period of a seizure. Of these, 49 subjects, including 10 subjects age 6 to 11 years, 5 subjects age 12 to 16 years, and 34 subjects over 16 years completed PK assessments after dosing during the ictal period.

The PK of diazepam after intranasal administration of VALTOCO in patients suffering from epilepsy was not notably altered by their physiological condition (seizure [ictal or peri-ictal state] or non-seizure [normal state]) for any of the age groups or at any dose evaluated ([Figure 5](#), [Figure 6](#)).

[REDACTED]

The comparable AUC₀₋₆ and C_{max} values among the three doses indicated that the appropriate dose was used for the subject's body weight.

Figure 5: Mean Plasma Concentration versus Time Profiles of Diazepam, Sorted by Condition: Linear Scale

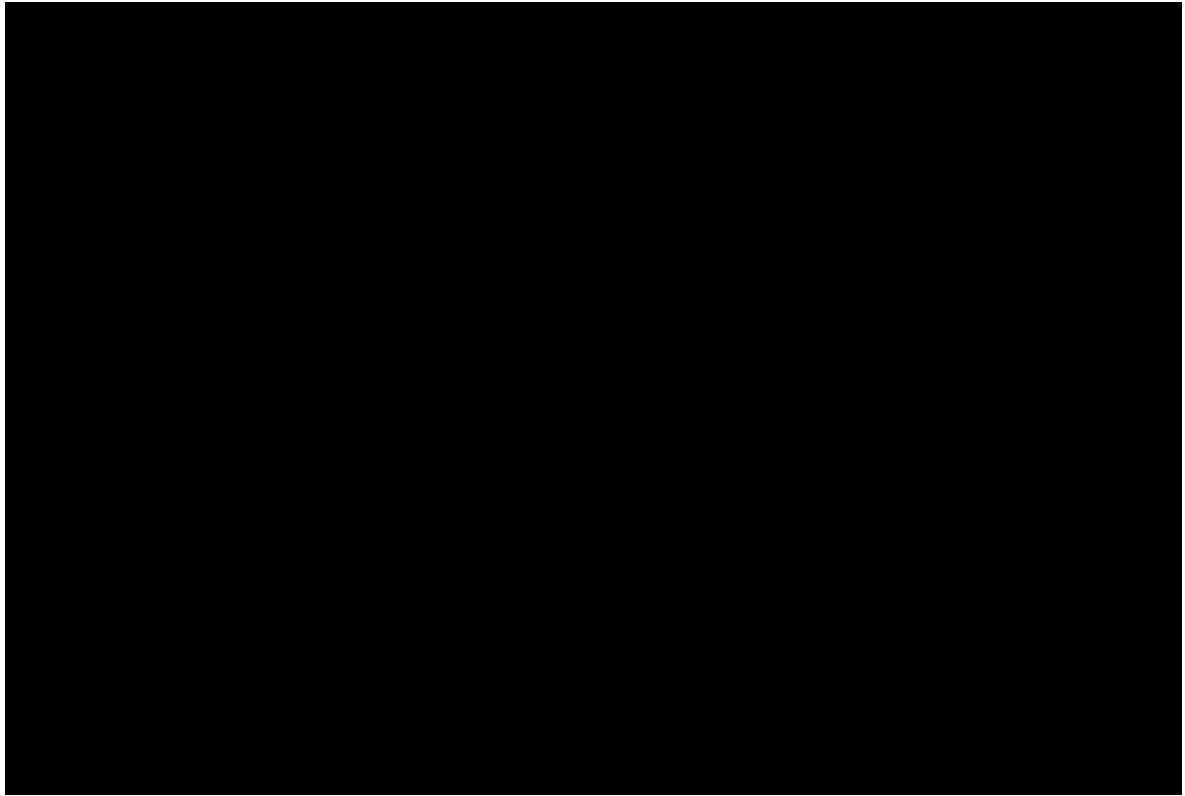


Figure 6: Mean Plasma Concentration versus Time Profiles of Diazepam by Age Group, Sorted by Condition: Linear Scale

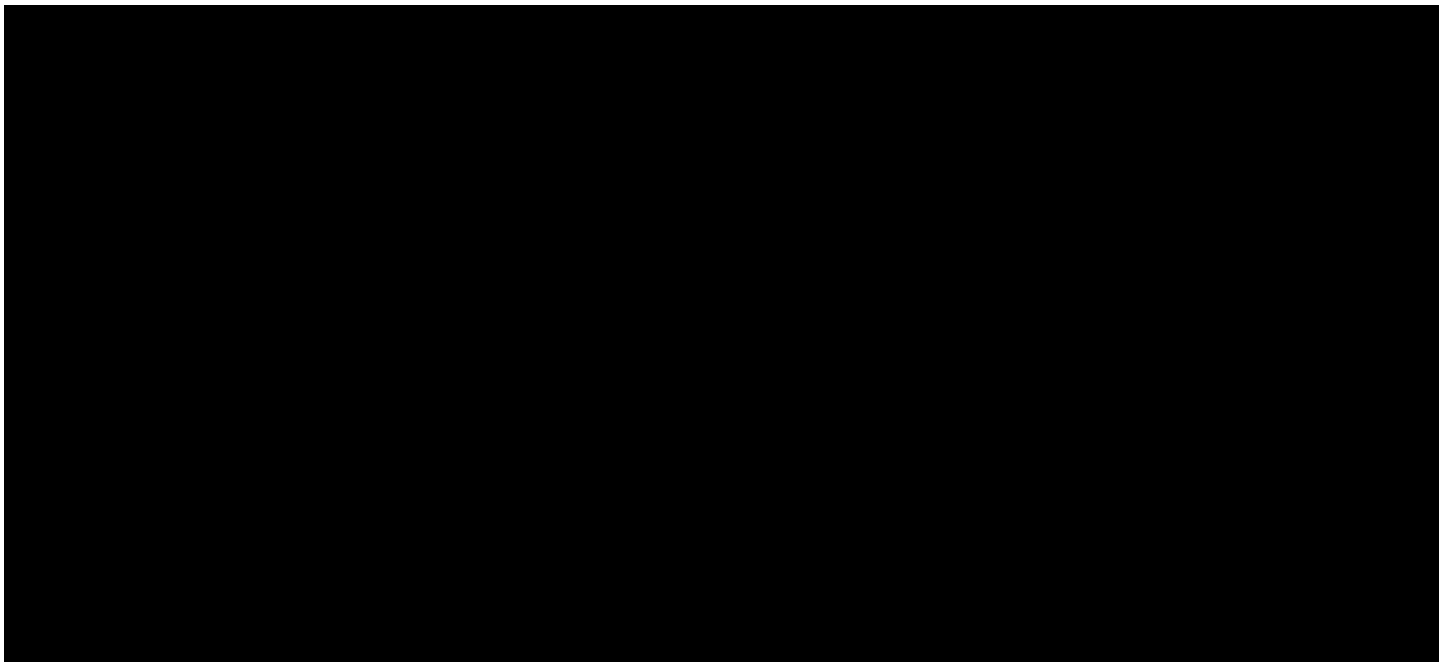


Table 2: Bioequivalence of Diazepam with Respect to C_{max} and AUC_{0-6} under Seizure and Normal Conditions for Subjects Age 6 Years and Above

Seventeen of the 58 subjects (29.3%) experienced at least one TEAE. One subject (1/58, 1.7%) had two SAEs requiring prolonged hospitalization (recurrent seizures, static encephalopathy) that were considered mild in severity and unlikely to be related to study drug. No TEAEs were considered life threatening and no deaths occurred in the study. The majority (25 of 28, 89.3%) of TEAEs were mild in severity. Dysgeusia (3 subjects, 5.2%), and seizure, nasopharyngitis, and nasal discomfort (2 subjects, 3.4%) were the most frequently reported AE occurrences.

1.1.1.1 Study DIAZ.001.05

Study DIAZ.001.05 was a Phase 3, repeat-dose, open-label, safety study in subjects with epilepsy who have frequent breakthrough seizures or ARS. The primary objective of this study was to assess the safety of VALTOCO in the intended patient population after repeated intranasal doses of diazepam over a 1-year period. The study consisted of a screening period, a baseline period, a 12-month treatment period and a follow up period.

One hundred seventy-five (175) subjects were enrolled, of which 163 received at least one dose of VALTOCO and were included in the safety population. Fifty-three (53) of the enrolled subjects were between the ages of 6 and 11 years old, of which 45 received at least one dose of VALTOCO. One hundred and twenty-two (122) of the enrolled were ≥ 12 years old and 118 of these subjects received at least one dose of VALTOCO and were included in the safety population.

There was a total of 4015 seizure episodes treated with VALTOCO in 163 subjects. Overall, 134 of 163 subjects (82.2%) had at least one adverse event of which 30 subjects (18.4%) had AEs that were considered treatment-related as determined by the Investigator. Of the 134 subjects, 50 subjects (30.7%) had AEs that were considered serious. A total of 120 SAEs were reported.

None of the SAEs were determined to be treatment-related. One (1) death (sudden, unexplained death) was reported during the study and was determined to be unrelated to study treatment by the Investigator. This subject died of Sudden Unexplained Death in Epilepsy on 23July2019; the last recorded administration of study drug was on 06April2019. One (1) SAE (major depression) resulted in the discontinuation from the study.

The treatment-related events were nasal discomfort (10 subjects, 6.1%); headache (4 subjects, 2.5%); epistaxis, dysgeusia, and somnolence (3 subjects each, 1.8%); cough, rhinalgia, rhinorrhoea, migraine, eye irritation, lacrimation increased, and fatigue (2 subjects each, 1.2%); and nasal mucosal disorder, nasal pruritus, rash, throat irritation, tonsillar hypertrophy, lethargy, loss of consciousness, sensory integrative dysfunction, ocular hyperemia, nausea, retching, insomnia, sleep disorder, and administration site pain (1 subject each, 0.6%). It is worth noting that there were no respiratory depression adverse events.

[REDACTED]

Overall, the results from the Phase 3 safety study demonstrated that VALTOCO is safe and well tolerated in subjects with epilepsy who have frequent breakthrough seizures. Overall, 49 subjects (30.1%) experienced TEAEs that were considered mild, 53 subjects (32.5%) experienced TEAEs that were considered moderate, and 31 subjects (19.0%) experienced TEAEs that were considered severe in severity and no SAEs were attributable to VALTOCO.

1.2.2. VALTOCO FDA Approved Label

See [Appendix D](#).

1.2.3. Pharmacokinetics and Product Metabolism in Humans

Oral Administration:

[REDACTED]

In young healthy males, the volume of distribution at steady-state is 0.8 to 1.0 L/kg. The decline in the plasma concentration-time profile after oral administration is biphasic. The initial

distribution phase has a half-life of approximately one hour, although it may range up to 3-hours (3).

