A Double-Blind, Placebo-Controlled, Inpatient, Dose-Ranging Efficacy Study of Staccato Alprazolam (STAP-001) in Subjects with Epilepsy with a Predictable Seizure Pattern

INVESTIGATIONAL PRODUCT:	*Staccato* Alprazolam (STAP-001)
PROTOCOL NUMBER:	ENGAGE-E-001
PROTOCOL VERSION:	7.0
PROTOCOL DATE:	01 February 2019
EudraCT NUMBER:	Not Applicable
IND NUMBER:	132,755
SPONSOR NAME / ADDRESS:	Engage Therapeutics, Inc. 31 Lenox Road Summit, NJ 07901

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

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Emergency Contact Information	
	site specific phone tree to be provided

Engage SIGNATURE PAGE

PROTOCOL TITLE: A Double-Blind, Placebo-Controlled, Inpatient, Dose-Ranging Efficacy Study of *Staccato* Alprazolam (STAP-001) in Subjects with Epilepsy with a Predictable Seizure Pattern

[redacted]

Sponsor Representative Signature **dd mmm yyyy**

[redacted]

Printed Name of Sponsor Representative

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: ENGAGE-E-001

Version: 7.0

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**	

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Investigational Review Board procedures, instructions from Engage representatives, the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

1. SYNOPSIS

Name of Sponsor/Company: Engage Therapeutics, Inc.	
Name of Investigational Product: Staccato Alprazolam (STAP-001)	
Name of Active Ingredient: alprazolam (8-Chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine)	
Title of Study: A Double-Blind, Placebo-Controlled, Inpatient, Dose-Ranging Efficacy Study of Staccato Alprazolam (STAP-001) in Subjects with Epilepsy with a Predictable Seizure Pattern	
Study center(s): Approximately 50 Study Sites with access to Clinical Research Unit (CRU) or Epilepsy Monitoring Unit (EMU) in the US, Canada, Australia and Jamaica	
Studied period (years): Estimated date first subject screened: March 2018 Estimated date last subject completed: August 2019	**Phase of development:** 2b
Objectives: The primary objectives are: • To assess the efficacy of STAP-001 in treating a seizure episode • To assess the clinical feasibility and safety of the inhalation of STAP-001 in subjects during a seizure episode • To assess the sedation associated with administration of STAP-001	
Methodology: This is a multi-center, double-blind, randomized, parallel group, dose-ranging study to investigate the efficacy and clinical usability of STAP-001 in adult (18 years of age and older) subjects with epilepsy with a predictable seizure pattern. These subjects have an established diagnosis of focal or generalized epilepsy with a documented history of predictable seizure episodes as outlined in inclusion criterion #3. This is an in-patient study. The subjects will be admitted to a Clinical Research Unit (CRU) or Epilepsy Monitoring Unit (EMU) for study participation. The duration of the stay in the in-patient unit will be 2-8 days. One seizure event per subject will be treated with study medication. A treatable seizure event includes a predictable seizure episode, such that a change in the persistence of the seizure episode can be detected. The duration and timing of the seizure event and occurrence of subsequent seizures will be assessed by the Staff Caregiver(s)[1] through clinical observation and confirmed with video electroencephalogram (EEG).	

[1] Staff member(s) assigned and trained to observe the subject throughout the entire Treatment Phase and facilitate the study drug administration as appropriate. Staff Caregivers will be accountable for the study medication and each handoff will be recorded.

The study consists of two parts: Part 1 Open-Label Feasibility; Part 2 - Double-Blind. Each part is divided into four phases: Screening; Qualification prior to entering the in-patient unit; Treatment in the in-patient unit; and Post-Treatment Safety Follow-Up. Subjects will provide appropriately-obtained informed consent or will have a legally authorized representative (LAR) sign the informed consent on his or her behalf prior to completing any study-related procedures.

The Screening Visit will involve the items identified in the Schedule of Events, including Informed Consent and distribution of the seizure diary. As part of the screening process the seizure events of the subjects must be confirmed as acceptable for continuation in the study by the Epilepsy Study Consortium Review Board. Eligible subjects will enter a Qualification phase during which the subject must have at least 4 or more predictable seizure episodes in a 28-day Qualification Period with no more than one week without a predictable episode. The Qualification Period may be extended beyond 28 days up to 56 total days to provide flexibility for scheduling of the Qualification Visit and Treatment Visit. The 28 days of the seizure diary activity immediately prior to the Qualification Visit will be assessed for qualification. At the end of the Qualification Period the Medical Monitor will review the seizure diary to confirm acceptable seizure frequency and subject's advancement into the Treatment Phase. Subjects meeting the qualification criteria will enter the CRU/EMU within 7 days from the end of the Qualification Period.

Part 1 Open-Label Feasibility

The first subjects enrolled in the study will participate in an open-label feasibility evaluation. Enrollment in this phase will end when there are data from at least eight individual subjects with a treated single seizure episode in a CRU/EMU. The subjects will be enrolled in 3-8 sites, up to three subjects per site. Eligible and qualified subjects will receive a single dose of 1 mg STAP-001 at the onset of their predictable seizure episode. The subjects will undergo all study procedures and evaluations as outlined in this protocol. The feasibility data (with special emphasis on the drug administration and clinical assessment procedures) from these eight subjects will be analyzed and reviewed by the Sponsor and study team before starting the double-blind part of the study. If deemed necessary based on the feasibility data, the study protocol will be amended (for example, to change the drug administration procedure or to redefine the time frame for primary endpoint assessment), before starting the double-blind part of the study.

Part 2: Double-Blind

After admission to the in-patient unit, eligible and qualified subjects will be randomly assigned (1:1:1) to one of two doses of STAP-001 (1 mg or 2 mg) or Staccato placebo. Randomization will be stratified by the use of inducing vs non-inducing AEDs and for use of chronic daily benzodiazepines (yes or no). For each subject, a single seizure episode will be treated and assessed. Study medication will be self-administered (when feasible) or administered by a Staff Caregiver when a predictable seizure episode starts. Assessment of the seizure activity is based on clinical observation by the Staff Caregiver using a stopwatch. In addition, a video EEG will record the occurrence, start time, and duration of the seizure event. Pharmacokinetic (PK) samples will be collected 10, 30 and 60 minutes, and 2 and 6 hours after the administration of the study drug. If possible, subjects will signal when they experience a seizure event. Subject will be under video EEG surveillance throughout the Treatment Phase. The Staff Caregiver will signal the event for the video EEG recording, start the stop watch at the time of drug

administration, and mark the occurrence of the seizure event on a seizure diary. If the seizure episode does not stop within 5 minutes of the study drug administration, rescue medication other than alprazolam may be administered at the discretion of the principal investigator per the protocol of the research unit. The study exit procedures will be conducted 24 to 32 hours after the administration of study medication or when the subject discontinues from the study.

After discharge from the in-patient unit there will be a safety-follow-up phone contact 14 days (±2 days) after the subject received the study medication.

Number of subjects (planned):

Assuming a 10% drop-out/protocol violation rate, approximately 115 subjects will be randomized in the double-blind part of the study to provide approximately 35 evaluable subjects per treatment arm. Approximately 30% of the overall study population randomized in the study may be subjects being treated with chronic daily benzodiazepines as part of their epilepsy management. Approximately 9 subjects will be enrolled in the open-label feasibility part to provide 8 evaluable subjects. Approximately 50 trial sites will be recruited to conduct the study. The data base will be locked after the last subject included in the double-blind treatment period completes the study.

Diagnosis and main criteria for inclusion:

Subjects eligible for enrollment in the study must meet all of the following inclusion criteria and none of the exclusion criteria:

Inclusion Criteria:

1. Subject is able to provide, personally signed, and dated informed consent to participate in the study or will have a legally authorized representative (LAR) sign the informed consent on his or her behalf before completing any study related procedures.
2. Male or female ≥ 18 years of age.
3. Has an established diagnosis of focal or generalized epilepsy or focal and generalized epilepsy with a documented history of predictable seizure episodes that includes at least one of the following:
   - Generalized seizure episodes starting with a flurry of absence seizures or myoclonic seizures with a minimum duration of 5 minutes
   - Episodes of a prolonged focal seizure with a minimum duration of 3 minutes
   - Episodes of multiple (≥2) seizures within a 2-hour time period
4. Prior to randomization, has experienced ≥4 seizure episodes with predictable pattern during the last 4 weeks (qualification period) and no more than one week without a predictable seizure episode before entry into the in-patient unit.
5. Female participants (if of child-bearing potential and sexually active) and male participants (if sexually active with a partner of child-bearing potential) who agree to use a medically acceptable and effective birth control method throughout the study and for 1 week following the end of the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide,

intrauterine device (IUD), surgical sterilization, and progestin implant or injection. Prohibited methods include: the rhythm method, withdrawal, condoms alone, or diaphragm alone.

6. Subject is able to comply by the requirements of the protocol, particularly the requirements and specific Institution policies during the in-patient stay.

Exclusion Criteria:

1. History or diagnosis of non-epileptic seizures (e.g. metabolic or pseudo-seizures).
2. History of status epilepticus in the 6 months prior to Screening
3. Has a progressive neurological disorder such as brain tumor, demyelinating disease, or degenerative central nervous system (CNS) disease that is likely to progress in the next 3 months
4. Use of strong CYP 3A4 inhibitors; including azole antifungal agents (e.g., etoconazole, itraconazole), nefazodone, fluvoxamine, cimetidine, HIV protease inhibitors (e.g., ritonavir)
5. Has severe chronic cardio-respiratory disease
6. History of HIV-positivity.
7. Pregnant or breast-feeding.
8. Clinically significant renal or hepatic insufficiency (hepatic transaminases >2 times the upper limit of normal (ULN) or creatinine ≥ 1.5 x ULN).
9. History of acute narrow angle glaucoma, Parkinson's disease, hydrocephalus, or history of significant head trauma.
10. Subjects who use medications to treat airways disease, such as asthma or COPD or have any acute respiratory signs/symptoms (e.g., wheezing).
11. Use of any investigational drug within 30 days or 5 half-lives of the investigational drug prior to administration of study medication, whichever is longer
12. A history within the past 1 year of drug or alcohol dependence or abuse.
13. Positive urine screen for drugs of abuse at Screening (positive Cannabis/Cannabinol results are acceptable if there is a documented history of stable use for medical purposes).
14. Known allergy or hypersensitivity to alprazolam.
15. History of glaucoma.
16. Subjects who currently have an active major psychiatric disorder where changes in pharmacotherapy are needed or anticipated during the study.
17. Hypotension (systolic blood pressure ≤90 mm Hg, diastolic blood pressure ≤50 mm Hg), or hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥100 mm Hg) measured while seated at screening or baseline.
18. Significant hepatic, renal, gastroenterologic, cardiovascular (including ischemic heart disease and congestive heart failure), endocrine, neurologic or hematologic disease.

19. Subjects who, in the opinion of the Investigator, should not participate in the study for any reason, including if there is a question about the stability or capability of the subject to comply with the trial requirements.

Investigational product, dosage and mode of administration: STAP-001 is a hand-held, single-dose, single-use drug-device combination product using the *Staccato* delivery system. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free alprazolam to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration. Each product is packaged inside a sealed foil pouch. Removal of a pull-tab from the product renders it ready for use, as indicated by illumination of a green light. Successful dosing is signaled by the extinguishing of the green light.
Reference therapy, dosage and mode of administration: Matching *Staccato* Placebo (exactly same inhalation device without coated alprazolam film)
Duration of treatment: Subjects will receive a single dose of study medication.
Duration of study participation: Subjects will participate in the study for up to 12 weeks, including Screening and Follow-Up. The Screening/Qualification Phase will last no more than 63 days. After that the subjects will participate in the Treatment Phase in the in-patient unit for approximately 2-8 days. Finally, there's a safety follow-up phone contact 14 days (±2 days) after the subject received the study treatment.
Criteria for evaluation: ***Efficacy:*** The following will be assessed for every seizure episode and the 12-hour period following study medication administration: Primary endpoint: Proportion of responders in each treatment group achieving seizure activity cessation within 2 minutes after the administration of the study drug and no recurrence of seizure activity within 2 hours. Secondary endpoints: Seizure episode severity assessed by subject and/or Staff Caregiver Use of rescue medication Secondary generalization (evolution to a complex partial seizure and/or a generalized tonic-clonic seizure) Exploratory endpoints: Number of seizures during the 4, 6, and 12 hour time periods after study drug administration Time to next seizure event with start time >2 minutes after study drug administration

Pharmacokinetics:

Blood samples will be collected for plasma alprazolam concentration measurement pre-dose and at 10, 30, and 60 minutes, and 2 and 6 hours after the dosing of the study drug.