Intravenous Administration:

[REDACTED]



Rectal Administration:

[REDACTED]



Intranasal Administration:

Several clinical studies with intranasal formulations of diazepam have been reported in the literature. Generally, absolute bioavailability of these formulations was low (approximately 50%) and have been conducted in both healthy volunteers and patients with similar outcomes.

Gizurarson *et al.* administered a 2 mg dose of a 20 mg/mL diazepam solution dissolved in 5% glycofurol in polyethylene glycol 200. The mean bioavailability was $50.4 \pm 23.3\%$ with a time to peak concentration of 18 ± 11 minutes (21).

Lindhardt *et al.* evaluated an intranasal formulation of diazepam with doses of 4 mg and 7 mg in polyethylene glycol 300 in seven healthy volunteers as compared to a 5 mg IV dose. The intranasal formulations had relative bioavailability of 45% and 42%, $C_{\max}$ of 99 ng/mL and 179 ng/mL and $t_{\max}$ of 18 and 42 minutes for the 4 mg and 7 mg doses, respectively (22).

Ivaturi *et al.* conducted a study of the bioavailability and tolerability of intranasal diazepam in healthy volunteers. They compared 5 mg and 10 mg intranasal diazepam doses of their investigational formulation with a 5 mg dose of diazepam solution administered intravenously. Following the 5 mg and 10 mg doses, the median $t_{\max}$ were 20 and 30 minutes respectively and the mean $C_{\max}$ were 134.3 ± 62 ng/mL and 247.6 ± 61 ng/mL. Estimated bioavailability was 75% for both doses. In the same study, a group of subjects was evaluated to compare 5 mg of diazepam and 5 mg of midazolam with intranasal and IV routes of administration. Intranasal diazepam was rapidly absorbed, with a $t_{\max}$ of 28.8 ± 20.96 minutes. $C_{\max}$ was 179.2 ± 8.85 ng/mL and the half-life was 22.4 ± 3.45 hours (23).

The results of the DIAZ.001.01 study with VALTOCO are provided in [Section 1.2.1](#).

In a relative bioavailability study in healthy adult subjects, diazepam exposure ($C_{\max}$ and AUCs) was evaluated following administration of 15 mg and 20 mg of VALTOCO nasal spray and diazepam rectal gel. The diazepam PK parameters were 2 to 4-fold less variable for VALTOCO and within the range of those seen with diazepam rectal gel.

Intranasal Use of Intravail in Human Subjects:

Intravail A3 is being evaluated in human clinical trials. As of September 2014, Intravail A3 has been used in: (i) eight intranasal human programs with a total of 13 human studies; and (ii) three human oral programs with a total of five human studies. These human studies have been conducted in the US and India and have included more than 280 subjects with over 3,500 aggregate doses. Each study has been a single dose study with the exception of one 7 day study with 24 subjects and one six-week study with 75 subjects. No clinically relevant AEs have been observed to date that were attributable to Intravail A3.

In three (3) completed and one ongoing clinical studies conducted outside the US with an undisclosed active pharmaceutical ingredient, 84 normal subjects have been exposed to 1 to 3 single 100 µL intranasal doses of Intravail A3 at concentrations of 0.1-0.2%. Two hundred

thirty-eight (238) AEs have been reported with 237 being mild and of a nature expected with the active drug. One SAE (pancreatitis) was reported during the study, but the subject had not received the reference product containing Intravail A3.

The current toxicology and clinical studies with Intravail A3 show no evidence of any concerning or non-reversible findings at the dose levels anticipated to be used in humans.

In 2007 alkylpolyglycosides, the class of compounds, which includes Intravail A3, were the subject of a GRAS Exemption Claim submitted to the FDA (24). The subject of this claim was the use of alkylpolyglycosides as “surfactants for use in the cleaning of food products, the cleaning of equipment used to process food, the manufacture of products that come in contact with food, fruits and vegetables including meat and poultry carcasses, the cleaning of materials that subsequently come in contact with food, paper, cardboard, plastic or stainless steel lines and/or production vessels, and the cleaning and sanitizing of surfaces in food preparation areas.”

In the response to the GRAS Exemption Claim (24), the FDA (Office of Food Additive Safety, Center for Food Safety and Applied Nutrition) had no questions with respect to the conclusion reached by the Applicant, stating that: “Based on the information provided by Cognis, as well as other information available to the FDA, the agency has no questions at this time regarding Cognis' conclusion that alkylpolyglycosides are GRAS under the intended conditions of use.” The Agency noted that it has not, however, made its own determination regarding the GRAS status of the subject use of alkylpolyglycosides. Nonetheless, alkylpolyglycosides and Intravail A3 are commonly regarded as GRAS (25).

In September 2005, the US EPA determined that there is a reasonable certainty of no harm from aggregate exposure to residues of C10-C16-alkyl glycosides and that establishing an exemption from the requirement of a tolerance for C10-C16-alkyl glycosides will be safe for the general population including infants and children (26).

1.3. Study Rationale

The effectiveness of diazepam rectal gel has been established in two adequate and well-controlled clinical studies in children and adults exhibiting seizure patterns consistent with ARS. The efficacy of VALTOCO is based on the relative bioavailability of VALTOCO nasal spray compared to diazepam rectal gel in healthy adults. Diazepam rectal gel is indicated for selected, refractory patients with epilepsy on stable regimens of ASDs who require intermittent use of diazepam to control bouts of increased seizure activity, i.e., ARS in patients 2 years of age and older. For patients between the ages of 2 and 5 years, an approximate dosage of 0.5 mg/kg of diazepam rectal gel is indicated with low risk of adverse events.

VALTOCO was approved by the US FDA in 2020 for marketing in patients with epilepsy 6 years of age and older. This study will provide information on the PK, safety and tolerability (including local tolerability) of VALTOCO in the 2 to 5 years old pediatric epilepsy population.

2. STUDY OBJECTIVES

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to assess the PK of diazepam after a single intranasal dose of VALTOCO administered to subjects with epilepsy 2 to 5 years of age. The primary PK variables to determine bioavailability will be $C_{\max}$ and the area under the curve through 6 hours ($AUC_{(0-6)}$).

2.1.2. Secondary Objectives

The secondary objectives of this study include:

- To assess the safety and tolerability of diazepam after intranasal administration of VALTOCO in the subject population.
- To assess the long-term safety and tolerability of diazepam after repeated exposure to intranasal administration of VALTOCO in the subject population.

2.2. Description of Study Design

This is a Phase 1/2a, open-label, single-dose, PK study of VALTOCO with a 180 day open-label safety period in pediatric subjects with epilepsy age 2 to 5 years. A single 5 mg, 10 mg or 15 mg dose of intranasal VALTOCO will be administered based on the subject's body weight in a clinical setting followed by PK sampling. All doses will be administered by a trained medical professional as per the Instructions for Use for VALTOCO. Appropriate entertainment is allowed to help the subject remain relaxed and distracted during study procedures. The study consists of a screening period, a baseline period, single-dose period, an open-label safety period, a follow-up phone call, and an optional extension period.

At the screening visit and after signing informed consent, each subject will be assigned a screening number. in the format xx-yyy, where xx represents the site number (e.g., 01 for site #1), and yyy represents the subject screening number, which will increase sequentially at each site (e.g., 001, 002).

At the baseline visit and after all pre-dose assessments are completed, the system will automatically assign to each qualified subject a 'subject ID' in the format xx-yyy-z, where xx is the site number, yyy (e.g., 001, 002) represents the subject number and z=1, 2 or 3 represents the blood sampling sequence as listed below. The system will automatically rotate the sequence numbers as subjects are sequentially enrolled across all sites.

A total of six (6) blood samples for PK evaluation will be collected from each subject at specific times depending on sequence:

- [REDACTED]

- [REDACTED]
- [REDACTED]

A range of ± 5 minutes will be allowed for time points from 15 to 60 minutes and ± 10 minutes for time points from 75 to 360 minutes. For all blood samples the actual time of collection will be recorded and entered into the electronic case report form (eCRF).

In the single-dose period, VALTOCO will be administered during an interictal period to subjects with epilepsy 2 to 5 years of age. The pre-dose PK blood sample will be collected at baseline after all pre-dose safety assessments are completed. Once the pre-dose PK sample has been collected, a single dose of VALTOCO will be administered and the PK collection will continue for up to 6 hours after dosing to determine the diazepam plasma concentration versus time profile.

The process will continue until at least 30 PK subjects have completed the single-dose period with at least one post-dose PK sample collected. The sponsor has the option to enroll additional subjects if any do not complete the full 360 minutes of PK sampling.

Subjects who discontinue for any reason prior to dosing and/or obtaining at least 120 minutes of blood samples for PK assessment may be replaced at the discretion of the Sponsor. If a subject discontinues after dosing but prior to completing the PK assessment, they may continue in the open-label safety portion of the study.

If the subject experiences a seizure during the blood sampling period, PK blood draws will be suspended as long as required for the subject's medical care and should resume when clinically feasible according to the Investigator, provided that the subject is not treated with any other diazepam containing product. If the subject experiences a seizure after VALTOCO dosing and is administered an exclusionary medication (such as IV, oral or rectal diazepam), PK blood draws will be stopped, time of dosing diazepam will be recorded, and the Medical Monitor will be notified. All other safety procedures will be performed as per the protocol Schedule of Study Procedures.

Subjects may be discharged after the 6-hour post-dose assessments are complete provided that there are no clinically meaningful signs of sedation. For the open-label safety portion of this study, subjects will be supplied with VALTOCO to use as rescue medication as needed for frequent breakthrough seizures or ARS (as per the VALTOCO prescribing information). Subjects and caregivers will be provided an electronic diary on their own device to record any usage of VALTOCO for seizures including, but not limited to, the date of use, time of seizure onset, time of dosing, and time of seizure resolution ([Appendix F](#)). Up to two reminder messages will be sent to the caregiver if the electronic diary is not completed daily.

Subjects will return to the site on Day 30 (± 4 days) and Day 90 (± 4 days) for safety evaluations and to be provided with additional supply of study medication, and on Day 180 (± 4 days) for

safety evaluations. A phone call will be conducted on Day 60, Day 120, and Day 150 (± 4 days) to determine if any AEs have occurred and to follow-up on any ongoing AEs. In addition, any concomitant medications taken during this time will be collected.

[REDACTED]

Seven days (± 4 days) after the last study visit, a follow-up phone call will be conducted to determine if any AEs have occurred and to follow-up on any AEs ongoing since last communication with the subject. In addition, any ongoing or new concomitant medications taken during this time will be collected.

Safety assessments include: AEs, physical examination, vital signs, laboratory examinations, and nasal irritation assessments. Site personnel will be trained on the conduct of nasal irritation assessments based on a standardized scale ([Appendix G](#)). Additional assessments including the seizure severity questionnaire ([Appendix H](#)) and caregiver assessment ([Appendix I](#)) will also be conducted at clinic visits by trained study personnel.

All study drugs received, dispensed, and returned must be accounted for in the study Drug Accountability Log.

2.3. Study Endpoints

2.3.1. Primary Endpoint

The primary endpoint of this study is to characterize the PK of diazepam after a single intranasal dose of VALTOCO administered to subjects with epilepsy 2 to 5 years of age.

2.3.2. Secondary Endpoints

The secondary endpoints in this study include:

- Assessment of the safety and tolerability of diazepam after a single intranasal administration of VALTOCO in the subject population.
- Assessment of the long-term safety and tolerability of diazepam after repeated exposure to intranasal administration of VALTOCO in the subject population.

2.3.3. Randomization/Assignment to Study Drug

There are no randomization/assignments to study drug as this is an open-label study.

2.4. Study Drug

2.4.1. Test Product

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.4.2. Dose and Dose Justification

The dose of 5 mg, 10 mg, or 15 mg of VALTOCO in this study will be selected according to the subject's weight (rounded to the nearest kg) based on the following:

For Children Age 2-5 Years (0.5 mg/kg based on Diastat label):

- 6 kg to 11 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.
- 12 kg to 22 kg body weight will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.
- 23 kg to 33 kg body weight will receive a 15 mg dose (75 mg/mL, 2 x 100 µL) administered as two 7.5 mg sprays with one spray in each nostril (the left nostril will be sprayed first followed by the right nostril).

2.4.3. Pharmacokinetic Plasma Sampling

Blood samples (3 mL) will be collected in this study to measure diazepam plasma concentrations following a single dose of intranasal VALTOCO.

At the Baseline visit pre-dose and following the completion of the safety assessments, a PK sample will be collected prior to the administration of the single dose of VALTOCO®.

Following the pre-dose PK sample collection, a single dose of VALTOCO will be administered during an interictal period. Five blood samples for PK will be collected at baseline post-dose at additional timepoints based on the subject's assigned sequence schedule. Samples will be collected for up to 6 hours following the initial time of dosing of VALTOCO to determine the diazepam plasma concentration versus time profile.

A total of six (6) blood samples (3 mL each) for PK evaluation will be collected from each subject at specific times depending on the blood sampling sequence number assigned:

- [REDACTED]
- [REDACTED]
- [REDACTED]

A range of ± 5 minutes will be allowed for time points from 15 to 60 minutes and ± 10 minutes for time points from 75 to 360 minutes. For all blood samples the actual time of collection will be recorded and entered into the eCRF.

The diazepam concentrations in the single-dose period will be analyzed using model-independent methods to calculate PK parameters such as $C_{\max}$, $t_{\max}$, and $AUC_{(0-6)}$. Other PK parameters may be calculated, if needed. PK parameters will be determined using actual times of sample collection relative to the administration of VALTOCO.

Concentrations below the limit of quantitation (BLQ) before the first quantifiable concentration will be assigned a value of zero; other BLQ concentrations at any other time points will be reported as missing.

2.4.4. Bioanalytical Method

Plasma samples will be evaluated by a validated LC/MS/MS method capable of detecting diazepam.

2.5. Concomitant Medications

2.5.1. Prior and Concomitant Medications

Prior medications are defined as medications that were taken within 30 days prior to initial dosing with study drug.

Concomitant medications are defined as medications taken any time after the start of dosing until the discharge.

2.5.2. Restricted Concomitant Medications

Treatment with any known strong or moderate inhibitors or inducers of metabolizing enzymes (e.g., CYP-P450 enzymes or MAO), including herbal medicine, within fourteen (14) days prior to the first dose of VALTOCO, or during the study, is prohibited without approval from the Medical Monitor.

2.6. Procedures for Monitoring Subject Compliance

Subjects will be in the Clinical Research Unit or equivalent (i.e., Epilepsy Monitoring Unit [EMU]) for the single dosing of study drug and PK sampling and may be discharged after the 6-

hour post-dose assessments are complete provided that there are no clinically meaningful signs of sedation.

3. STUDY POPULATION

The study population will be subjects between the age of 2 to 5 years with a clinical diagnosis of epilepsy who, in the opinion of the Investigator, may need a benzodiazepine intervention for seizure control and have used rescue medication at least once in the past three months.

3.1 Inclusion Criteria

Subjects must meet **ALL** of the following Inclusion criteria to be enrolled in this study:

1. Male or female subjects between the ages of 2 and 5 years, inclusive, at time of enrollment.
2. Written informed consent by legal guardian to participate in the study.
3. Subject has a clinical diagnosis of epilepsy and, in the opinion of the Investigator, may need benzodiazepine intervention for seizure control.
4. Subjects having either partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness, for which rescue medications have been used at least once in the last 3 months or in the opinion of the Investigator, may need a benzodiazepine intervention for seizure control 1 – 2 times every 3 months on average.
5. In the opinion of the Investigator, no clinically significant abnormal findings that could impact the subject safety or the validity of study results in the medical history, on the physical examination, ECG (corrected QT interval [QTcF] < 440 msec), or in clinical laboratory results during screening including baseline (pre-dose visit) or within past 30 days of screening visit.
6. Caregivers must agree to comply with all required study procedures.

3.2 Exclusion Criteria

Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment:

1. Subjects whose body weight are < 6 kg or > 33 kg.
2. Subject is undergoing intracranial electroencephalogram (EEG) monitoring.
3. In the opinion of the Investigator, a history of clinically significant medical history that would jeopardize the safety of the subject or impact the validity of the study results (such as significant gastrointestinal, renal, nasal polyps or any nasal passage abnormality that could interfere with nasal spray administration).
4. Subject has had significant traumatic injury, major surgery or open biopsy within 30 days prior to study screening.
5. Subjects who donated blood or plasma within 30 days of the first dose of study drug.

6. Participation in a clinical trial within 30 days prior to the first dose of study drug. Participation in an observational (non-interventional) study is not excluded as long as there are no scheduling conflicts with this study.
7. Inadequate or difficult venous access that may jeopardize the quality or timing of the PK samples.
8. Changes to the dose of phenobarbital or primidone within 30 days of the anticipated dosing visit (i.e., baseline). Adjustments to the dose of phenobarbital or primidone are permitted after PK collection is complete.
9. Treatment with warfarin or dabigatran or other blood thinners within 30 days of the anticipated dosing visit (i.e., baseline).
10. Treatment with any diazepam containing products within 14 days of the anticipated dosing (i.e., baseline).
11. Use of nasal decongestants or nasal steroids within 7 days prior to the screening visit or the baseline PK visit.

3.3 Other Restrictions

1. Treatment with any known strong or moderate inhibitors or inducers of metabolizing enzymes (e.g., CYP-P450 enzymes or MAO), including herbal medicine, within fourteen (14) days prior to the first dose of VALTOCO, or during the study, is prohibited without approval from the Medical Monitor.

3.4 Stopping or Suspending the Study

If the trial is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

In addition, if the Investigator or the Sponsor terminates or suspends a trial,

- the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the Institutional Review Board/Ethics Committee (IRB/IEC) (and the Sponsor, if applicable) and should provide the Sponsor and/or the IRB/IEC a detailed written explanation of the termination or suspension.
- the Sponsor should promptly inform the Investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension.

4. SAFETY ASSESSMENTS

4.1 Collection of Adverse Events Data

Data regarding TEAEs will be collected in this study. TEAEs are events that are not present at baseline, or if present at baseline, have worsened in severity. AE collection will begin after baseline assessments are complete, following treatment with VALTOCO, and continue until the follow-up telephone contact is conducted 7 days after the final study visit.

Any AE reported by the subject or noted by the Investigator or his/her designee will be recorded on the eCRF regardless of the Investigator opinion of causality. The following information will be recorded for each AE: description of the event, date and time of onset, date and time of resolution, severity, causal relationship to study drug, outcome, action taken with the study drug and any treatment given.

All clinically significant abnormal changes from baseline in physical examination findings, vital signs, ECGs, and laboratory evaluations will be collected, graded with regards to severity or clinical significance, assessed for causal relationship and recorded on the eCRF.

4.2 Clinical Laboratory Evaluations

Screening evaluations must be performed during screening including baseline pre-dose visit or within past 30 days of screening visit. Screening procedures are performed only once prior to the first dose of study medication.

Subjects with clinically significant abnormal laboratory values during the study will be monitored until the value is no longer considered clinically significant or no further change is anticipated. All abnormal changes from baseline in laboratory values will be collected, graded with regards to severity, assessed with regards to causality and recorded in the eCRF to be reported as abnormal laboratory findings. Only clinically significant abnormal laboratory findings associated with clinical sequelae or that require therapeutic intervention are considered AEs. All clinical laboratory analyses will be performed at the clinical site and the results will be recorded on the appropriate eCRF. Clinical laboratory reports must be reviewed, signed, and dated by the Investigator. The Investigator will assess each abnormal test result for clinical significance and the result of the evaluation will be recorded on the eCRF.

4.2.1. Hematology

Complete blood cell count (CBC) will include red blood cell (RBC), RBC morphology, reticulocyte count, hemoglobin, hematocrit, white blood cell (WBC) with differential, and platelet count.

4.2.2. Serum Chemistry

Comprehensive metabolic panel will include serum alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, calcium, phosphorus, chloride, sodium, potassium, blood urea nitrogen (BUN), creatinine, total bilirubin, albumin, total protein, amylase, bicarbonate/carbon dioxide (CO₂), uric acid, and lactate dehydrogenase (LDH).

4.2.3. Urinalysis

Urinalysis will include appearance, color, pH, specific gravity, glucose, protein, ketones, blood, creatinine clearance, and a detailed microscopic analysis. Microscopic analysis will be performed regardless of macroscopic results and will include the following: WBC, RBC, cast/type, crystal/type, and bacteria. Standard urinalysis will be conducted on the same day as blood chemistry.

4.2.4. Other Blood Tests

The presence of HIV antibody, Hepatitis B surface antigen (HbSAg), and Hepatitis C antibody will be assessed at screening.

If the subject is positive for HIV, Hepatitis B or Hepatitis C or if the caregiver refuses to have the subject take the test for these screenings, the subject cannot be enrolled in the study.

4.3. Physical Examinations and Medical History

4.3.1. Physical Examinations

The Investigator or designee will perform a complete physical examination, at screening and a targeted physical examination at baseline pre-dose and post-dose, and at Day 30, Day 90, and Day 180 visits. For subjects who continue on treatment in the optional Extension Period, targeted physical examinations will be performed at each study visit conducted every 90 days. Results will be recorded on the appropriate page of the eCRF.