Safety:

Safety and tolerability of STAP-001 will be assessed by evaluating adverse events, vital signs, clinical laboratory and physical exams.

Sedation will also be assessed using a patient VAS.

Statistical methods:

Sample Size:

There are no studies in the literature to provide reliable estimates of active treatment or placebo response rates. A total of 115 subjects will be enrolled in the double-blind part of the study to provide approximately 35 evaluable subjects per treatment arm [105 patients with approximately 30% of the overall study population randomized in the study being subjects with chronic daily benzodiazepines as part of their epilepsy management]. Power calculations assume a 2-sided test and significance level of 0.05 with 90% power and are based on the assumption that the proportion of responders with *STAP-001* is 57% (best active) whereas the assumed placebo responder rate is 20%.

Efficacy Analyses:

The efficacy population will include all subjects who have a seizure event and receive study drug during the double-blind Treatment Period. Data will be summarized by active treatment by dose level versus placebo-treated subjects (i.e., by treatment group). Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

All statistical tests will be 2-sided with a significance value of 0.05. There will be no adjustments for multiple comparisons.

The primary efficacy analysis will be conducted following completion of the double-blind Treatment Period for the last subject. Additional details for statistical methods will be provided in the Statistical Analysis Plan.

Pharmacokinetic Analyses:

The PK population will include all patients who receive study drug and have at least one pharmacokinetic sample drawn and analyzed. Plasma concentrations will be summarized by descriptive statistics as appropriate and will be listed by patient.

Safety Analyses:

The safety population will include all subjects who receive study drug in the Treatment phase from both Part 1 and Part 2. Adverse events will be coded by system organ class (SOC) and preferred term with the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical (WHODrug-ATC) classification and preferred term. Adverse events (AEs), vital sign measurements, physical examination findings, electrocardiogram, clinical laboratory information, and concomitant medications will be tabulated and summarized by treatment and dose level. Separate tabulations will be produced for all treatment emergent AEs (TEAEs), TEAEs (by relationship to study drug), serious AEs (SAEs), discontinuations due to AEs or TEAEs, and AEs ≥ Grade 3 severity. By-subject listings will be provided for any deaths, SAEs, and AEs leading to discontinuation of treatment.

Schedule of Events

	Qualification Phase			Treatment Phase	Exit Procedures[a]	Follow-up Phone Call
	Screen Visit	Qualification Period[b]	Qualification Visit			
Procedures	**Day -35 (May extend to Day -63)**	**Day –35 to Day –8 (May extend to Day -63)**	**Day -7 to Day -1**	**Day 1 up to Day 8**		**14 ±2 days from Study Drug Administration**
Informed consent	X					
Review of inclusion/exclusion criteria	X		X	X[c]		
Medical history	X			X[c]		
Physical examination	X			X[c]	X	
Neurological examination	X			X[c]	X	
Temperature (oral)	X			X[c]		
Height	X					
Weight	X			X[c]		
Respiratory rate and heart rate	X			X	X	
Blood pressure	X			X	X	
O_2 saturation by pulse oximetry (SpO_2)				X[de]		
Seizure Episode Severity Rating Scale				X[f]		
Sedation VAS				X[g]		
Dispense and begin Seizure Diary	X			X[h]		
Seizure Diary Completion		X		X		
Seizure Diary Collection and Review			X	X		
12-Lead ECG	X			X[c]	X	
Chemistry, hematology and urinalysis	X			X[c]	X	

[a] 24 to 32 hours after the treatment administration for patients who received dosing; and at the time of exit for those who didn't seize.
[b] During the Qualification Period the subject will record their seizure activity on the seizure diary. The Qualification Period may be extended beyond 28 days up to 56 total days to provide flexibility for scheduling of the Qualification Visit and Treatment Visit. The 28 days of the seizure diary activity immediately prior to the Qualification Visit will be assessed for qualification.
[c] At Entry to CRU/EMU
[d] At timepoint 0 (+2 min), and 10 (±2 min), 30(±2 min) and 60 (±5 min) minutes, 2 (±5 min) and 6 (±5 min) hours after the dosing of the study drug.
[e] Attached at Entry into CRU/EMU
[f] At timepoint 6 (±5 min) hours after the dosing of the study drug.
[g] When multiple procedures are scheduled at the same time point, the VAS assessment should be performed first, immediately followed by the PK draw. Collected at timepoints 10 (±2 min), 30 (±2 min) and 60 (±5 min) minutes, 2 (±5 min) and 6 (±5 min) hours after the dosing of the study drug.
[h] Staff Caregiver completes the seizure diary during the Treatment Phase

	Qualification Phase			Treatment Phase	Exit Procedures[a]	Follow-up Phone Call
	Screen Visit	**Qualification Period[b]**	**Qualification Visit**			
Procedures	**Day -35 (May extend to Day -63)**	**Day –35 to Day –8 (May extend to Day -63)**	**Day -7 to Day -1**	**Day 1 up to Day 8**		**14 ±2 days from Study Drug Administration**
Urine drug screen[i]	X			X[c]		
Urine Pregnancy test **(if applicable)**	X			X[c]		
PK Sample collection				X[j]		
Device training	X			X[c]		
EEG Recording				X[ck]		
Study drug administration[l]				**X**		
Adverse event assessment[m]	X	X	X	X	X	X
Subject seizure events forms sent to Epilepsy Study Consortium Review Board	X[n]					
Completed seizure diary sent to Medical Monitor for review			X			

[i] Drug Screen needs to be negative to allow entry into the CRU/EMU and dosing of the study drug.
[j] PK sample will be collected at pre-dose (at time of admission to unit) and then at 10 (±2 min), 30 (±2 min) and 60 minutes (±5 min), 2 hours (±5 min) and 6 hours (±5 min) after the dosing of the study drug. If the PK sample is drawn outside of the timeframe, the sample will still be collected and evaluated.
[k] Video EEG Recording will be throughout the subject's stay at the CRU/EMU
[l] At the onset of the predictable seizure
[m] Adverse Events will be collected throughout the study after Informed Consent is signed and through Follow-Up
[n] Forms completed and sent to review board within 48 hours after the subject or subject's LAR signs informed consent at the Screening Visit.

Schedule of Events – Procedures in CRU/EMU

	Entry to CRU/ EMU	Treatment Day: Schedule for day of Seizure Episode only						
		Time 0	10 min	30 min	1h	2 h	6 h	24h[a]/ Exit Procedures
Medication history	X							
Review of eligibility criteria	X							
Physical Examination	X							X
Neurological Examination	X							X
Urine pregnancy test (**if applicable**)	X							
12-Lead ECG	X							X
Chemistry, hematology and urinalysis	X							X
Urine drug screen	X							
Weight	X							
Temperature (oral)	X							
Vital Signs (BP, HR, RR)	X		X[e]	X[e]	X[f]	X[f]	X[f]	X
Attach EEG electrodes	X							
Device training	X							
EEG Recording	X	----------	----------	----------	----------	----------	----------	X
Study Med administration		**X[bcd]**						
Start Stopwatch[d]		X	----------	----------	----------	----------	----------	X
Insert Indwelling Catheter for PK samples	X							
PK Sampling	X		X[e]	X[e]	X[f]	X[f]	X[f]	
Sedation VAS[g]			X[e]	X[e]	X[f]	X[f]	X[f]	
Pulse Oximetry (SpO_2)[h]		X[e]	X[e]	X[e]	X[f]	X[f]	X[f]	
Adverse Event Assessment[i]		X	----------	----------	----------	----------	----------	X
Seizure Diary	X	----------	----------	----------	----------	----------	----------	X
Seizure Episode Severity Rating Scale							X[f]	

[a] Patient can be discharged after 24 to 32 hr assessments at the discretion of the study staff
[b] Time 0 is defined as the *start* of inhalation
[c] Subjects should have minimal postural changes for the first 1.5 hours after administration of study drug
[d] at seizure episode onset
[e] ± 2 minutes
[f] ± 5 minutes
[g] When multiple procedures are scheduled at the same time point, the VAS assessment should be performed first, immediately followed by the PK draw.
[h] Attached at Entry into CRU/EMU
[i] Post treatment

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse Event
AED	Antiepileptic drug
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CRU	Clinical Research Unit
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450 3A4
DMC	Data monitoring committee
DMP	Data Management Plan
eCRF	Electronic case report form
ECG	Electrocardiogram
EEG	Electroencephalogram
FDA	Food and Drug Administration
GABA-A	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IPS	Intermittent Photic Stimulation
IRB	Institutional Review Board
IV	Intravenous
LAR	Legally authorized representative
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate (Fridericia's method)
SAE	Serious Adverse Event
SPR	Standardized Photosensitivity Range
TEAE	Treatment-emergent adverse events

ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHODrug-ATC	World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical

4. INTRODUCTION AND RATIONALE

4.1. Background Information

Staccato Alprazolam (STAP-001) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of alprazolam. STAP-001 represents a new dosage form for alprazolam.

STAP-001 is based on the proprietary *Staccato* delivery system developed by Alexza Pharmaceuticals, the product manufacturer (Section 4.2.2). STAP-001 is delivered orally to the deep lung for systemic delivery. The pharmacokinetics of STAP-001 is therefore similar to IV injections. The *Staccato* delivery system is user-friendly. Device actuation, aerosol formation, and delivery of the aerosolized drug to the deep lung are all accomplished with a single, normal breath by the subject. Achievement of peak plasma levels within minutes via a simple, user-friendly delivery system makes STAP-001 ideal for the acute treatment of seizures.

Epilepsy is a brain disorder characterized by predisposition to experience recurrent seizures. It can occur as a result of a neurological injury, a structural brain lesion, as a part of many systemic medical diseases or may be genetic in origin. When seizures are not well controlled patients might have a need for acute treatment in addition to their maintenance anti-epileptic drug (AED) or might experience seizures emergencies.

Alprazolam was selected as the drug to incorporate with *Staccato* for these acute seizures for several reasons. Benzodiazepines are the drug class of choice in treating seizure emergencies. Like the other benzodiazepines, alprazolam is an allosteric modulator at multiple GABA-A receptor subtypes, which is important since antiseizure properties are believed to be mediated by actions on different GABA-A subtypes. Second, alprazolam is potent and efficacious in various animal models of antiseizure activity (De Sarro et al, 1996; Herink 1997; Jenck et al, 1992; Ueki et al, 1981) and in one comparator study was more potent than either clonazepam or diazepam in reducing audiogenic seizures (De Sarro et al, 1996). Alprazolam's well-documented anxiolytic action could also be of benefit in calming the individual.

There are many advantages of STAP-001 for the acute treatment of seizures compared to existing therapy or products in development. Alprazolam is a potent, well-characterized and well-tolerated benzodiazepine, has rapid onset with a Tmax of 2 minutes, and the *Staccato* system delivers drugs non-invasively to the deep lung producing reliable IV-like pharmacokinetics. The breath-activated device delivers the drug while the subject simply takes a single inspiration through the mouthpiece without any other coordination needed. This drug delivery allows for self-administration and high reliability of delivery, producing rapid drug delivery and fast onset of action.

STAP-001 was assessed in the Intermittent Photic Stimulation (IPS) model in subjects with photosensitive epilepsy as a proof of concept study (Protocol AMDC 002-202) for its potential as an AED. The positive results generated in this study provided the basis and rationale for this current protocol in studying STAP-001in subjects experiencing a seizure episode. The clinical development program for STAP-001 will focus on subtypes of subjects diagnosed with focal or generalized seizure disorder in which acute treatment with a benzodiazepine for a rapid anti-seizure activity could be beneficial. STAP-001 has been shown to produce a rapid rise in alprazolam plasma levels (< 2min) and effects on EEG in subjects with photosensitive epilepsy

within 2 minutes. The clinical development program will include subjects with seizure events that include predictable seizure episodes, such that a change in the persistence of the seizure episode can be detected, including subjects with myoclonic epilepsy or absence seizures.