4.3.2. Medical History

A medical history will be obtained at screening. Medical history will include demographic data (age, sex, race/ethnicity, etc.). In addition, seizure history will be obtained. The number of rescue medications used per month for the previous three (3) months will be reported on the eCRF. The average number of seizures over the last three (3) months will be used as the baseline.

4.4. ECG

A standard supine (after resting for at least 5 minutes) 12-lead ECG will be performed in triplicate by the trained study staff at screening and baseline.

ECGs will be assessed by the Investigator or a cardiologist, and a comparison to baseline ECGs will be performed. The ECG report must be reviewed, signed, and dated by the Investigator or cardiologist. The original ECG results will be kept on file at the site as source documentation.

4.5. Height and Weight

Height will be measured in centimeters at screening, baseline and the Day 30, Day 90, and Day 180 visits. Body weight will be measured in kilograms at screening, baseline and the Day 30, Day 90, and Day 180 visits. For subjects who continue on treatment in the optional Extension Period, body weight will be measured at each study visit conducted every 90 days. Height and weight will be recorded on the eCRF.

4.6. Vital Signs

Vital signs (temperature, pulse, respiratory rate, and blood pressure) are to be obtained at screening, baseline (just prior to dosing), and at 30 (± 5 min) minutes, 1 (± 10 min), 2 (± 10 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, upon discharge from the Clinical Research Site or equivalent (i.e., EMU), and at the Day 30, Day 90, and Day 180 visits. For subject who continue on treatment in the optional Extension Period, vital signs will be obtained at each study visit conducted every 90 days. Vital signs will be recorded on the eCRF.

4.7. Nasal Irritation Assessments

Objective evaluations of nasal irritation will be assessed by a trained observer after administration of the intranasal formulation. Nasal irritation will also be evaluated prior to administration of VALTOCO (baseline) and at 2 (± 15 min), 4 (± 30 min), and 6 (± 30 min) hours post dose, and at discharge.

Nasal irritation evaluations will also be assessed at the Day 30, Day 90 and Day 180 visits. For subjects who continue on treatment in the optional Extension Period, evaluations will be assessed at each study visit conducted every 90 days.

4.8. Subject Diary

Subjects and caregivers will be provided an electronic diary on their own device to record any usage of VALTOCO for seizures including, but not limited to, the date of use, time of seizure onset, time of dosing, and time of seizure resolution ([Appendix F](#)). Up to two reminder messages will be sent to the caregiver if the electronic diary is not completed daily.

4.9. Caregiver Assessment

A Caregiver Assessment to obtain information about the caregiver's worries and daily activities as the main caregiver for the subject will be collected. The assessment will also be conducted at clinic visits by trained study personnel ([Appendix I](#)).

4.10. Seizure Severity Questionnaire

A Seizure Severity Questionnaire to obtain the most common type of seizure that the subject has had during the past 4 weeks will be collected. The questionnaire will be conducted at clinic visits by trained study personnel ([Appendix H](#)).

5. PHARMACOKINETICS

Blood samples (3 mL each) will be collected in this study to measure diazepam plasma concentrations following the initial intranasal administration of VALTOCO in the single-dose period during the interictal state.

At the Baseline pre-dose visit and following the completion of the safety assessments, a PK sample will be collected prior to the administration of the single dose of VALTOCO®.

Following the pre-dose PK sample collection, a single dose of VALTOCO will be administered during an interictal period. Five (5) additional blood samples for PK will be collected at additional timepoints based on the subject's assigned sequence and continue for up to 6 hours after the time of dosing to determine the diazepam plasma concentration versus time profile.

A total of six (6) blood samples (3 mL each) for PK evaluation will be collected from each subject at specific times depending on the blood sampling sequence number assigned:

- [REDACTED]
- [REDACTED]
- [REDACTED]

A range of ± 5 minutes will be allowed for time points from 15 to 60 minutes and ± 10 minutes for time points from 75 to 360 minutes. For all blood samples the actual time of collection will be recorded and entered into the eCRF.

The diazepam concentrations in the single-dose period will be analyzed using model-independent methods to calculate PK parameters such as $C_{\max}$, $t_{\max}$, and $AUC_{(0-6)}$. Other PK parameters may be calculated, if needed. PK parameters will be determined using actual times of sample collection relative to the administration of VALTOCO.

BLQ concentrations before the first quantifiable concentration will be assigned a value of zero; other BLQ concentrations at any other time points will be reported as missing.

Plasma samples will be analyzed for diazepam plasma concentration by a validated LC/MS/MS method capable of detecting diazepam.

6. EFFICACY

No efficacy measures will be assessed during this study.

7. STUDY VISITS

Refer to [Appendix A](#) for the Schedule of Study Procedures.

Within a period of 21 days before dosing, all screening tests establishing subject eligibility will be performed

In addition to the legal guardian signing the Informed Consent Form (ICF) and the subject meeting the protocol-specified entrance criteria, eligible subjects and their caregivers must agree to return to the study site for all study visits, including the confinement periods. The study schedule will be provided in writing for the subject's legal guardian's review and signature acknowledging agreement.

7.1. Screening

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant and legal guardian. The potential participant and legal guardian must be allowed to review the study information and to ask questions before being asked to sign the ICF. Written informed consent must be provided by the legal guardian prior to initiation of any screening evaluations or other study-related procedures. The signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

After written informed consent is obtained from the legal guardian, the subject will be assigned a screening number and will undergo the designated screening procedures listed in [Appendix A](#) within 21 days prior to study drug administration. The Investigator will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in [Section 3.0](#).

7.2. Screening Evaluations (Days -21 to -1)

After the subject's legal guardian has signed an IRB/EC approved ICF for the purpose of this study, the subject will begin the screening process. Screening evaluations may be performed up to 21 days in advance of dosing but must be completed at least one (1) day prior to dosing.

The following study evaluations and procedures are required to determine eligibility:

- Medical history, seizure history, demographics, prior medications including rescue medication use, and concomitant medications.
- Complete physical examination, height and weight measurements.
- Vital signs consisting of temperature, pulse, respiratory rate, and blood pressure.

- Blood and serum samples for the following laboratory evaluations:
 - Hematology
 - Serum chemistry
 - HIV antibody
 - Hepatitis screening
- Urinalysis
- 12-lead ECG (in triplicate)

7.3. Baseline Evaluations (Day 1, pre-dose)

Following the screening visit, subjects determined to be eligible for participation in the study will undergo baseline assessments after admission to the clinical site on Day 1.

Baseline assessments include the following:

- Any restricted concomitant medications
- Targeted physical examination including height and weight
- Vital signs consisting of temperature, pulse, respiratory rate, and blood pressure
- Blood and serum samples for the following laboratory evaluations:
 - PK
- 12-lead ECG (in triplicate)
- Nasal irritation assessment
- Diary to record seizure (if any) and VALTOCO administration
- Seizure severity questionnaire
- Caregiver assessment

7.4. Drug Administration

Subjects will be admitted during the morning hours to a clinical research facility or equivalent (i.e., EMU). In the single-dose period, VALTOCO will be administered during an interictal period to epilepsy subjects age 2 to 5 years. The dose of 5 mg, 10 mg, or 15 mg of VALTOCO will be selected according to the subject's weight (rounded to the nearest kg) based on the following:

For Children Age 2-5 Years (0.5 mg/kg based on the Diastat label):

- 6 kg to 11 kg body weight will receive a 5 mg dose (50 mg/mL, 100 µL) administered as one spray in the left nostril.

- 12 kg to 22 kg body weight will receive a 10 mg dose (100 mg/mL, 100 µL) administered as one spray in the left nostril.
- 23 kg to 33 kg body weight will receive a 15 mg dose (75 mg/mL, 2 x 100 µL) administered as two 7.5 mg sprays with one spray in each nostril (the left nostril will be sprayed first followed by the right nostril).

After a single administration of VALTOCO, PK sampling will be collected to determine the diazepam plasma concentration versus time profile.

If the subject experiences a seizure during the blood sampling period, PK blood draws will be suspended as long as required for the subject's medical care and should resume when clinically feasible according to the Investigator, provided that the subject is not treated with any other diazepam containing product. If the subject experiences a seizure after VALTOCO dosing and is administered an exclusionary medication (such as IV, oral or rectal diazepam), PK blood draws will be stopped, time of dosing diazepam will be recorded, and the Medical Monitor will be notified. All other safety procedures will be performed as per the protocol Schedule of Study Procedures.

Study site personnel are responsible for administering all study drugs. The calendar date and 24-hour clock time of all doses will be recorded on the eCRF.

7.5. Collection of Blood Samples

Blood samples (3 mL) for the measurement of plasma concentrations of diazepam will be collected in blood collection tubes (e.g., Vacutainers[®]) containing K₂-ethylenediaminetetraacetic acid (EDTA) [1 x 6 mL].

Following the pre-dose PK sample and single dose administration, five (5) additional blood samples (3 mL each) for PK evaluation will be collected from each subject at specific times depending on the blood sampling sequence number assigned:

- [REDACTED]
- [REDACTED]
- [REDACTED]

A range of ± 5 minutes will be allowed for time points from 15 to 60 minutes and ± 10 minutes for time points from 75 to 360 minutes. For all blood samples the actual time of collection will be recorded and entered into the eCRF.

The calendar date and 24-hour clock time of all blood samples will be recorded on the eCRF. The clock used for recording sample and procedure times should be the same as that used for dosing.

Blood samples will be stored on ice prior to processing, which will begin within 60 minutes of collection. Plasma will be separated by centrifugation (e.g., 3000 rpm x 10 minutes at 0°C to approximately 4°C) and equal aliquots transferred to two (2) clearly labeled tubes and stored in a freezer at approximately -20°C. Temperature excursions will be allowed as per the current standard operating procedure (SOP) at the clinic or laboratory.

Samples will be packed in Styrofoam shipping containers with a sufficient amount of dry ice to maintain frozen conditions for at least 72 hours (3 days). The address for the sample shipment is described in [Appendix E](#).

The remaining aliquots will be sent to the analytical laboratory after the site receives written confirmation that the originals have been received and inventoried.

7.6. Day 1 (Post-dose)

Post-dose assessments include the following (Refer to [Appendix A](#) for the timing of each assessment):

- Targeted physical examination
- Vital signs consisting of temperature, pulse, respiratory rate, and blood pressure
- Blood samples for PK
- Nasal irritation assessment
- Concomitant medications
- AEs
- Diary to record seizure (if any) and VALTOCO administration

7.7. Day 1 (Discharge)

Subjects may be discharged after the 6-hour post-dose assessments are complete provided that there are no clinically meaningful signs of sedation. The following assessments will be completed prior to discharge:

- Vital signs consisting of temperature, pulse, respiratory rate, and blood pressure
- Concomitant medications
- AEs

7.8. Day 2 to Day 180 (Open Label Safety Period)

For the open-label safety portion of this study, subjects will be supplied with VALTOCO to use as rescue medication as needed for frequent breakthrough seizures or ARS (as per VALTOCO prescribing information). A second dose may be administered as needed 4-12 hours after the initial dose of VALTOCO. Additionally, the dosage may be increased or decreased for efficacy

or safety reasons, if determined by the Investigator that a different dose is needed and there are no safety concerns.

Subjects and caregivers will be provided an electronic diary on their own device to record any usage of VALTOCO for seizures including, but not limited to, the date of use, time of seizure onset, time of dosing, and time of seizure resolution. Up to two reminder messages will be sent to the caregiver if the electronic diary is not completed daily.

Subjects will return to the site on Day 30 ($\pm$ 4 days) and Day 90 ($\pm$ 4 days) for safety evaluations and to be provided with additional supply of study medication, and on Day 180 ($\pm$ 4 days) for safety evaluations. A phone call will be conducted on Day 60, Day 120, and Day 150 ($\pm$ 4 days) to determine if any AEs have occurred and to follow-up on any ongoing AEs.

The following assessments will be completed at the Day 30, Day 90, and Day 180 ($\pm$ 4 days) visits:

- Vital signs consisting of temperature, pulse, respiratory rate, and blood pressure
- Targeted physical examination including height and weight
- Concomitant medications
- AEs
- Nasal irritation assessments
- Diary to record seizures and VALTOCO administration
- Drug accountability log
- Seizure severity questionnaire
- Caregiver assessment

The following assessments will be completed at the Day 180 ($\pm$ 4 days) visit:

- Blood and serum samples for the following laboratory evaluations:
 - Hematology
 - Serum chemistry
- Urinalysis

The following assessments will be completed at the Day 60, Day 120, and Day 150 ($\pm$ 4 days) phone call:

- AEs
- Concomitant medications
- Diary to record seizures and VALTOCO administration

7.9. Follow-up Telephone Contact (7 Days After Day 180 Visit)

Follow-up phone calls will be conducted 7 days (± 4 days) after the Day 180 visit for subjects not continuing in the optional Extension Period to determine if any AEs have occurred and to follow-up on any AEs ongoing since last communication with the subject. In addition, any concomitant medications taken during this time will be collected.

7.10.

[REDACTED]

The following assessments will be completed at each study visit conducted every 90 days (± 4 days):

- Vital signs consisting of temperature, pulse, respiratory rate, and blood pressure
- Targeted physical examination including height and weight
- Concomitant medications
- AEs
- Nasal irritation assessments
- Diary to record seizures and VALTOCO administration
- Drug accountability log
- Seizure severity questionnaire
- Caregiver assessment

7.11. Follow-up Telephone Contact (7 Days After Final Study Visit in Optional Extension Period)

Follow-up phone calls will be conducted 7 days (± 4 days) after the final study visit for subjects continuing in the optional Extension Period to determine if any AEs have occurred and to follow-up on any AEs ongoing since last communication with the subject. In addition, any concomitant medications taken during this time will be collected.

7.12. Termination Procedures

At early termination, all subjects will be contacted by phone calls approximately 7 days after the final dose of VALTOCO. In the event a caregiver wishes to prematurely discontinue from the study, every effort will be made to bring the subject to the research facility for the final visit (Day 180 procedures), where all safety and seizure assessments can be completed. At this visit, the caregiver will return any unused kits of study drug to the site for drug accountability. If the subject or caregiver is unwilling to return to the facility, a phone call will be made by the study coordinator to assess any adverse events and concomitant medications since the last visit. In addition, the site can send a prepaid and addressed box where the caregiver can return used and unused study drug kits to the research facility.

8. PREMATURE DISCONTINUATION FROM STUDY

A premature discontinuation from the study will occur when a subject whose legal guardian provided signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria before receiving first dose of study drug has been administered
- Death
- Significant safety event that in the opinion of the Investigator warrants discontinuation
- Lost to follow-up after every attempt has been made to contact the subject's caregiver/legal guardian, including sending a registered letter
- Subject/caregiver withdraws consent
- Protocol deviation

The Principal Investigator (PI) and the IRB/EC reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons.

Subjects will be followed for one-week after the administration of the last dose of study drug for early termination (Termination Procedures).

9. PRODUCT SPECIFICATIONS

9.1. Description

Diazepam, illustrated in [Figure 1](#), is a benzodiazepine anticonvulsant with the chemical name; 7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepin-2-one. It is a white or almost white crystalline compound, insoluble in water. The empirical formula is C₁₆H₁₃ClN₂O and the molecular weight is 284.75.

VALTOCO is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, ARS) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.

VALTOCO is manufactured under current Good Manufacturing Practices (cGMP) at a contract manufacturing facility.

9.2. Formulation, Packaging, and Labeling

VALTOCO will be supplied for this study as a dose of 5 mg, 10 mg, or 15 mg per application.

[REDACTED]

Each sprayer unit of VALTOCO study drug will be affixed with a single label panel containing the following information:

[REDACTED]

9.3. Receipt, Storage, and Stability of Study Drug

VALTOCO will be packaged in a glass vial with a rubber stopper, which is assembled with the commercially available UDS, and then placed in boxes. Excursions are permitted to 15- 30 °C (59°F to 86 °F), and after receipt should be stored at 15 - 25 °C (59 °F-77°F) [see USP Controlled Room Temperature] until use.

VALTOCO is a Schedule IV controlled drug substance and should be kept under appropriate controlled storage conditions to avoid access to persons who are not authorized to prescribe or use VALTOCO.

9.4. Preparation of Study Drug

VALTOCO is supplied as a solution for intranasal administration. There is no manipulation or preparation of study drug required. VALTOCO will be dispensed to study staff responsible for administration to study subjects and reconciliation will occur after dosing.

9.5. Administration of Study Drug

VALTOCO is for intranasal use only.

No device assembly is required. VALTOCO is a ready-to-use nasal spray device. VALTOCO nasal spray delivers its entire contents upon activation. Do not prime or attempt to use for more than one administration per device.

9.6. Ordering and Distribution of Study Drug

[REDACTED]

9.7. Accountability of Study Drug

All study drugs received, dispensed, and returned must be accounted for in the study drug Dispensing Log, including:

- Subject number and initials
- Date study drug was dispensed
- Quantity of study drug dispensed
- Quantity of study drug returned

All study drugs received and dispensed by the Investigator or pharmacist will be inventoried and accounted for throughout the study. Caregivers should bring unused study drug supply to each visit to confirm use of study drug with entries in the diary and to determine additional drug supply to be dispensed. The study drugs must be stored in a restricted area with limited access. Contents of the study drug containers must not be combined.

The Investigator or pharmacist must maintain an accurate, up to date Dispensing Log for all study drugs supplied by the Sponsor. Study drugs dispensed for all subjects must be recorded on the Drug Accountability Form. The study drug Dispensing Log and remaining drug inventory will be reviewed at each monitoring visit by the Sponsor-designated clinical monitor.

The study drugs supplied for this study are for use only in subjects properly consented and enrolled into this protocol. Study drugs must be kept in a secure location physically separated from standard clinic or office drug supplies.

9.8. Study Drug Product Complaints

For any study drug product complaints or device errors, the site should write a description of the complaint or error in an email and send to [REDACTED]. The description should include as much detail as available regarding the complaint/error including date, dose, and type of complaint or error. The email should be signed by the Study Coordinator or the Investigator.

If available, the device should be brought back to the site so that it may be returned to Sharp Clinical Services, Inc. Instructions and a shipping label to send the device back to Sharp will be provided to the site upon request.

10. SAFETY MONITORING AND ADVERSE EVENTS

10.1. Adverse Events

Data regarding TEAEs will be collected in this study. TEAEs are events that are not present at baseline, or if present at baseline, have worsened in severity.

Definition of Adverse Events and Adverse Drug Reactions:

AEs in the eCRF will be classified according to the most recent FDA definitions and in a manner consistent with International Conference on Harmonization (ICH) guidelines. As such the following definitions will be used:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the “Adverse Event” case report form only if it is associated with clinical sequelae or requires therapeutic intervention.

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 ([Appendix B](#)).

The reporting period for AEs starts after baseline assessments are complete, following treatment with VALTOCO, on Day 1 and ends when the follow-up telephone contact is completed 7 days after the Day 180 final visit. For subjects that continue on in the optional Extension Period, the reporting period for AEs will continue up to the final study visit.

If an AE remains unresolved at the telephone contact 7 days after the final study visit, the subject will be followed, at the Investigator’s discretion, until resolution of the event. SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period.

Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The Investigator will assess AEs for severity, relationship to IP, and as to whether the event meets one or more of the definitions of an SAE. The assessments will be recorded on the source documents and AE eCRF, using the categories defined below.

Causality Category	Description
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an “Adverse Event”.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol, an event that has possible relationship to study medication will be defined as a “Suspected Adverse Drug Reaction”.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. For the purpose of this protocol, an event that has probable relationship to study medication will be defined as an “Adverse Drug Reaction”.

In order to classify adverse events and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered on the eCRF, using MedDRA.

For those AEs that are not described on the CTCAE v 5.0, such AEs will be graded on a 5-point scale (mild, moderate, severe, life-threatening, and death) and reported as indicated on the eCRF. Intensity of such an AE is defined as follows:

Table 3: Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 5.0)

CTCAE Grade	Common Term	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

CTCAE Grade	Common Term	Description
4	Life-Threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Death related to AE.

10.2. Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events

Hospitalization admissions scheduled prior to the study are not considered SAEs unless the hospitalization is prolonged due to an AE. Hospitalizations for scheduled treatment of a preexisting condition that has not worsened, and hospitalization for fewer than 24 hours and emergency room/department visits do not meet the category of “New or prolonged hospitalization”.

10.2.1. Reporting Requirements for Serious Adverse Events

All SAEs must be reported to the Sponsor by the Investigator, study coordinator, other designated study personnel, or clinical research associate within 24 hours of notification of the SAE. To report such events, an SAE eCRF in the electronic data capture (EDC) system and an SAE report in the eSafety Module must be completed by the Investigator, study coordinator, or other designated study personnel, then an SAE report with relevant information will be sent to Medical Monitor or its designee for review.

Within the 48 hours following the initial SAE report, the Investigator must provide further information on the SAE in the eSafety Module which will assist in the understanding of the event. Significant new information on ongoing SAEs should be provided promptly as a follow-up.

The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution.