4.2. Study Drug Description

4.2.1. Alprazolam

Alprazolam has been approved for marketing in the United States since 1981 (Upjohn Pharmaceuticals' XANAX® Tablets). It is indicated for the management of anxiety disorder or the short-term relief of symptoms of anxiety. Alprazolam is also indicated for the treatment of panic disorder, with or without agoraphobia. Alprazolam is available as tablets in doses of up to 2 mg, extended-release tablets in doses up to 3 mg, and oral concentrate solution of 1 mg/mL, with oral doses used clinically in the range of 0.25 mg to 10 mg per day.

Since its introduction in the 1980s, alprazolam has been one of the most commonly prescribed drugs in the United States. The side effects associated with acute oral administration of alprazolam include drowsiness, light-headedness, fatigue, memory impairment, and dizziness. These side effects are usually mild and transient. Oral alprazolam does not have significant non–CNS side effects (reviewed by Verster and Volkerts, 2004). A review of the oral product, including the current product label for alprazolam tablets, is found in the Investigator's Brochure for STAP-001.

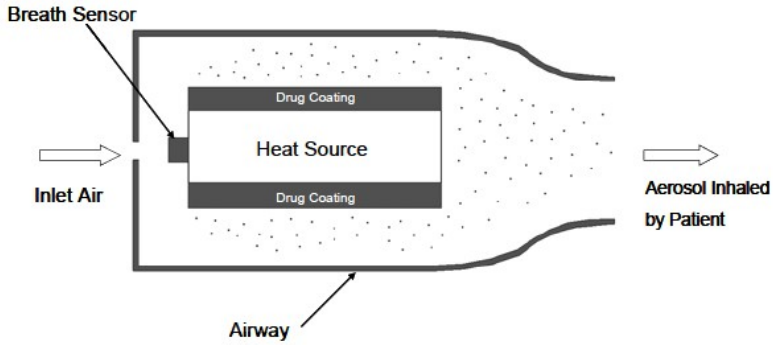
4.2.2. Staccato Alprazolam for Inhalation

STAP-001 is a hand-held, single-dose, single-use drug-device combination product using Alexza's proprietary *Staccato* delivery system. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free alprazolam to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

The principal components of STAP-001 (shown schematically in Figure 1) are as follows:

- Breath sensor: The breath-activation mechanism that initiates actuation of the heat source
- Heat source (ie, heat package): [redacted]
- Drug coating: The thin film of excipient-free alprazolam on the exterior surface of the stainless steel substrate
- Airway: The medical-grade plastic housing surrounding the heat package; it controls and directs the airflow over the vaporizing drug.

Figure 1. Schematic Side-View of Staccato Alprazolam



[redacted]

Each product is packaged inside a sealed foil pouch. Removal of a pull-tab from the product renders it ready for use, as indicated by illumination of a green light. Successful dosing is signaled by the extinguishing of the green light.

4.3. Preclinical Information for Staccato Alprazolam

For a full discussion of the preclinical data generated to date with STAP-001, please see the Investigator Brochure.

4.4. Clinical Information for Staccato Alprazolam

4.4.1. Pharmacokinetics

For a full discussion of the pharmacokinetic data generated to date with STAP-001, please see the Investigator Brochure. Of importance, in a clinical study with the current device technology, median time to maximum plasma concentration (T_{max}) after inhalation was 2 min.

4.4.2. Clinical Studies

For a full discussion of the clinical data generated to date with STAP-001, please see the Investigator Brochure. There have been 4 clinical studies conducted with STAP-001 in a total of approximately 140 subjects. Note that STAP-001 is also under evaluation for a psychiatric

indication under an open IND in the Division of Psychiatry Products and some of the studies conducted under that IND are not directly applicable to the STAP-001 epilepsy program and therefore will not be discussed below.

Relevant to this protocol, a Phase 1 clinical study in healthy volunteers evaluating pharmacokinetics and safety of STAP-001 following single doses of 0.125 mg to 2 mg (Study 002-101) and a Phase 2A trial to assess the safety, efficacy and pharmacokinetics of a single inhaled dose of STAP-001 on the IPS model in photosensitive epilepsy subjects (Study 002-202) have been conducted.

In healthy volunteers (Study 002-101), the overall percentage of subjects who experienced at least one AE during treatment was 68%. The overall percent of subjects experiencing adverse events was higher (range 50 - 100%) in the STAP-001 groups than in the placebo group (10%). Within the STAP-001 group, the incidence appeared to be dose dependent with adverse events reported in 100% subjects after the highest dose (2 mg). The most frequently reported AEs were dizziness, dysgeusia, fatigue, and somnolence. In general, the adverse events observed following STAP-001 administration were those expected based on the pharmacological activity of the compound and were similar to AEs reported after oral delivery of comparable alprazolam doses.

STAP-001 was assessed in the IPS model as a proof of concept study (Protocol AMDC 002-202) to evaluate it as a potential AED. The study was a multicenter, randomized, double-blind, crossover, placebo-controlled study in 5 subjects with a known stable photoparoxysmal response on EEG. STAP-001 0.5 mg, 1 mg, and 2 mg were compared to single doses of *Staccato* Placebo. The subjects received placebo on 2 study days, and active medication on 3 study days. During the study days, several procedures and IPS assessments were performed at 8 pre-determined times over the course of the day (1 assessment pre-dose and 7 assessments post-dose). After the screening visit, subjects returned 5 additional times and received *Staccato* Placebo (2 times) and STAP-001 0.5 mg, 1 mg, and 2 mg in random order. Visits were at least 7 days apart.

All 5 of the subjects in the study were white female adult volunteers. The subjects ranged in age from 23 to 39 years (mean, 27.2 years) and had a mean weight and body mass index (BMI) of 70.4 kg and 25.4kg/m2, respectively.

A total of 4 subjects (80.0%) experienced at least 1 treatment-emergent adverse event (TEAE) during the study. The number of subjects experiencing AEs was similar between each of the treatments, with STAP-001 2 mg (n=4) and STAP-001 1 mg (n=3) having the most subjects reporting AEs. All of the AEs reported were mild or moderate in intensity. Nervous system disorders were reported by the highest number of subjects (n=4). There were no reports of dyspnea, wheezing or bronchospasm in any of the subjects.

STAP-001 was effective in reducing the Standardized Photosensitivity Range (SPR) at the earliest measured time point (2 min) and the effect was sustained through the 4-hour time point for the 0.5 mg dose and the 6 hour time point for the 1 and 2 mg dose. A dose effect was apparent from 0.5 to 1 mg, however there was no apparent difference between the 1 and 2 mg dose on SPR.

There was a rapid and marked effect of treatment with STAP-001 relative to *Staccato* Placebo treatment on the pharmacodynamics measures of sedation and sleepiness. The magnitude of effect was greater for the 2 mg doses and less for the 0.5 mg dose at all time points. In addition, the duration of the sedation/sleepiness appears to vary by dose with the 0.5 mg dose resulting in

the shortest duration (approximately 4 hrs) and the 2 mg dose resulting in the longest duration (6 hrs or greater) relative to baseline. The 1 mg dose generally fell between the low and high dose for both magnitude and duration of sedation/sleepiness effects.

5. ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312, and the International Conference on Harmonisation (ICH) guidelines and directives. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki and applicable local regulatory requirements and law.

The Investigator is responsible for protecting the rights, safety, and welfare of subjects under his/her care, and for the control of the medications under investigation. All ethical, regulatory, and legal requirements must be met before the first subject is enrolled in the study.

5.1. Institutional Review Board (IRB)

The Institutional Review Board (IRB)/Ethics Committee (EC) will meet all FDA requirements governing IRBs according to CFR, Title 21, Part 56 and applicable country and local regulatory requirements and law. The Investigator (or designee) must submit this study protocol and any amendments, the Sponsor's approved informed consent form(s) (ICF), subject information sheets, subject recruitment materials, and other appropriate documents to the IRB/EC for review and approval. Following review of the submitted materials a copy of the written and dated approval/favorable opinion will be forwarded to the Sponsor (or designee).

Any advertisements used to recruit subjects for the study will be reviewed by the Sponsor and the IRB/EC prior to use.

5.2. Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or from the subject's legally authorized representative (LAR).

Whenever possible, investigators should attempt to obtain informed consent directly from the research participant. If this is not possible, then use of a LAR is permitted. Investigators are required to assess "obvious" incapacity. "Obviousness" would be based on three factors of capacity:

- Ability to receive and to evaluate information effectively;
- Ability to process the information according to the subject's value system; and
- Ability to make and to communicate a decision.

The ICF, as specified by the clinical site's IRB/EC, must follow the Protection of Human Subjects regulations listed in the Title 21 CRF, Part 50 and in applicable country regulatory requirements. The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary must be explained to the subject or the subject's LAR. The subject or the subject's LAR must be given sufficient time to consider whether to participate in the study.

A signed and dated copy of the ICF must be given to the subject or the subject's LAR. Confirmation of a subject's informed consent must also be documented in the subject's source

documentation prior to any testing under this protocol, including screening tests and assessments. The original signed consent form will be retained with the study records.

All ICFs used in this study must be approved by the appropriate IRB/EC and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB/EC and the Sponsor.

6. STUDY OBJECTIVES

The overall objectives of the study are to assess the efficacy and safety of a single administration of STAP-001 in subjects with epilepsy with a predictable seizure pattern.

The primary objectives are:

- To assess the efficacy of STAP-001 (1.0 mg and 2.0 mg) compared to placebo in treating a seizure episode
- To assess the clinical feasibility and safety of the inhalation of STAP-001 (1.0 mg and 2.0 mg) compared to placebo in subjects during a seizure episode
- To assess the sedation associated with administration of STAP-001 (1.0 mg and 2.0 mg) compared to placebo

7. OVERALL STUDY DESIGN

This is a multi-center, dose-ranging study to investigate the efficacy, safety, and clinical usability of STAP-001. Subjects (18 years of age and older) who have an established diagnosis of focal or generalized epilepsy with a documented history of predictable seizure episodes will be enrolled. This is an in-patient study. Eligible and qualified subjects will be admitted to a CRU or EMU for study participation. The duration of the stay in the in-patient unit during the Treatment phase will be 2-8 days. One seizure event per subject will be treated with study medication. A treatable seizure event includes a predictable seizure episode, such that a change in the persistence of the seizure episode can be detected. The duration and timing of the seizure event and occurrence of subsequent seizures will be assessed by the study Staff Caregiver(s)[1] through clinical observation and confirmed with video EEG.

The study consists of two parts: Part 1- Open-Label Feasibility; Part 2 - Double-Blind. Each Part is divided into four phases: Screening; Qualification prior to entering the in-patient unit; Treatment in the in-patient unit; and Post-Treatment Safety Follow-Up. Subjects or the subject's LAR will provide appropriately-obtained informed consent prior to completing any study-related procedures.

The Screening visit will involve the items identified in the Schedule of Events (Appendix 1A), including Informed Consent and distribution of the seizure subject diary. As part of the screening process the seizure events of the subjects must be confirmed as acceptable for continuation in the study by the Epilepsy Study Consortium Review Board. Eligible subjects will enter a Qualification phase during which the subject must have at least 4 or more seizure episodes in a 28-day Qualification Period, with no more than one week without a predictable seizure episode. The Qualification Period may be extended beyond 28 days up to 56 total days to provide flexibility for scheduling of the Qualification Visit and Treatment Visit. The 28 days of the seizure diary activity immediately prior to the Qualification Visit will be assessed for qualification. At the end of the Qualification Period the Medical Monitor will review the seizure diary to confirm acceptable seizure frequency and subject's advancement into the Treatment Phase. Subjects meeting the qualification criteria will enter the CRU/EMU within 7 days from the end of the Qualification Period.