10.2.2. Recording of Serious Adverse Events

The eSafety EDC Module will be used for reporting, reviewing, follow up and tracking of SAEs. Information including, but not limited to, site number, subject basic information, SAE information (SAE term, CTCAE grade, serious criterion, action taken, outcome, causality), study treatment, relevant medical information, narrative and medical assessment will be recorded in the eSafety Module.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size

Approximately 30 male or female subjects age 2 to 5 years with a clinical diagnosis of epilepsy who, in the opinion of the Investigator, may need a benzodiazepine for seizure control and are frequent rescue medication users will be enrolled.

11.2. Statistical Analysis

Individual subject diazepam plasma concentrations, actual sampling times, and PK parameters will be listed by analyte and treatment. Descriptive statistics will be calculated by analyte and treatment for plasma concentrations and PK parameters. Individual subject and mean plasma concentrations will be displayed on linear and semi-logarithmic axes.

C_{max} , t_{max} , and $AUC_{(0-6)}$ will be determined and normalized to the 10 mg dose prior to analysis. Confidence intervals (CI) (90%) will be constructed for the GMR of the two parameters (C_{max} and $AUC_{(0-6)}$) between the two treatments using the log-transformed data.

In addition, plasma concentration data from this study will be fitted to a previously developed population model for diazepam PK after administration of VALTOCO in children (6-12 years) and adult subjects using NONMEM software (V 7.3, Icon Ltd). The relationship between diazepam PK parameters and age will be evaluated. Additional covariates that may explain variability in exposure may be investigated in this analysis. Exposure parameters in the 2-5 years population will be compared to exposure with other pediatric age groups and in adults, if feasible. Details about these analyses will be described in a separate population PK analysis plan, and the results from this analysis will be reported elsewhere.

11.3. Pharmacokinetic Data Analyses

The diazepam concentrations in the single-dose period will be analyzed using model-independent methods to calculate PK parameters such as C_{max} , t_{max} , and $AUC_{(0-6)}$. Other PK parameters may be calculated, if needed. PK parameters will be determined using actual times of sample collection relative to administration of VALTOCO.

BLQ concentrations before the first quantifiable concentration will be assigned a value of zero; other BLQ concentrations at any other time points will be reported as missing.

PK calculations will be performed using appropriate software, e.g., Phoenix™ WinNonlin® (Version 6.3 or higher, Pharsight Corporation) and/or SAS® (Version 9.4 or higher, SAS Institute Inc.). PK parameters will be summarized by age group and dose using descriptive statistics.

A nonlinear mixed-effects model will then be used to model the drug concentration-time profiles and PK parameters will be estimated using Phoenix 8.1 (Certara) or NONMEM v 7.3 (Non-Linear Mixed Effects Modeling Software, Icon Ltd). A first-order absorption, two-compartmental structural PK model will be used and modified if necessary.

11.4. Safety

Safety Population: subjects who took at least one dose of study drug.

Safety data will be summarized and descriptive statistics will be provided for actual values and change from baseline values for physical examination, vital signs, and clinical laboratory tests (serum chemistry, hematology, and urinalysis).

The incidence and severity of TEAEs reported during the study and their relationship to study drug will be tabulated. TEAEs will be coded using the MedDRA and will be presented by body system.

The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort.

Nasal Irritation Assessments:

Objective evaluations of nasal irritation will be assessed by a trained observer after administration of the intranasal formulation. Nasal irritation will also be evaluated prior to administration of VALTOCO (baseline) and at 2 ($\pm$ 15 min), 4 ($\pm$ 30 min), and 6 ($\pm$ 30 min) hours post dose, and at discharge.

See [Appendix G](#) for the Nasal Irritation Assessment Form

Nasal irritation evaluations will also be assessed at the Day 30, Day 90 and Day 180 visits. For subjects who continue on treatment in the optional Extension Period, nasal irritation evaluations will be assessed at each study visit conducted every 90 days.

12. DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

12.1. Data Collection and Reporting

A eCRF will be completed for each subject who receives at least one dose of study drug. All entries on the eCRF must be supported by original source documentation (e.g., laboratory

reports, medical records) maintained at the investigational site.

The Investigator will make all safety assessments (AEs, clinical laboratory tests, ECGs, vital signs, and results from physical examinations) on an ongoing basis. The Investigator is required to review all entries on the eCRF and sign at appropriate time intervals.

12.2. Study Monitoring

All aspects of the study will be monitored carefully by the Sponsor's designees with respect to cGMP and SOPs for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including eCRFs, source documents, etc., for review and inspection by the clinical monitor.

All eCRFs will be verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject using a risk-based approach. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of eCRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

12.3. Data Disclosure and Subject Confidentiality

Subject medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the subject, except as necessary for monitoring by the IRB/EC, the FDA, or the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor.

13. PROTECTION OF HUMAN SUBJECTS

13.1. Basic Principles

This research will be carried out in accordance with the clinical research guidelines established by the Basic Principles defined in the US 21 Code of Federal Regulations (CFR) Parts 11, 50, 56, and 312, the principles enunciated in the Declaration of Helsinki concerning medical research in humans (“Ethical Principles for Medical Research Involving Human Subjects,” Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996), and the Good Clinical Practice (GCP) guidelines of the ICH of the Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH E6 (May 1996).

13.2. Institutional Review Board/Ethics Committee

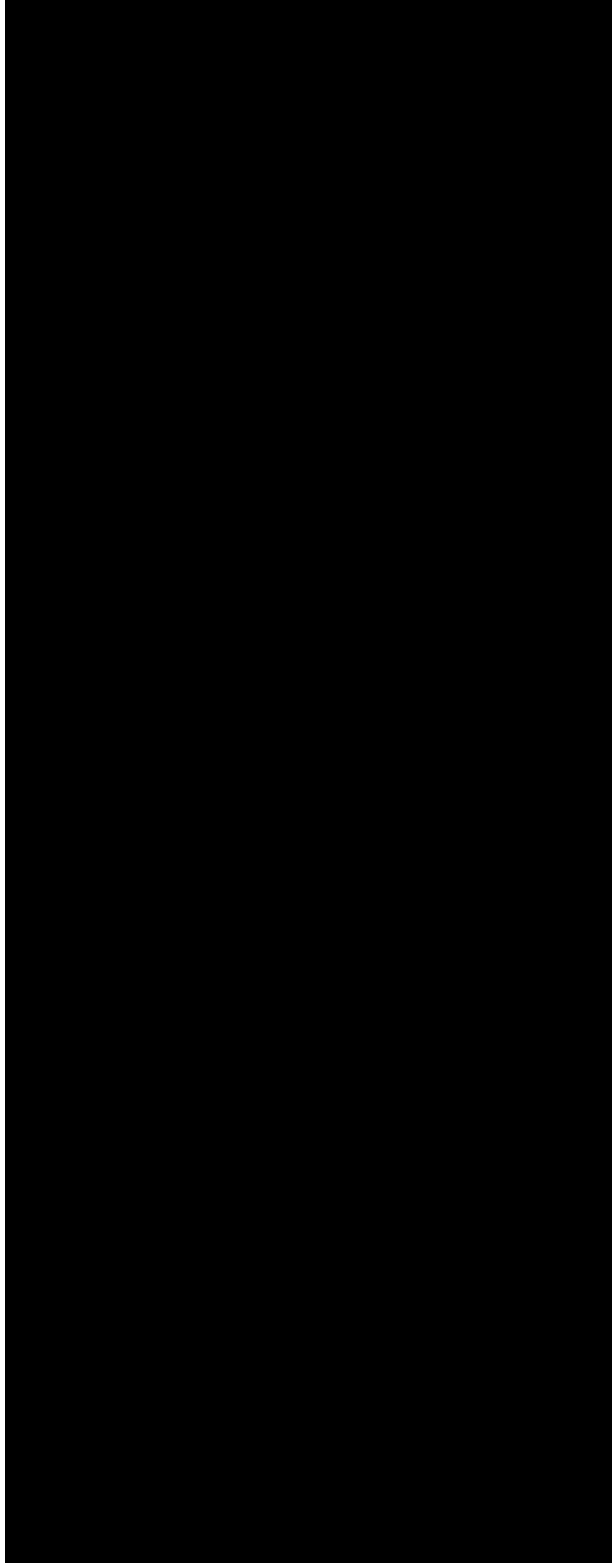
The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the ICF. The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56.

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[illegible]



APPENDIX B: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

APPENDIX C: List of Prohibited Medication

Amiodarone	Ketoconazole
Amprenavir	Lopinavir/Ritonavir
Aprepitant	Methoxsalen
Atazanavir	Mexiletine
Boceprevir	Mibefradil
Bupropion	Miconazole
Cinacalcet	Moclobemide
Ciprofloxacin	Nefazodone
Clarithromycin	Nelfinavir
Conivaptan	Omeprazole
Darunavir/Ritonavir	Oxandrolone
Diltiazem	Paroxetine
Duloxetine	Phenylpropanolamine
Enoxacin	Posaconazole
Erythromycin	Quinidine
Esomeprazole	Ritonavir
Fluconazole	Saquinavir
Fluoxetine	Telaprevir
Fluvoxamine	Telithromycin
Fosamprenavir	Terbinafine
Gemfibrozil	Thiabendazole
Grapefruit Juice	Ticlopidine
Imatinib	Verapamil
Indinavir	Voriconazole
Itraconazole	Zileuton