Part 1: Open-Label Feasibility

The first subjects enrolled in the study will participate in an open-label feasibility evaluation. Enrollment in this phase will end when there are data from at least eight individual subjects with a treated single seizure episode in a CRU/EMU. The subjects will be enrolled in 3-8 sites, up to

[1] Staff member(s) assigned and trained to observe the subject throughout the Treatment Phase and facilitate the study drug administration as appropriate. Staff Caregivers will be accountable for the study medication and each handoff will be recorded.

three subjects per site. Eligible subjects will receive a single, dose of 1 mg STAP-001 at the onset of their predictable seizure episode. The subjects will undergo all study procedures and evaluations as outlined in this protocol. The feasibility data (with special emphasis on the drug administration and clinical assessment procedures) from these eight subjects will be analyzed and reviewed by the Sponsor before starting the double-blind part of the study. If deemed necessary based on the feasibility data, the study protocol will be amended (for example, to change the drug administration procedure or to redefine the time frame for primary endpoint assessment), before starting the double-blind part of the study.

Part 2: Double-Blind

After admission to the in-patient unit eligible and qualified subjects will be stratified by the use of inducing vs non-inducing AED and for the use of chronic daily benzodiazepines (yes or no) and randomly assigned (1:1:1) to one of two doses of STAP-001 (1 mg or 2 mg) or *Staccato* placebo. A blood sample for PK analysis (pre-dose) will be obtained. For each subject, a single seizure episode will be treated and assessed. Study medication will be self-administered (when feasible) or administered by a Staff Caregiver when a predictable seizure episode starts. Assessment of the seizure activity is based on clinical observation by the Staff Caregiver using a stop watch. In addition, a video EEG will record the occurrence, start time, and duration, of the seizure event. PK samples will be collected 10, 30 and 60 minutes, and 2 and 6 hours after the administration of the study drug. If possible, subjects will signal when they experience a seizure event. Subject will be under video EEG surveillance throughout the Treatment Phase. The Staff Caregiver will signal the event for the video EEG recording, starts the stop watch at the time of drug administration, and mark the occurrence of the seizure event on a seizure diary. If the seizure episode does not stop within 5 minutes of the study drug administration, rescue medication other than alprazolam may be administered at the discretion of the principal investigator per the protocol of the research unit. The study exit procedures will be conducted 24 to 32 hours after the administration of study medication or when the subject discontinues from the study.

After discharge from the in-patient unit there will be a safety-follow-up phone contact 14 ±2 days after the subject received the study medication.

7.1. Number of Subjects and Sites

Assuming a 10% drop-out/protocol violation rate, approximately 115 subjects will be randomized in the double-blind part of the study to provide approximately 35 evaluable subjects per treatment arm. Enrollment may be stopped after 105 evaluable subjects have completed the double-blind phase of the study. Approximately 30% of the overall study population randomized in the study may be subjects being treated with chronic daily benzodiazepines as part of their epilepsy management. Approximately nine subjects will be enrolled in the open label feasibility part to provide at least eight evaluable subjects. Approximately 50 trial sites will be recruited to conduct the study.

7.2. Method of Treatment Assignment and Blinding (Double Blind Phase)

After admission to the in-patient unit subjects will be randomly assigned (1:1:1) to one of 2 doses of STAP-001 (1 mg or 2 mg) or *Staccato* placebo. Randomization will be stratified by the use of inducing vs non-inducing AEDs, and by use of daily benzodiazepines (yes or no) to ensure even distribution of treatment assignments in the two cohorts.

All study participants will be blinded to study drug assignment. The device and packaging of STAP-001and placebo will be identical in appearance.

7.3. Rationale for Study Design

Part 1 is open-label and designed to assess feasibility of the study. Part 2 is double blind and randomized and is designed to assess treatment efficacy and safety. Double-blind, randomized, placebo-controlled studies are considered optimal for obtaining unbiased estimates of the efficacy and safety of investigational products. The single dose administration of STAP-001 during a seizure episode is sufficient to evaluate the safety and potential of the product as an acute treatment of an epileptic episode.

A large proportion of subjects with epilepsy with a predictable seizure pattern are taking chronic daily benzodiazepine medication. It has been speculated that the efficacy of STAP-001 may be reduced in these subjects because of potential cross-tolerance between benzodiazepines. However, it is deemed important to evaluate the efficacy of STAP-001 in this population. It is also important to evaluate the tolerability and safety of STAP-001 in subjects on chronic benzodiazepine treatment in a controlled environment. Therefore, approximately 30% of the overall study population randomized in the study may be subjects being treated with chronic daily benzodiazepines as part of their epilepsy management. The subjects will be stratified by concomitant chronic daily benzodiazepine use to ensure even distribution of benzodiazepine use across treatment arms.

7.3.1. Rationale for Dose Selection

To date, STAP-001 has been studied in approximately 140 subjects, including healthy volunteers, subjects with panic disorder, individuals with a history of sedative abuse, subjects with photosensitive epilepsy, and in subjects with epilepsy with predictable seizure patterns. In all cases, the drug was generally well tolerated with dosing up to 2 mg. Sedation is a common side effect of alprazolam and also provides a pharmacodynamic marker of CNS activity. In all studies to date, the sedation observed has been temporally associated with peak plasma levels, which typically occur within a few minutes of dosing, and sedation tended to be more pronounced with the 2 mg dose. In Study 002-202 (see summary in Section 4.4.2), the effects on IPS were observed for the 0.5 mg, 1 mg and 2 mg doses. The IPS effect seemed similar for the 1 mg and 2 mg doses but there did appear to be a slightly greater extent and a longer duration of sedation at the 2 mg dose. Therefore, the 0.5 mg and 1 mg doses were initially chosen for this study.

The analysis of the first five patients in the open label feasibility part of this study (ENGAGE-E-001) has shown a 60% responder rate with the 1 mg dose. In addition, the plasma alprazolam

concentrations of the first subjects that were dosed have been low. A further analysis of the PK data from previous studies has shown that the 2 mg dose consistently provides a higher exposure to alprazolam during the first 2 minutes after administration, whereas the 0.5 mg or 1 mg doses provide more flat concentrations of alprazolam. Based on these analyses it is likely that 0.5 mg of Staccato alprazolam will not be an efficacious dose. Staccato alprazolam has been generally well tolerated with dosing up to 2 mg. Therefore, the two doses of Staccato alprazolam for the double-blind part of the study will be amended from 0.5 mg and 1 mg to 1 mg and 2 mg.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects eligible for enrollment in the study must meet all of the following inclusion criteria and none of the exclusion criteria.

8.1. Subject Inclusion Criteria

1. Subject is able to provide written, personally signed, and dated informed consent to participate in the study or will have a legally authorized representative (LAR) sign the informed consent on his or her behalf before completing any study related procedures.
2. Male or female ≥ 18 years of age.
3. Has an established diagnosis of focal or generalized epilepsy or focal and generalized epilepsy with a documented history of predictable seizure episodes that includes at least one of the following:
   a. Generalized seizure episodes starting with a flurry of absence seizures or myoclonic seizures with a minimum duration of 5 minutes
   b. Episodes of a prolonged focal seizure with a minimum duration of 3 minutes
   c. Episodes of multiple (≥2) seizures within a 2-hour time period
4. Prior to randomization, has experienced ≥4 seizure episodes with predictable pattern during the last 4 weeks (qualification period) and no more than one week without a predictable seizure episode before entry into the in-patient unit.
5. Female participants (if of child-bearing potential and sexually active) and male participants (if sexually active with a partner of child-bearing potential) who agree to use a medically acceptable and effective birth control method throughout the study and for 1 week following the end of the study. Medically acceptable methods of contraception that may be used by the participant and/or his/her partner include abstinence, birth control pills or patches, diaphragm with spermicide, intrauterine device (IUD), surgical sterilization, and progestin implant or injection. Prohibited methods include: the rhythm method, withdrawal, condoms alone, or diaphragm alone.
6. Subject is able to comply by the requirements of the protocol, particularly the requirements and specific Institution policies during the in-patient stay.

8.2. Subject Exclusion Criteria

1. History or diagnosis of non-epileptic seizures (e.g. metabolic or pseudo-seizures).
2. History of status epilepticus in the 6 months prior to Screening
3. Has a progressive neurological disorder such as brain tumor, demyelinating disease, or degenerative central nervous system (CNS) disease that is likely to progress in the next 3 months

4. Use of strong CYP 3A4 inhibitors; including azole antifungal agents (e.g., etoconazole, itraconazole), nefazodone, fluvoxamine, cimetidine, HIV protease inhibitors (e.g., ritonavir)
5. Has severe chronic cardio-respiratory disease
6. History of HIV-positivity.
7. Pregnant or breast-feeding.
8. Clinically significant renal or hepatic insufficiency (hepatic transaminases >2 times the upper limit of normal (ULN) or creatinine ≥ 1.5 x ULN).
9. History of acute narrow angle glaucoma, Parkinson's disease, hydrocephalus, or history of significant head trauma.
10. Subjects who use medications to treat airways disease, such as asthma or COPD or have any acute respiratory signs/symptoms (e.g., wheezing).
11. Use of any investigational drug within 30 days or 5 half-lives of the investigational drug prior to administration of study medication, whichever is longer
12. A history within the past 1 year of drug or alcohol dependence or abuse.
13. Positive urine screen for drugs of abuse at Screening (positive Cannabis/Cannabinol results are acceptable if there is a documented history of stable use for medical purposes).
14. Known allergy or hypersensitivity to alprazolam.
15. History of glaucoma.
16. Subjects who currently have an active major psychiatric disorder where changes in pharmacotherapy are needed or anticipated during the study.
17. Hypotension (systolic blood pressure ≤90 mm Hg, diastolic blood pressure ≤50 mm Hg), or hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥100 mm Hg) measured while seated at screening or baseline.
18. Significant hepatic, renal, gastroenterologic, cardiovascular (including ischemic heart disease and congestive heart failure), endocrine, neurologic or hematologic disease.
19. Subjects who, in the opinion of the Investigator, should not participate in the study for any reason, including if there is a question about the stability or capability of the subject to comply with the trial requirements.

8.3. Subject Withdrawal Criteria

All subjects are free to withdraw from participation in the study at any time, for any reason, and without prejudice. The Investigator must withdraw any subject from the study if the subject requests to stop participating in the study. The Investigator, Sponsor, or its designee may remove a subject from the study at any time and for any reason. In addition, subjects should be withdrawn if they:

- Require a medication that is prohibited by the protocol

- Do not follow guidelines specified in the protocol (i.e., is noncompliant with protocol procedures)

In addition, subjects may be withdrawn for any medically appropriate reason or significant protocol violation, in the opinion of the Investigator.

Subjects who withdraw or are withdrawn from the study will not be replaced.

8.3.1. Subject Withdrawal Procedures

A subject who prematurely discontinues study participation should have all assessments performed per the Exit Procedures if possible.

If a subject terminates early from the study, the Investigator will record the reason(s) for early termination on the relevant electronic case report form (eCRF). The specific reason for the withdrawal should be carefully documented on the eCRF.

Adverse events resulting in subject early termination will be followed to the satisfactory resolution and determination of outcome, as ascertained by the Investigator (and/or Sponsor, or its designee); See Section 12.1.2: Adverse Events. The data will be recorded on the appropriate eCRF.

8.4. Emergency Unblinding of Treatment Assignment

In the case of a medical requirement to break the blind to determine appropriate treatment for an adverse event, unblinding of a subject's treatment assignment can be achieved through the study-specific Interactive Web Response System (IWRS). If possible, the Investigator should discuss the circumstances with the Medical Monitor prior to accessing unblinding information. In the event of a blind break, the Medical Monitor will be notified through the electronic data capture system. The subject for whom the blind is broken should be subsequently withdrawn from the study. The details regarding the process of breaking the blind are outlined in the Pharmacy Manual.

9. STUDY SCHEDULE AND PROCEDURES

Subjects enrolled in this study will undergo only those procedures described in this protocol. No study-related procedures can be performed prior to receiving informed consent from the subject or the subject's LAR. See the Schedule of Events and Schedule of Events – Procedures in CRU/EMU (Appendix 1A and Appendix 1B) for a summary of the study procedures.

9.1. Part 1: Open Label Feasibility

9.1.1. Screening Visit

At the Screening Visit, it will be confirmed that the subject meets all inclusion and exclusion criteria and the procedures described in the Schedule of Events (Appendix 1A) will be performed, including: a full neurological and physical examination; vital signs assessment; medical history; blood draw for routine labs; 12 lead ECG; and urine drug and alcohol screen. A urine pregnancy test will be performed on females of childbearing potential.

After screening, the doses of the background AEDs should be kept stable if possible. If dose changes are deemed necessary, continued study participation of the subject should be discussed with the Medical Monitor.

9.1.2. Qualification Phase

Subjects meeting all the requirements during the Screening visit will be given a Seizure Diary and asked to record their seizure episodes over the next 4 weeks. In order for the subject to remain eligible and qualify for the study, they will have to have at least 4 predictable seizure episodes, within the 28-day Qualification Period. The Qualification Period may be extended beyond 28 days up to 56 total days to provide flexibility for scheduling of the Qualification Visit and Treatment Visit. The 28 days of the seizure diary activity immediately prior to the Qualification Visit will be assessed for qualification. There will be a visit at the end of the Qualification Period, during which the subject will turn in their seizure diary. At the end of the Qualification Period, the Medical Monitor will review the Seizure Diary to confirm acceptable seizure frequency and subject's advancement into the Treatment Phase. Subjects meeting the qualification criteria will enter the CRU/EMU within 7 days from the end of the Qualification Period.

9.1.3. Treatment Phase

The first subjects enrolled in the study will participate in an open-label feasibility evaluation and enrollment in this phase will end when there are data from eight individual subjects having seizure events in the CRU/EMU. Subjects meeting eligibility and qualification criteria will be admitted to the CRU/EMU, be assessed for continued eligibility according to the procedures in the Schedule of Events – Procedures in CRU/EMU (Appendix 1B), and be hooked up with EEG recording electrodes which will remain in place for the duration of the study. It is required that a Staff Caregiver be present to provide 1:1 coverage with the subject while in the CRU/EMU to watch for signs of a seizure episode. After the EEG electrode hook-up is complete, each subject

will be assigned a single 1 mg STAP-001 device that will be removed from the pouch and dispensed to the Staff Caregiver until drug administration. At the onset of the predictable seizure episode, the Staff Caregiver will activate the device and give to the subject if the subject is capable of self-administration or will assist in helping the subject to administer the drug. The Staff Caregiver will signal the onset of the seizure event on the video EEG, start the stopwatch and mark the occurrence of the seizure event on a seizure diary. At 2 minutes after study drug administration, the Staff Caregiver will record whether the seizure event has ceased or is still ongoing. The Staff Caregiver will observe the subject for the next 2 hours and record seizure activity on a seizure diary during this time period. After this the Staff Caregiver will continue observation throughout the 24 hours following drug administration. If over the course of 7 days there is no treatable seizure episode, the subject will be dismissed, after completing Exit Procedures. Note that the procedures in the Schedule of Events for the treatment day are only conducted on the day there is a treatable seizure event and drug has been administered.

The feasibility data (with special emphasis on the drug administration and clinical assessment procedures) from these eight subjects will be analyzed and reviewed by the Sponsor and study team before continuing to enroll subjects in the double-blind part of the study. If necessary, the study protocol will be amended (for example, to change the drug administration procedure or to redefine the time frame for primary endpoint assessment) before starting the double-blind part of the study.

When multiple procedures are scheduled at the same time point, the VAS assessment should be performed first, immediately followed by the PK draw.

All *Staccato* doses will be administered as one puff from a single inhalation device by the subject with or without the assistance of the study Staff Caregiver. The exact time of administration and correct intake of the medication will be noted and recorded in the CRF.

Subjects should have minimal postural changes for the first 1.5 hours after administration of study drug.

9.2. Part 2: Double-Blind

9.2.1. Screening Visit

At the Screening Visit, it will be confirmed that the subject meets all inclusion and exclusion criteria and the procedures described in the Schedule of Events (Appendix 1A) will be performed, including: a full neurological and physical examination; vital signs assessment; medical history; blood draw for routine labs; 12 lead ECG; and urine drug and alcohol screen. A urine pregnancy test will be performed on females of childbearing potential. Device training including study drug administration procedures will be conducted. Training may include subject use of a practice 'dummy' device that does not contain any active drug.

After screening, the doses of the background AEDs should be kept stable if possible. If the dose changes are deemed necessary, continued study participation of the subject should be discussed with the Medical Monitor.

9.2.2. Qualification Phase

Subjects meeting all the requirements during the Screening visit will be given a Seizure Diary and asked to record their seizure episodes over the next 4 weeks. In order for the subject to remain eligible and qualify for the study, they will have to have at least 4 predictable seizure episodes, within the 28-day Qualification Period. The Qualification Period may be extended beyond 28 days up to 56 total days to provide flexibility for scheduling of the Qualification Visit and Treatment Visit. The 28 days of seizure diary activity immediately prior to the Qualification Visit will be assessed for qualification. There will be a visit at the end of the Qualification Period, during which the subject will turn in their seizure diary. At the end of the Qualification Period the Medical Monitor will review the Seizure Diary to confirm acceptable seizure frequency and subject's advancement into the Treatment Phase. Subjects meeting the qualification criteria will enter to the CRU/EMU within 7 days from end of the Qualification Period.

9.2.3. Treatment Phase

Subjects meeting eligibility criteria will be admitted to the CRU/EMU and be assessed for continued eligibility according to the procedures for CRU/EMU entry in the Schedule of Events – Procedures in CRU/EMU (Appendix 1B). Device training including study drug administration procedures will be conducted. Training may include subject use of a practice 'dummy' device that does not contain any active drug. Eligible subjects will be stratified for use of inducing vs. non-inducing AEDs and for the use of chronic daily benzodiazepines, and randomly assigned to a treatment arm and be hooked up with EEG recording electrodes which will remain in place for the duration of the study. It is required that a Staff Caregiver be present to provide 1:1 coverage with the subject while in the CRU/EMU to watch for signs of a seizure episode. After randomization and EEG electrode hook-up is complete, the study medication, assigned to the subject, will be removed from the pouch and dispensed to the Staff Caregiver until drug administration. At the onset of the predictable seizure event, the Staff Caregiver will activate the device and give to the subject if the subject is capable of self-administration or will assist in helping the subject to administer the drug. The Staff Caregiver will signal the onset of the seizure event on the video EEG, start the stopwatch and mark the occurrence of the seizure event on a seizure diary. At 2 minutes after study drug administration, the Staff Caregiver will record whether the seizure event has ceased or is still ongoing. The Staff Caregiver will observe the subject for the next 2 hours and record seizure activity on a seizure diary during this time period. After this the Staff Caregiver will continue observation throughout the 24 hours following blinded study medication administration. During the seizure episode period, study procedures will be conducted according to the schedule in the Schedule of Events – Procedures in

CRU/EMU (Appendix 1B). If over the course of 7 days there is no recordable seizure episode, the subject will be dismissed, after completing the Exit Procedures. Note that the procedures in the Schedule of Events for the treatment day are only conducted on the day there is a treatable seizure event and drug has been administered.

When multiple procedures are scheduled at the same time point, the VAS assessment should be performed first, immediately followed by the PK draw.

All *Staccato* doses will be administered as one puff from a single inhalation device by the subject with or without the assistance of the study Staff Caregiver. The exact time of administration and correct intake of the medication will be noted and recorded in the CRF.

Subjects should have minimal postural changes for the first 1.5 hours after administration of study drug.

10. DESCRIPTION OF STUDY TREATMENTS

10.1. Description of Treatments

After admission to the in-patient unit subjects will be stratified by use of inducing vs. non-inducing AEDs and for use of chronic daily benzodiazepines, and randomly assigned (1:1:1) to one of 2 doses of STAP-001 (1 mg or 2 mg) or *Staccato* placebo.

10.2. Study Drug Materials and Management

Please consult the Pharmacy Manual for a complete description of the study drug and requirements for storage, handling, dispensing, accountability, returns and destruction.

10.2.1. Physical Description of Study Drug

Study drug will include STAP-001and matching *Staccato* placebo. Details regarding formulation and dosage are presented in Table 1: Investigational Product

Table 1: Investigational Product

	Investigational Product (*Staccato* Alprazolam (STAP-001) or Staccato Placebo)
Product Name:	Staccato Alprazolam (STAP-001) or Matching Staccato placebo
Dosage Form:	Inhalation device
Dosage Strength of STAP-001	1 mg, 2 mg, or placebo, per device
Route of Administration	Oral inhalation
Physical Description	White to off-white plastic device

10.2.2. Study Drug Packaging, Labeling, and Storage

Study drug will be packaged inside a sealed foil pouch. Blinding of study medication will be done according to the randomization schedule and performed by an unblinded observer or vendor who shall not be involved in any other aspect of this study.

Detailed instructions for unblinding will be provided to the site in the event of an emergency and it is necessary to find out the study treatment assigned to an individual subject. If feasible, the Medical Monitor should be consulted before breaking the blind, and if this is not feasible, the medical monitor should be advised of the unblinding within 24 hours.

The label(s) for the investigational product and placebo will include sponsor name, address and telephone number, the protocol number, investigational product name, dosage form, storage conditions, and required caution statements and/or regulatory statements, as applicable. Additional information may be included on the label as applicable per local regulations.

Details of the packaging, labeling and dispensing instructions can be found in the Pharmacy Manual.

Adequate supplies of study drug will be provided to each site. Study drug should be stored in the original package between 15°C to 25°C (59°F to 77°F), as stated on the product label, in a secure, temperature-monitored, locked area, under the responsibility of the Investigator or other authorized individual until dispensed to the subjects.

10.2.3. Study Drug Preparation and Administration

Each product is packaged inside a sealed foil pouch. Removal of a pull-tab from the product activates it and renders it ready for use, as indicated by illumination of a green light. Successful dosing is signaled by the extinguishing of the green light.

10.2.4. Study Drug Return and Disposal

The Sponsor (or designee) will review with the Investigator and relevant site personnel the process for study treatment return, disposal, and/or destruction, including responsibilities for the site versus the Sponsor (or designee). Specific requirements for destruction or return are defined in the Pharmacy Manual.

10.2.5. Study Drug Accountability

To satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled in full. The Investigator or designee must maintain accurate records of the receipt of study drug, including date received, lot number, amount received, condition of the package, and the disposition of study drug.

Current dispensing records will also be maintained, including the date and amount of medication dispensed to each individual subject. Returned study drug records will be maintained and final study drug reconciliation will also be recorded for each subject.

10.3. Concomitant Medications and Procedures

All medications, including over-the-counter therapies (e.g., vitamins, herbal, and nutritional supplements), taken at the time of the Screening Visit through the Follow-Up Visit will be recorded in the subject's source documentation and documented in the eCRF.

With the exception of acetaminophen or ibuprofen for pain, ongoing doses of oral contraceptives, and stable background AEDs, medications other than study drug are not allowed from 12 hours before entry into the CRU/EMU until the end of the Treatment Phase, unless medically required.

After screening, the doses of the background AEDs should be kept stable if possible. If dose changes are deemed necessary, continued study participation of the subject should be discussed with the Medical Monitor**.**

Any concomitant medications taken during the Treatment Phase (up to 24 h after study drug administration), including any medication taken for the treatment of adverse events, will be recorded on the appropriate CRF. Recording of the concomitant medication will include the medication name, indication, dose, route, frequency, and time.

If a seizure episode does not stop within 5 minutes, rescue medication may be administered at the discretion of the principal investigator per the protocol of the research unit. If seizure activity continues despite use of rescue medication, the standard treatment protocol of the institution should be applied as appropriate.

In case a subject experiences respiratory distress, an inhaled short-acting beta-agonist bronchodilator should be available for use under standard dosing conditions as needed. Any concomitant medication deemed necessary for the wellbeing of the subject may be given at the discretion of the Investigator. Use of medications that are prohibited per protocol will require subject withdrawal from the study.

11. STUDY ASSESSMENTS DESCRIPTIONS

The schedule of assessments and procedures is presented in the Schedule of Events (Appendix 1A and 1B) and should be referenced for details regarding the collection of each assessment at each visit.