APPENDIX D: VALTOCO FDA Approved Label

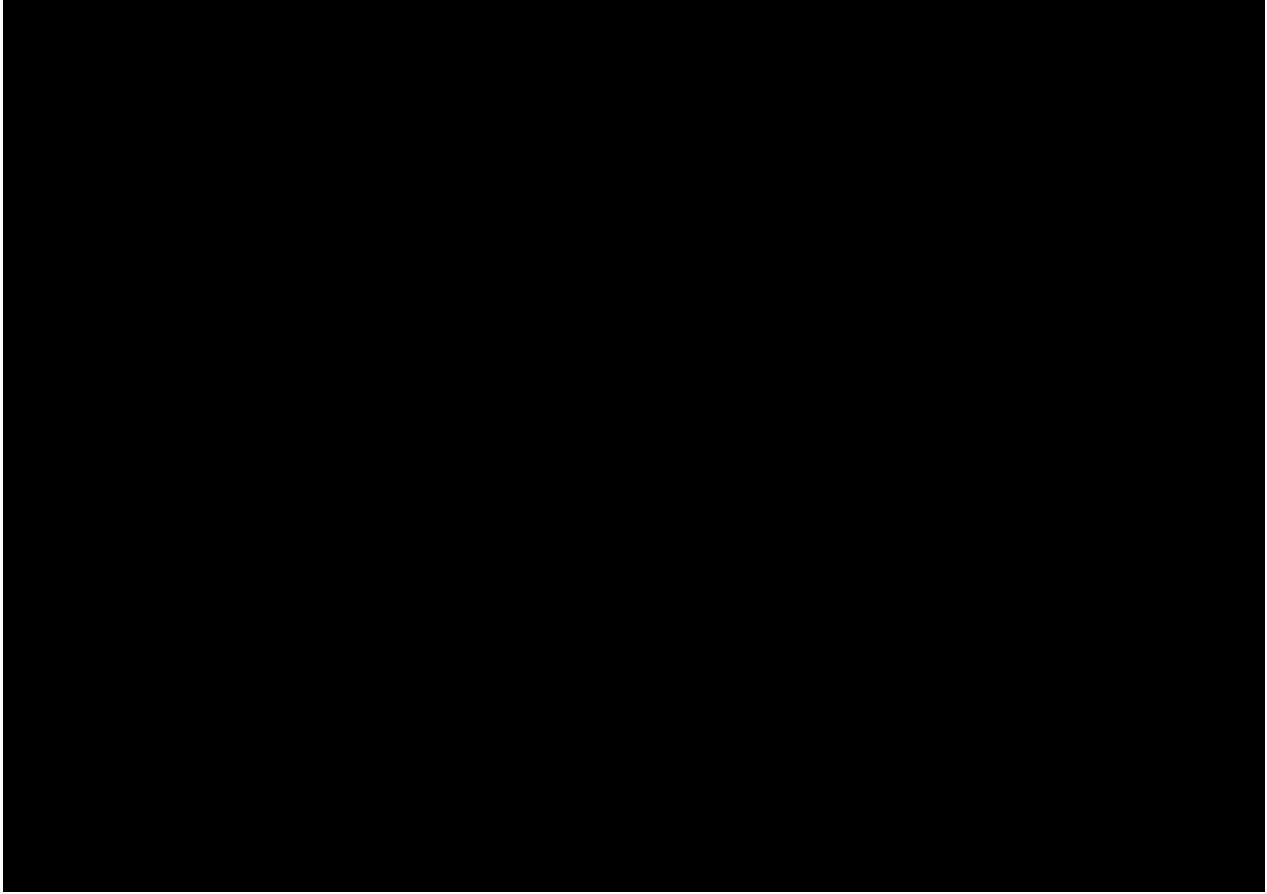
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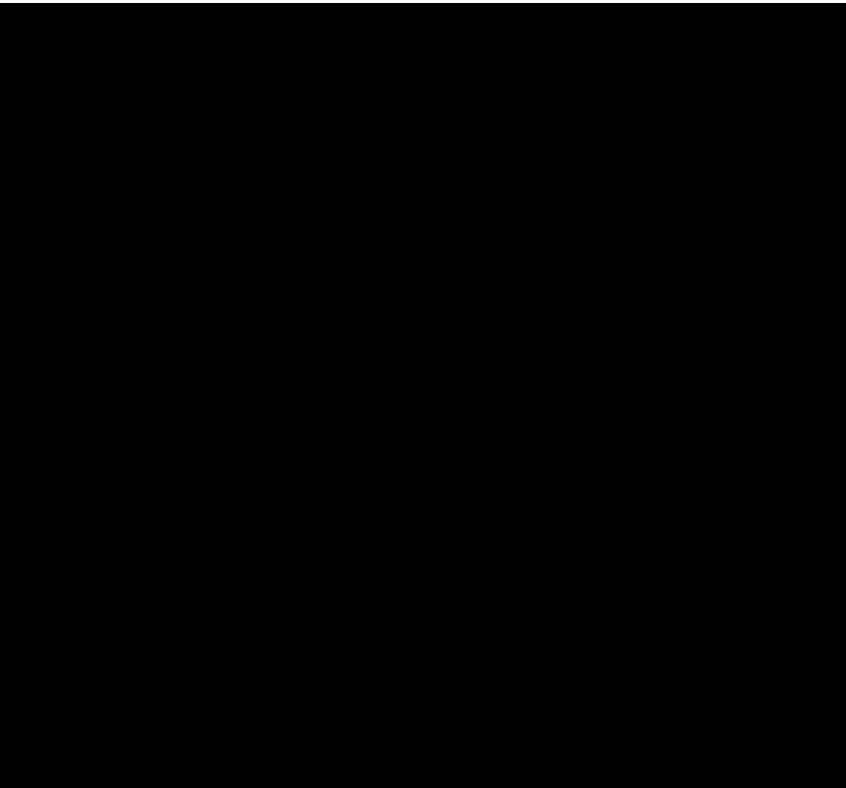
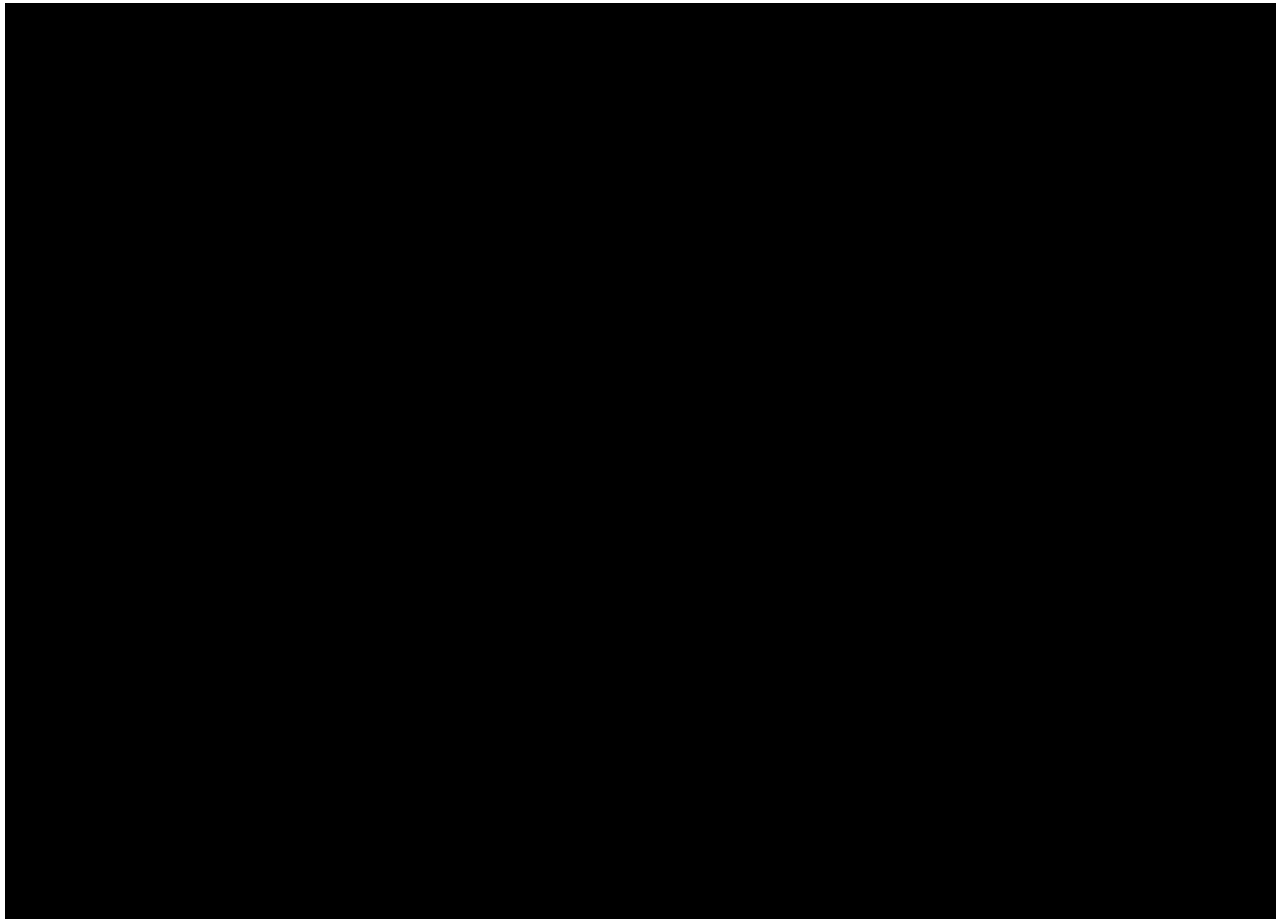
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APPENDIX E: Address for the Sample Shipment

One aliquot of each sample will be sent by courier to:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]







APPENDIX H: Seizure Severity Questionnaire

Baseline Questionnaire

SEIZURE SEVERITY QUESTIONNAIRE – Baseline			
Date	Patient Name	Patient No.	Page 1 of 4

Please describe the **MOST COMMON TYPE OF SEIZURE** that you have had in the past 4 weeks. Include information from observers. _____

Consider only this type of seizure when answering questions.

(To be completed by the doctor)

Seizure Classification Subtype (International Classification code): SPS ____ CPS ____ GTC ____

When answering the following questions, please mark or circle the number that best describes your feelings about each topic. For example, "Somewhat helpful", "Same", "Moderate"

BEFORE Seizures

1. Warning

A. Did you have a **warning** (aura) **BEFORE** this type of seizure (smell, feeling, sensation, etc.) in the past 4 weeks?

Yes No [If no, skip to question 2]

1A. If "yes", was the warning (aura) **HELPFUL**; for example, did it allow you to prepare for the seizure?

1 2 3 4 5 6 7
very helpful somewhat helpful no help

DURING Seizures

2. Did you have **movements or actions** **DURING** this type of seizure in the past 4 weeks (such as automatic movements, uncontrollable actions, falling, injury, tongue biting, wetting pants with urine, etc.)?

Yes No [If no, skip to question 3]

2A. If yes, how **SEVERE (INTENSE)** were the movements or actions overall?

1 2 3 4 5 6 7
very mild moderate very severe

2B. How **BOTHERSOME** (interfere with your life) were the movements or actions overall?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

3. Did you have **ONLY altered consciousness (blank-out) or sensations** (no movements or actions) with this type of seizure in the past 4 weeks?

(Answer "yes" only if question 2 was answered "no")

Yes No [If no, skip to question 4]

3A. If yes, how **BOTHERSOME** (interfere with your life) were these periods of altered consciousness?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

Seizure Severity Questionnaire, V2.2, Baseline, © JA. Cramer 2010.

SEIZURE SEVERITY QUESTIONNAIRE – Baseline

Date	Patient Name	Patient No.	Page 2 of 4
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AFTER seizures

4. Did it take a while to recover (get back to normal) AFTER this type of seizure in the past 4 weeks?

Yes No, I recovered immediately from my seizures. [If no, skip to question 8]

5. Did you have Cognitive Effects (confusion, loss of memory or speech, walk or talk without purpose, etc.) AFTER seizures in the past 4 weeks?

Yes No [If no, skip to question 6]

5A. If yes, how OFTEN did you have Cognitive Effects AFTER seizures?

1 2 3 4 5 6 7
never sometimes always

5B. How SEVERE (INTENSE) were the Cognitive Effects AFTER seizures?