11.1. Demographic Characteristics and Medical History

Demographic characteristics (i.e., gender, race and ethnic origin, date of birth, and calculated body mass index) will be collected at the Screening Visit, and detailed on the eCRF.

Thorough medical history, including EEG and brain imaging (MRI/CT) findings within the last 5 years, history of seizures, seizure pattern, frequency and characteristics during the last 12 months. Current medications, and co-morbidities will be collected at the Screening Visit and reviewed and updated at entry into the CRU/EMU for the Treatment Phase. Epilepsy history and seizure documentation are collated and submitted to the Epilepsy Study Consortium Review Board for review.

11.2. Vital Signs, Weight, and Height

Vital signs will be measured after the subject has been in a supine or semi-supine position for at least 5 minutes and will include blood pressure, pulse rate, respiratory rate, and oral temperature as defined in the Schedule of Events.

Weight will be measured per institution standard of care. Subjects should wear light clothing and remove his/her shoes before weight is measured. Height will be measured per institution standard of care, after the subject has removed his/her shoes. Height will only be measured at the Screening Visit. Weight and vital signs will be measured at each study visit according to the Schedule of Events. Weight and height will be used to calculate the subject's body mass index at Screening. Weight and height will be converted as needed to kilograms and centimeters, respectively, prior to statistical analyses.

11.3. Physical and Neurological Examination

A complete physical examination will include an examination of all major organ systems, and will be performed as indicated in the Schedule of Events (Appendix 1A and Appendix 1B). A complete neurological examination will be performed as indicated in the Schedule of Events (Appendix 1A and Appendix 1B).

11.4. 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed after the subject has rested in a supine or semi-supine position for at least 5 minutes. Individual parameters including heart rate, PR, QT, QTcF, QRS, and RR intervals will be collected. Repeat ECGs (if deemed necessary) should be performed at least 5 minutes apart. The Investigator should indicate review of the electrocardiogram reports throughout the study by signing and dating each report.

11.5. Seizure Assessment

11.5.1. Staff Caregiver Seizure Episode Recording

It is required that a Staff Caregiver be present to provide 1:1 coverage with the subject while in the CRU/EMU. At the onset of the predictable seizure episode, the Staff Caregiver will activate the device and give to the subject if the subject is capable of self-administration or will assist in helping the subject to administer the drug. The Staff Caregiver will signal the onset of the seizure episode on the video EEG, start a stopwatch and record the onset of the seizure episode. At 2 minutes after study drug administration, the Staff Caregiver will record whether the seizure episode has ceased or is still ongoing. The Staff Caregiver will observe the subject for the next 2 hours and record seizure activity on a seizure diary during this time period. After this the Staff Caregiver will continue observation throughout the 24 hours following drug administration.

11.5.2. Video Electroencephalogram (EEG)

A 19-21-channel recording system will be used with a bipolar derivation. The display montage will include T4-T6-O2-O1-T5-T3 and T4-P4-Pz-P3-T3, apart from 2x4 (8) frontal to occipital leads.

Subjects will be fitted with EEG electrodes according to the international 10-20 system upon reporting to the CRU/EMU. The EEG electrodes will remain in place for the duration of the stay in the CRU/EMU.

EEG data will be sent to a central reader and evaluated in a blinded fashion.

11.5.3. Seizure Episode Severity Assessment

At the 6 hour time point after dose administration the subject will assess the seizure episode just experienced in relation to previous seizures experienced by the subject using the assessment tool found in the Appendix 3.

11.6. Pharmacokinetic Sampling

Blood samples will be collected into evacuated K2 EDTA tubes, e.g., Vacutainer®, from each subject according to the times specified in the Schedule of Events – Procedures in CRU/EMU (Appendix 1B). An indwelling catheter inserted into the forearm, or direct venipuncture may be used during the blood sampling procedure.

The total volume of blood drawn from each subject during this study will be approximately 100 mL, which includes approximately 24 mL for pharmacokinetic analysis and approximately 70 mL for standard pre-study and post study clinical laboratory tests.

Specific sample collection, preparation and shipping instructions will be provided to the study site. Samples will be assayed using validated methods. Instructions for harvesting and preparing plasma samples prior to freezing and additional procedures for blood sample collection will be provided in separate study laboratory manual.

11.7. Sedation Assessment - Visual Analog Scale (VAS)

The visual analog scale is a distinct 100 millimeter line anchored on the left end at full degree of impairment and on the right end at no degree of impairment, where indication of the degree of impairment perceived at the time of assessment is captured by marking the appropriate position

on the line between the anchor points. The measured distance of the mark from the left anchor will be recorded in millimeters

As specified in the Schedule of Events – Procedures in CRU/EMU (Appendix 1B), sedation will be measured using a 100-mm linear visual analogue scale (VAS). The subject will be given 2 scales, 1 anchored by "Sedated" and "Alert, the other by "Sleepy and "Awake" and asked to "Place a vertical mark on the line indicating your feelings RIGHT NOW". The location of the mark will be measured at a later time and the results will be recorded in mm from the left on the appropriate eCRF.

An example of the subject VAS is provided in Appendix 2. The paper scales will be provided to the sites and only originals can be used for subject assessment. Photocopies cannot be provided for subject assessment.

11.8. Clinical Laboratory Assessments

Blood and urine samples will be collected according to standard medical guidelines and processed at a clinical laboratory. Sample collections, handling and shipping instructions are provided in the clinical laboratory document. Study-related clinical laboratory assessments are presented below in Table 2: Clinical Laboratory Assessments

Clinical laboratory samples should be collected according to the Schedule of Events -Procedures in CRU/EMU (Appendix 1B).

The results of clinical laboratory tests conducted at the Screening Visit (and prior to dosing) must be assessed by the Investigator to determine each subject's eligibility for participation in the study. Laboratory values that are out of range at screening may be repeated at the investigator's discretion. The Investigator should indicate review of the laboratory reports throughout the study by signing and dating each report.

Following study drug administration, all clinical laboratory results that fall outside the reference range will be interpreted by the Investigator as Abnormal, not clinically significant, or Abnormal, clinically significant. Laboratory results deemed Abnormal, clinically significant should be fully investigated and repeated for verification. Additional tests and evaluations required to establish the significance or etiology of a clinically significant abnormal result or to monitor the course of an adverse event should be obtained when clinically indicated. All clinically significant out-of-range laboratory values will be followed until they return to normal or stabilize; the investigator will treat the subject as medically required at appropriate intervals until this occurs.

Any significant laboratory abnormalities that are either serious or unexpected will be promptly reported to the Sponsor. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be reported to the Sponsor or designee.

Laboratory values will be reported as an adverse event following the guidelines in section 12.1.1.

Table 2: Clinical Laboratory Assessments

Hematology (Blood)	**Chemistry (Serum)**	**Pregnancy** *Females of childbearing potential only*
Complete blood count Platelet count White blood cell count with differential Hemoglobin Hematocrit	Alanine aminotransaminase Albumin Alkaline phosphatase Amylase Aspartate aminotransaminase Total bilirubin Direct bilirubin Indirect bilirubin Blood urea nitrogen Calcium Carbon dioxide Chloride Creatinine Creatine kinase Glucose Lipase Total protein Phosphorus Potassium Sodium Uric Acid	At screening: Urine Human Chorionic Gonadotropin At CRU/EMU entry: Urine Human Chorionic Gonadotropin
Drug Screen (Urine)		**Urinalysis**
delta-9-tetrahydrocannabinol barbiturates opioids amphetamines methamphetamines methylenedioxymethamphetamine cocaine phencyclidine ethanol propoxyphene		Bilirubin Blood Clarity Urobilirubin Glucose, Urine Ketones Leukocyte Esterase Nitrate pH Protein, Urine Specific Gravity

12. ADVERSE EVENTS

12.1.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an adverse event. A diagnosis or syndrome should be recorded on the adverse event page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome. A worsening of the condition under study will not be reported as an adverse event.

All subjects will be monitored for adverse events during the study. Assessments may include monitoring of the following parameters: the subject's clinical symptoms, laboratory, physical examination findings, or findings from other tests and/or procedures.

An adverse event reported after informed consent and occurring before the first dose of study drug in the CRU/EMU, will be considered a pretreatment adverse event and will be captured on the eCRF. Adverse events will be considered treatment-emergent if the onset is after the first dose of study drug.

An abnormal laboratory value is considered to be an adverse event or a component of an adverse event if the abnormality:

- results in discontinuation from the study;
- is judged by the Investigator to be of significant clinical importance requiring treatment, modification/interruption of investigational product dose, or any other therapeutic intervention

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the adverse event eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the adverse event. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

12.1.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to seriousness, severity/intensity, relationship to study drug, duration, action taken, and outcome.

12.1.2.1. Serious Adverse Event

A serious adverse event is an adverse event, as per Title 21 CFR 312.32 and ICH E2A.II.B that fulfills the following criteria:

- Is fatal (results in death);
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; or
- Constitutes an important medical event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Events **not considered** to be serious adverse events are hospitalizations for:

- A procedure for protocol/disease-related investigations (e.g., sampling for laboratory, pharmacokinetic, and pharmacodynamic tests). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- A procedure that is planned (i.e., planned prior to the starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable serious adverse event.
- An elective treatment of or an elective procedure for a pre-existing medical condition that does not worsen.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an adverse event is considered serious, the adverse event eCRF must be completed.

For each serious adverse event, the Investigator will provide information on severity, start and stop dates, relationship to investigational product, action taken regarding investigational product, and outcome.

Queries pertaining to serious adverse events will be handled through the electronic data capture system or other appropriate means. Urgent queries (e.g., missing causality assessment) may be handled by telephone.

12.1.2.2. Severity/Intensity

For both adverse events and serious adverse events, the Investigator must assess the severity/intensity of the event.

The National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 should be used to grade the severity/intensity of all events. These criteria will be provided in the Site Operations Manual. If a CTCAE criterion does not exist, the Investigator should grade the severity according to the following criteria:

- Grade 1 (mild): does not interfere with the subject's usual function
- Grade 2 (moderate): interferes to some extent with subject's usual function
- Grade 3 (severe): interferes significantly with subject's usual function
- Grade 4 (life-threatening): results in a threat to life or in an incapacitating disability
- Grade 5 (death): results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

12.1.2.3. Relationship to Study Drug

Relationship should be assessed and provided for every adverse event/serious adverse event based on currently available information. Relationship is to be reassessed and provided as additional information becomes available. Adverse events will be classified by the Investigator as follows:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The event would be considered as definitely related to the study drug upon results of a positive re-challenge procedure.

Probably Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors that may have contributed to the event (e.g., the subject's clinical condition, other concurrent disease, concomitant medications or events) is unlikely.

Possibly Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concurrent disease, concomitant medications or events).

Unlikely Related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or concurrent or underlying disease provide plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Not related: The adverse event is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

12.1.2.4. Duration

For all adverse events whether or not considered serious, the Investigator will provide a record of the start and stop dates of the event. Every effort should be made to resolve all adverse events with continued follow-up with the subject until appropriate resolution can be achieved. If an event is unresolved at the end of the study it will be recorded as ongoing.

12.1.2.5. Action Taken

The Investigator will record the action taken with investigational product as a result of an adverse event or serious adverse event on the eCRF, as applicable (e.g., discontinuation, or interruption of investigational product, as appropriate) and record if concomitant and/or additional treatments were given for the event.

12.1.2.6. Outcome

The Investigator will record the outcome of adverse events on the eCRF, as applicable (e.g., recovered, recovered with sequelae, not recovered, or death (due to the adverse event).

12.1.3. Follow-Up

Adverse events assessed as not related to study drug, including clinically significant laboratory tests, electrocardiograms, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

Adverse events assessed as related to study drug and serious adverse events will be followed for as long as necessary to adequately evaluate the subject's safety, or until the event stabilizes, is otherwise explained, death occurs, or the subject is lost to follow up. If resolved, a resolution date should be provided. The Investigator is responsible for ensuring

that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the adverse event. This may include additional clinical laboratory testing or investigations, examinations, or consultation with other health care professionals as is practical.

12.1.4. Pregnancy

The Sponsor must be informed within 24 hours upon learning that a subject, or male subject's partner, has become pregnant any time after the first dose of study drug until 30 days after the last dose of study drug. The Pregnancy Notification eCRF should be used to report the pregnancy to the Sponsor or its designee. Subject pregnancies (or pregnancy of a male subject's partner) must be followed until termination of pregnancy or the birth of the child. The Pregnancy Outcome eCRF should be used to report information regarding the status of the infant.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking the investigational product should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

12.1.5. Recording Adverse Events

All adverse events (regardless of seriousness or relationship to study drug) including those from the time informed consent is obtained through to the final study visit are to be recorded in the eCRF. Each individual adverse event is to be listed as a separate entry. The Investigator will provide information about dates of onset and resolution, seriousness, severity, action(s) taken, outcome, and relationship to the study drug. All adverse events should be documented in the subject's source documents.

12.1.6. Reporting Adverse Events

The Investigator must report to Sponsor or its designee all adverse events that occur during the study from the time written informed consent is given until the final study visit or early termination, regardless of their relationship to the study drug. Serious adverse events and pregnancies will be reported from the time written informed consent is given through 30 days beyond the last dose of study drug.

12.1.6.1. Reporting Serious Adverse Events

The Investigator is required to notify the Sponsor, and the Sponsor's designated Drug Safety Unit within 24 hours after becoming aware of the occurrence of a serious adverse event. All serious adverse events will be reported through completion of the adverse event eCRF. The Investigator will be responsible for reporting serious adverse events to the IRB.

Medical Monitor:

[redacted]

Address: [redacted]

Phone: [redacted]

Email: [redacted]

Emergency (24/7) Contact Information:

site specific phone tree to be provided

Serious Adverse Event Reporting Contact Information:

SAEREPORT.ENGAGE@PEACHTREEBRS.COM

If an Investigator becomes aware of a serious adverse event within 14 days after the last dose of study drug and it is considered by him/her to be caused by the study drug with a reasonable possibility, the event must be documented and reported through completion of the adverse event eCRF.

12.1.6.2. Reporting Urgent Safety Issues

If the study site staff becomes aware of an actual or potential urgent safety issue, then the Sponsor and Sponsor's designee (Medical Monitor) must be immediately contacted so that appropriate urgent safety measures can be agreed upon. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include: (1) issues with an investigational drug or comparators; (2) study procedures; (3) inter-current illness; (4) concomitant medications; (5) concurrent medical conditions; or (6) any other issues related to the safe conduct of the study or that pose a risk to study subjects.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, the Investigators may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has resolved.

13. STATISTICAL METHODS

13.1. Sample Size Rationale

There are no studies in the literature to provide reliable estimates of active treatment or placebo response rates for this study. Assuming a 10% drop-out/protocol violation rate, approximately 115 subjects will be enrolled in the double-blind part of the study to provide approximately 35 evaluable subjects per treatment arm. Enrollment may be stopped after 105 evaluable subjects have completed the study.

Approximately 30% of the overall study population randomized in the study may be subjects being treated with chronic daily benzodiazepines as part of their epilepsy management. Since the effect of concomitant chronic daily benzodiazepines use on study treatment is unknown, a 50% response rate for chronic benzodiazepines users on active treatment arms is assumed. For subjects who are not chronic benzodiazepines users, a response rate of 60% for active treatment arms is assumed. With up to 30% of study population being chronic benzodiazepines users and these response assumptions, a 57% response for the active treatment arm is targeted.

Power calculations assume a 2-sided test and significance level of 0.05 with 90% power and are based on the assumption that the proportion of responders with STAP-001 is 57% (best active treatment arm) whereas the assumed placebo responder rate is 20%.

13.2. Endpoints

13.2.1. Efficacy

Primary efficacy endpoint:

The proportion of responders in each treatment group achieving seizure activity cessation within 2 minutes after the administration of the study drug and no recurrence of seizure activity within 2 hours.

Secondary endpoints:

- Seizure episode severity assessed by subject and/or Staff Caregiver
- Use of rescue medication
- Secondary generalization (evolution to a complex partial seizure and/or a generalized tonic-clonic seizure)

Exploratory endpoints:

- Number of seizures during the 4, 6 and 12 hour time periods after study drug administration
- Time to next seizure event with start time >2 minutes after study drug administration

Additional exploratory statistical analyses to further assess for treatment effect will be outlined in the Statistical Analysis Plan finalized prior to database lock for the Primary Efficacy Analysis.

13.2.2. Pharmacokinetic

Blood samples will be collected for plasma alprazolam concentration measurement pre-dose and then at 10, 30, and 60 minutes, and 2 and 6 hours after the dosing of the study drug.

13.2.3. Safety

Safety and tolerability will be assessed by evaluating adverse events, vital signs, concomitant medications, clinical laboratory, and electrocardiogram results, as well as physical examinations. Sedation will also be assessed using a subject VAS.

13.3. Analysis Populations

13.3.1. Treatment Period

The Efficacy Population (ITT population) will include all subjects who have a seizure event and receive study drug during the Treatment Period. Modified Intent to Treat (mITT) population will consist of all subjects who have a seizure event, receive study drug, and have had at least one evaluation after study drug administration. mITT will be used for primary efficacy analysis.

The PK Population will include all subjects who receive study drug and have at least one pharmacokinetic data point during the Treatment Period. Subjects who receive placebo will be excluded from the PK Population.

The Safety Population will include all subjects who receive study drug during the Treatment Period from both Part 1 Open-label Feasibility and Part 2 Double-blind.

The Per Protocol Population will include all subjects in the Efficacy Population who were dosed according to protocol and have no major protocol deviations.

13.4. Analyses

For the Treatment Period, data will be summarized by active treatment by dose level versus placebo-treated subjects (i.e., by treatment group). All data for analysis will be listed by subject.

Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

Additional details for statistical methods will be provided in the Statistical Analysis Plan.

13.4.1. Disposition and Baseline Characteristics

Disposition will be summarized by randomized treatment group. The number and percentage of subjects, who are randomized, treated, prematurely discontinued, and complete the study will be summarized.

Baseline characteristics will be summarized by treatment group.

The number of subjects in each cohort's treatment group will be summarized for each investigative site for the Treatment Period. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical (WHODRUG_ATC) classification and preferred term.

13.4.2. Efficacy

All statistical tests will be 2-sided with a significance level of 0.05. Testing will be performed only for the Treatment Period.

Data will be summarized by active treatment by dose level versus placebo-treated subjects (i.e., by treatment group). Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

The primary efficacy analysis will be conducted following completion of the Treatment Period for the last subject and data base lock.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of responders in each treatment group achieving seizure activity cessation within 2 minutes after the administration of the study drug and no recurrence of seizure activity within 2 hours. The primary endpoint will be analyzed with a chi-squared test. The overall treatment comparison, as well as pairwise comparisons between each dose level and placebo will be performed. The estimates of the treatment difference versus placebo and their 95% confidence interval will be presented.

There will be no adjustment for multiple treatment group comparisons in this dose-ranging Phase 2b study. The dose-response relationship will be explored with a regression analysis.

The handling of missing data will be summarized in the Statistical Analysis Plan.

Secondary and Exploratory Efficacy Endpoints

Secondary and exploratory endpoints will be summarized by treatment group and if applicable, by assessment time point. Exploratory statistical testing may be performed if warranted. The Cochran-Mantel-Haenszel (CMH) test for row mean score difference will be used to test the treatment difference in the seizure episode severity. The Kruskal-Wallis test will be used to compare seizure frequencies. The time-to-next-seizure data will be summarized and displayed with Kaplan-Meier plots. No multiplicity adjustment will be implemented for exploratory tests.

13.4.3. Pharmacokinetics

The collection status of PK samples will be listed for each visit with scheduled pharmacokinetic sampling. Plasma concentrations of study drug and the active metabolites may be summarized separately, as appropriate. PK parameters including maximum concentration (C_{max}), time to maximum (T_{max}), area under the concentration curve from 0 to the last measurable value (AUC_{last}) will be estimated for each subject using

noncompartmental methods. Since the time point range is 0 to 6 hours and the alprazolam half-life is 11 hours, we do not plan to estimate half-life or AUC_{inf}.

13.4.4. Safety

All safety summaries will be descriptive with no statistical hypothesis testing and based on the Safety Population. Subjects will be summarized according to the study drug received (i.e., as treated), should it differ from the randomized treatment arm. All safety endpoints will be listed in by-subject data listings.

Adverse events will be coded using MedDRA and summarized by system organ class and preferred term. Clinically significant deteriorations in physical examination findings will be reported and summarized as adverse events.

Laboratory values will be converted to the project-defined unit of measurement, as applicable, before analysis. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events.

Adverse Events

An adverse event reported after informed consent and occurring before the first dose of study drug in the CRU/EMU will be considered a pre-treatment adverse event. Treatment-emergent adverse events (TEAEs) will be defined as any adverse event that occurs after administration of study drug. The number and percentage of subjects who report TEAEs will be summarized by system organ class and preferred term.

Treatment emergent adverse events will also be summarized by intensity as well as relationship to study drug.

Subjects who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study drug when summarized by relationship. If a subject reports multiple preferred terms for a system organ class, the subject will be counted only once for that system organ class.

Proportions for adverse events that are gender-specific (e.g., dysmenorrhea) will be based on the number of subjects from that gender.

The number and percentage of subjects who experience TEAEs will be summarized by treatment group for the following:

- By system organ class and preferred term
- By severity/intensity, system organ class, and preferred term
- By relationship to study drug, system organ class, and preferred term
- Serious adverse events by system organ class and preferred term
- Serious adverse events by relationship to study drug, system organ class, and preferred term
- Adverse events resulting in discontinuation of study drug by system organ class and preferred term

- Adverse events that result in study drug dose interruption by system organ class and preferred term

By subject listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment.

Sedation Assessment

Sedation as measured by the dichotomous using a 100-mm linear VAS will be summarized by time point.

Clinical Laboratory

Clinical laboratory variables will be presented in 2 ways. First, change from Baseline to each scheduled assessment will be summarized descriptively. Baseline will be defined as the laboratory value obtained before the first dose of study drug on Day 1; if Day 1 values are unavailable, then values obtained at the Screening Visit will be used.

Second, treatment-emergent potentially clinically significant (PCS) laboratory values will be identified. Potentially clinically significant values are defined as those that meet Grade 3 or Grade 4 toxicity criteria from the CTCAE criteria. Treatment-emergent PCS laboratory values are those in which the baseline value is not PCS and the post-baseline value is PCS. The number and percentage of subjects with treatment-emergent PCS laboratory values will be summarized by treatment group for each clinical laboratory variable.

Vital Signs

The mean change from baseline to each scheduled assessment will be summarized descriptively by treatment group for each vital sign variable specified in this protocol.

Baseline will be defined as the last vital sign value obtained before the first dose of study drug on Day 1; if Day 1 values are unavailable, then values obtained at the Screening Visit will be used.

Electrocardiogram

The change from baseline in electrocardiogram intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group.

14. REGULATORY CONSIDERATIONS

It is the responsibility of the clinical site and staff to notify the Sponsor and Sponsor's designee immediately upon becoming aware of a serious breach of GCP or of the study protocol. It is the responsibility of the Sponsor or its designee to notify appropriate regulatory authorities of any serious breach which is likely to effect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study.

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from the IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2. Sponsor's Responsibilities

The Sponsor or its designee is responsible for the following:

- Selecting qualified Investigators
- Providing Investigators with the information they need to properly conduct an investigation
- Ensuring proper monitoring of the investigation
- Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding adverse events or risks associated with the medication being studied

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from Engage Therapeutics, Inc. or its representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed

- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations.
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to the Sponsor and those serious adverse events that met criteria for reporting have been forwarded to the IRB/EC and other applicable country and/or local regulatory authorities.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

As the Sponsor, Engage Therapeutics, Inc. has delegated some responsibilities to a designee, or Contract Research Organization.

14.3. Investigator's Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Each Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drug, and their study-related duties and functions. The Principal Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible from conducting or working on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Engage Therapeutics, Inc. The Investigator is required to immediately disclose to the Sponsor in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by the FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator should inform the IRB/EC of any event likely to affect the safety of subjects or the continued conduct of the study. Additionally, all updates to the Investigator's Brochure will be sent to the IRB/EC. A progress report will be sent to the IRB/EC and the protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by the IRB/EC or local regulations.