1 2 3 4 5 6 7
very mild moderate very severe

5C. How BOTHERSOME were the Cognitive Effects AFTER seizures?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

6. Did you have Emotional Effects (depression, anxiety, anger, etc.) AFTER seizures in the past 4 weeks?

☐ Yes No [If no, skip to question 7]

6A. If yes, how OFTEN did you have Emotional Effects AFTER seizures?

1 2 3 4 5 6 7
never sometimes always

6B. How SEVERE (INTENSE) were the Emotional Effects AFTER seizures?

1 2 3 4 5 6 7
very mild moderate very severe

6C. How BOTHERSOME were the Emotional Effects AFTER seizures?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

7. Did you have Physical Effects (sleepy, tired, weak, sore muscles, headache) AFTER seizures in the past 4 weeks?

☐ Yes No [If no, skip to question 8]

7A. If yes, how OFTEN did you have Physical Effects AFTER seizures?

1 2 3 4 5 6 7
never sometimes always

7B. How SEVERE (INTENSE) were the Physical Effects AFTER seizures?

1 2 3 4 5 6 7
very mild moderate very severe

7C. How BOTHERSOME were the Physical Effects AFTER seizures?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

SEIZURE SEVERITY QUESTIONNAIRE – Baseline			
Date	Patient Name	Patient No.	Page 3 of 4

SEVERITY and BOTHER Include your feeling about <u>ALL TYPES</u> of seizures you have had in the past 4 weeks.
--

8. How SEVERE (INTENSE) were your seizures overall in the past 4 weeks?

1 2 3 4 5 6 7
very mild moderate very severe

9. How BOTHERSOME (interfere with your life) were your seizures overall in the past 4 weeks?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

10. What is most bothersome about your seizures overall (mark only one):

- Warning (aura) before the seizure
- Activities during the seizure
- Recovery after the seizure

Describe:

***You have been describing the type of seizure that was most common before starting the new medication.
Thank you for answering these questions.***

Follow-Up Questionnaire

SEIZURE SEVERITY QUESTIONNAIRE – Follow-Up

Date	Patient Name	Patient No.	Page 1 of 4
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Please describe the severity and bothersomeness of the type of seizure that you had most commonly before starting the new medication. Answer the questions based on your experiences in the past 4 weeks. Include information from people who observed your seizures.

If you had NO seizures in the past 4 weeks, check here and stop:

If you now have a DIFFERENT TYPE of seizure, check here and proceed:

To be completed by the doctor: Code Seizure Classification Subtype (International Classification code):

SPS ____ CPS ____ GTC ____

When answering the following questions, please mark or circle the number that best describes your feelings about each topic. For example, "Somewhat helpful", "Same", "Moderate"

BEFORE Seizures

1. Warning

A. Did you have a warning (aura) BEFORE this type of seizure (smell, feeling, sensation, etc.) in the past 4 weeks?

Yes No [If no, skip to question 1B]

1A. If "yes", was the warning (aura) HELPFUL; for example, did it allow you to prepare for the seizure?

1 2 3 4 5 6 7
very helpful somewhat helpful no help

1B. Has there been any CHANGE in the helpfulness of the warning since starting the new medication?

0 1 2 3 4 5 6 7
more helpful same less helpful

(0=never had warning with these seizures)

DURING Seizures

2. Did you have movements or actions DURING this type of seizure in the past 4 weeks (such as automatic movements, uncontrollable actions, falling, injury, tongue biting, wetting pants with urine, etc.)?

Yes No [If no, skip to question 2C]

2A. If yes, how SEVERE (INTENSE) were the movements or actions overall?

1 2 3 4 5 6 7
very mild moderate very severe

2B. How BOTHERSOME (interfere with your life) were the movements or actions overall?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

2C. Has there been any CHANGE in the movements or actions since starting the new medication?

0 1 2 3 4 5 6 7
much milder same much stronger

(0= never had movements or actions with these seizures)

Seizure Severity Questionnaire, V2.2, Follow-up, © J.A. Cramer 2010

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3. Did you have **ONLY** altered consciousness (blank-out) or sensations (no movements or actions) with this type of seizure in the past 4 weeks?
(Answer "yes" only if question 2 was answered "no")
Yes No [If no, skip to question 3B]

3A. If yes, how **BOTHERSOME** (interfere with your life) were these periods of altered consciousness?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

3B. Has there been any **CHANGE** in these periods of altered consciousness since starting the new medication?

0 1 2 3 4 5 6 7
much milder same much stronger

(0= never had periods of altered consciousness)

AFTER seizures

4. Did it take a while to recover (get back to normal) **AFTER** this type of seizure in the past 4 weeks?
Yes No, I recovered immediately from my seizures. [If no, skip to question 8]

4A. Has there been any **CHANGE** in amount of time it takes to recover from this type of seizure since starting the new medication?

0 1 2 3 4 5 6 7
much faster same much slower

(0=never took time to recover from these seizures)

5. Did you have Cognitive Effects (confusion, loss of memory or speech, walk or talk without purpose, etc.) **AFTER** seizures in the past 4 weeks?
☐ Yes ☐ No [If no, skip to question 5D]

5A. If yes, how **OFTEN** did you have Cognitive Effects **AFTER** seizures?

1 2 3 4 5 6 7
never sometimes always

5B. How **SEVERE** (INTENSE) were the Cognitive Effects **AFTER** seizures?

1 2 3 4 5 6 7
very mild moderate very severe

5C. How **BOTHERSOME** were the Cognitive Effects **AFTER** seizures?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

5D. Has there been any **CHANGE** in Cognitive Effects since starting the new medication?

0 1 2 3 4 5 6 7
much milder same much more severe

(0=never had cognitive effects with these seizures)

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SEVERITY and BOTHER
Include your feeling about <u>ALL TYPES</u> of seizures you have had in the past 4 weeks.

8. How SEVERE (INTENSE) were your seizures overall in the past 4 weeks?

1 2 3 4 5 6 7
very mild moderate very severe

8a. Has there been any CHANGE in Seizure Severity (Intensity) since starting the new medication?

1 2 3 4 5 6 7
much milder same much more severe

9. How BOTHERSOME (interfere with your life) were your seizures overall in the past 4 weeks?

1 2 3 4 5 6 7
no bother at all moderate very bothersome

9a. Has there been any CHANGE in how bothersome your seizure have been since starting the new medication?

1 2 3 4 5 6 7
much less bother same much more bother

10. How have your seizures changed overall since starting the new medication?

1 2 3 4 5 6 7
much better same much worse

11. If there has been a change, describe what is the most important DIFFERENCE about your seizures since starting the new medication: (mark only one):

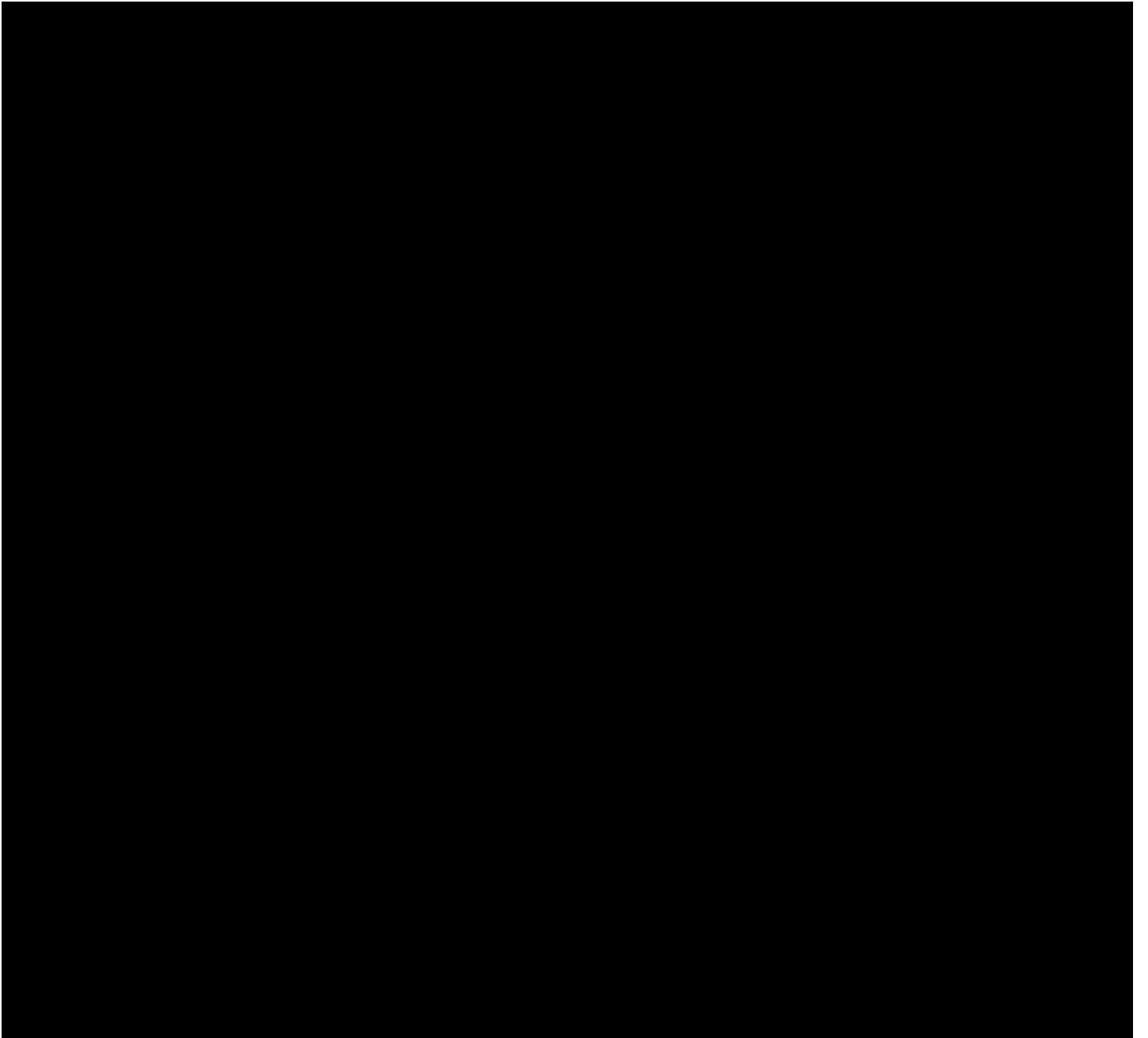
- Warning (aura) before the seizure
- Activities during the seizure
- Recovery after the seizure
- No change

Describe:

You have been describing the type of seizure that was most common before starting the new medication. Thank you for answering these questions.

APPENDIX I:

[REDACTED]



[REDACTED]

[REDACTED]

[REDACTED]