The Investigator will maintain a copy of all correspondence with the IRB/EC, including copies of approved documents. The Investigator will also maintain a copy of the IRB/EC

membership list with occupation and qualification (or a statement confirming compliance with GCP requirements for committee composition).

The Investigator will notify the IRB/EC of the conclusion of the clinical study within 1 month of completion or termination of the study. The final report sent to the IRB/EC will also be sent to the Sponsor along with the completed electronic case report forms (eCRFs) and all necessary regulatory documents, thereby fulfilling the Investigator's regulatory responsibility.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

14.4. Protocol Amendments

Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. All amendments to the protocol will be written by the Sponsor. The Investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB/EC. Except for administrative amendments, Investigators must await IRB/EC approval of protocol amendments before implementing the change(s). The Sponsor will ensure submission of any protocol amendments to the appropriate regulatory agencies.

Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the study. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB/EC notified within 5 days.

When, in the judgment of the chairman of the local IRB/EC, the Investigators, and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before continued participation under the new amendment.

14.5. Audits and Inspections

The Sponsor's Quality Assurance Unit (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of eCRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by Sponsor, its representatives, or any appropriate regulatory agencies.

14.6. Quality Control and Quality Assurance

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

A quality control and quality assurance plan addressing aspects of the study that may impact data integrity or the protection of human subjects may be instituted for this study. All audit findings will be summarized and placed on file with appropriate documentation of response/resolution.

15. DATA HANDLING AND RECORDKEEPING

15.1. Confidentiality

All information disclosed or provided by the Sponsor (or designee), or generated or produced during the study including, but not limited to, the protocol, the eCRFs, the Investigator's Brochure, and the results obtained during the course of the study, are confidential. The Investigator or any person under his/her authority agrees to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

Submission of this protocol and any other necessary documentation to the IRB is expressly permitted, IRB/EC members having the same obligation of confidentiality. Authorized regulatory officials and sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site. Study drug, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor and responsible ethics committee(s) or regulatory authorities.

Subjects' names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the subject are to remain at the site. This information will not be transferred to the Sponsor nor be contained in regulatory filings.

15.2. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., protected health information authorization).

Subjects will be identified only by unique subject numbers in eCRFs and other datasets generated for this study. The subject will not be identified by name in the eCRF, in any study samples or study reports. All data generated in this study is for research purposes only. The Sponsor, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

The Sponsor will protect individual subject information to the fullest extent possible during this study. At no time will a subject become identified in any publication or presentation. However, the subject may have to become identified in the event of a regulatory authority audit or inspection in order to verify the accuracy of the data. Access to subject information is at the discretion of the Sponsor and cannot occur prior to database lock or other specified events as determined solely by the discretion of the Sponsor.

15.3. Data Collection

All data obtained for analysis in the clinical study described in this protocol will use an electronic data capture system. Data reported in the eCRFs should be consistent with and

substantiated by the subject's medical record and original source documents. Any discrepancies must be explained.

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs.

15.4. Case Report Form Completion

Data within the eCRF will be monitored by a Clinical Research Associate according to the Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, the Sponsor's designee and the Sponsor may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The completed eCRF for each subject must be signed and dated by the Principal Investigator to signify that the Principal Investigator has reviewed the eCRF and certifies it to be complete and accurate.

15.5. Database Management, Data Clarification, and Quality Assurance

The Sponsor's designee (i.e., a designated Contract Research Organization) will be responsible for data management. Data Management will develop a Data Management Plan (DMP) document, and provide it to the Sponsor for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data-flows, eCRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Quality control procedures will be conducted prior to database lock according to the designated Contract Research Organization standard operating procedures.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between the Sponsor, Statistician, Data Manager, and Quality Assurance Auditor according to designated standard operating procedures of the Contract Research Organization.

15.6. Inspection of Records

According to the ICH guidelines for GCP, the Sponsor or designee must verify data entered in the eCRF entries against the source documents. The objective of source document verification is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source document verification means ensuring that source documents are an accurate and confirmable reflection of the subject's evaluations during participation in the study and that all relevant information recorded in the source document is accurately entered

into the eCRF. All source documents should be correctly labeled and filed and associated with a single, verifiable subject.

All data required for this study should be captured in source notes. No data obtained by the Investigator or other study personnel should be captured directly in the eCRF. All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not compliant with applicable regulatory guidance, they are not considered a valid source for this study. All subject progress notes must be dated and signed at the time of the visit. The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the eCRF the following information:

- Information to confirm that the subject exists (e.g., initials, date of birth, and sex);
- Confirmation that the subject satisfies the inclusion/exclusion criteria;
- Confirmation that the subject is taking part in the clinical study;
- Confirmation of the informed consent process;
- Visit dates and documentation of protocol assessments and procedures;
- Information concerning all adverse events;
- Details of concomitant and investigational medications.

Source document verification is not a substitute for clinical study monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and accurately completed, source document verification has been carried out, and the study timelines and enrollment goals and requirements have been met.

15.7. Retention of Records

For investigational drug studies, clinical Investigators must retain study records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

The Investigator must maintain all study documentation as confidential, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor. The relevant records shall be transferred to a mutually agreed upon designee.

16. PUBLICATION POLICY

The results of this study may be published in a medical publication, journal, or another public dissemination, or may be presented at a medical conference or used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

17. REFERENCES

De Sarro G, Gitto R, Rizzo M, Zappia M, De Sarro A (1996). 1,4-Benzodiazepine derivatives as anticonvulsant agents in DBA/2 mice. Gen Pharmacol. 27:935-941.

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Jenck F, Moreau JL, Bonetti EP, Martin JR, Haefely WE (1992). Ro 19-8022, a nonbenzodiazepine partial agonist at benzodiazepine receptors: neuropharmacological profile of a potential anxiolytic. J Pharmacol Exp Ther. 262:1121-1127.

Ueki S, Watanabe S, Yamamoto T, Kataoka Y, Tazoe N, Shibata S, Shibata K, Ohta H, Kawahara K, Takano M, Suwandi D, Lee SC, Liou SY (1981). Behavioral and electroencephalographic effects of alprazolam and its metabolites. Nihon Yakurigaku Zasshi. 77:483-509.

Verster JC, Volkerts ER (2004). Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. CNS. Drug Rev. 10:45-76.

Appendix 1A: Schedule of Events

(See Appendix 1B, Schedule of Events for detail of Treatment Period procedures)

	Qualification Phase			Treatment Phase	Exit Procedures[a]	Follow-up Phone Call
	Screen Visit	Qualification Period[b]	Qualification Visit			
Procedures	**Day -35 (May extend to Day -63)**	**Day –35 to Day –8 (May extend to Day -63)**	**Day -7 to Day -1**	**Day 1 up to Day 8**		**14 ±2 days from Study Drug Administration**
Informed consent	X					
Review of inclusion/exclusion criteria	X		X	X[c]		
Medical history	X			X[c]		
Physical examination	X			X[c]	X	
Neurological examination	X			X[c]	X	
Temperature (oral)	X			X[c]		
Height	X					
Weight	X			X[c]		
Respiratory rate and heart rate	X			X	X	
Blood pressure	X			X	X	
O_2 saturation by pulse oximetry (SpO_2)				X[de]		
Seizure Episode Severity Rating Scale				X[f]		
Sedation VAS				X[g]		

[a] 24 to 32 hours after the treatment administration for patients who receive dosing; and at the time of exit for those who didn't seize

[b] During the Qualification Period the subject will record their seizure activity on the seizure diary. The Qualification Period may be extended beyond 28 days up to 56 total days to provide flexibility for scheduling of the Qualification Visit and Treatment Visit. The 28 days of the seizure diary activity immediately prior to the Qualification Visit will be assessed for qualification.

[c] At Entry to CRU/EMU

[d] At timepoint 0 (+2 min), and 10 (±2 min), 30 (±2 min) and 60 (±5 min) minutes, 2 (±5 min) and 6 (±5 min) hours after the dosing of the study drug.

[e] Attached at Entry into CRU/EMU

[f] At 6 (±5 min) hours after the dosing of the study drug.i

[g] When multiple procedures are scheduled at the same time point, the VAS assessment should be performed first, immediately followed by the PK draw. Collected at timepoints 10 (±2 min), 30 (±2 min) and 60 (±5 min) minutes, 2 (±5 min) and 6 (±5 min) hours after the dosing of the study drug.

	Qualification Phase			Treatment Phase	Exit Procedures[a]	Follow-up Phone Call
	Screen Visit	Qualification Period[b]	Qualification Visit			
Procedures	**Day -35 (May extend to Day -63)**	**Day –35 to Day –8 (May extend to Day -63)**	**Day -7 to Day -1**	**Day 1 up to Day 8**		**14 ±2 days from Study Drug Administration**
Dispense and begin Seizure Diary	X			X[h]		
Seizure Diary Completion		X		X		
Seizure Diary Collection and Review			X	X		
12-Lead ECG	X			X[c]	X	
Chemistry, hematology and urinalysis	X			X[c]	X	
Urine drug screen[i]	X			X[c]		
Urine Pregnancy test (if applicable)	X			X[c]		
PK Sample collection				X[j]		
Device training	X			X[c]		
EEG Recording				X[ek]		
Study drug administration[l]				**X**		
Adverse event assessment[m]	X	X	X	X	X	X
Subject seizure events forms sent to Epilepsy Study Consortium Review Board	X[n]					
Completed seizure diary sent to Medical Monitor for review			X			

[h] Staff Caregiver completes the seizure diary during the Treatment Phase

[i] Drug Screen needs to be negative to allow entry into the CRU/EMU and dosing of the study drug.

[j] PK samples will be collected at 10 (±2 min), 30 (±2 min) and 60 minutes (±5 min), 2 hours (±5 min) and 6 hours (±5 min) after the dosing of the study drug. If the PK sample is drawn outside of the timeframe, the sample will still be collected and evaluated.

[k] Video EEG Recording will be throughout the subject's stay at the CRU/EMU

[l] At the onset of the predictable seizure

[m] Adverse Events will be collected throughout the study after Informed Consent is signed and through Follow-Up

[n] Forms completed and sent to review board within 48 hours after the subject or the subject's LAR signs informed consent at the Screening Visit.

Appendix 1B: Schedule of Events – Procedures in CRU/EMU

	Entry to CRU/EMU	Treatment Day: Schedule for day of Seizure Episode only						
		Time 0[b]	10 min	30 min	1h	2 h	6 h	24h[a]/ Exit Procedures
Medication history	X							
Review of eligibility criteria	X							
Physical examination	X							X
Neurological examination	X							X
Urine pregnancy test (i**f applicable**)	X							
12-Lead ECG	X							X
Chemistry, hematology and urinalysis	X							X
Urine drug screen	X							
Weight	X							
Temperature (oral)	X							
Vital Signs (BP, HR, RR)	X		X[e]	X[e]	X[f]	X[f]	X[f]	X
Attach EEG electrodes	X							
Device training	X							
EEG Recording	X	----------	----------	----------	----------	----------	----------	X
Study Med administration		**X[bcd]**						
Start Stopwatch[d]		X	----------	----------	----------	----------	----------	X
Insert Indwelling Catheter for PK samples	X							
PK Sampling	X		X[e]	X[e]	X[f]	X[f]	X[f]	
Sedation VAS[g]			X[e]	X[e]	X[f]	X[f]	X[f]	
Pulse Oximetry (SpO_2)[h]		X[e]	X[e]	X[e]	X[f]	X[f]	X[f]	
Adverse Event Assessment[i]		X	----------	----------	----------	----------	----------	X
Seizure Diary	X	----------	----------	----------	----------	----------	----------	X
Seizure Episode Severity Rating Scale							X[f]	

[a] Patient can be discharged after 24 to 32 hr assessments at the discretion of the study staff
[b] Time 0 is defined as the *start* of inhalation
[c] Subjects should have minimal postural changes for the first 1.5 hours after administration of study drug
[d] at seizure episode onset
[e] ± 2 minutes
[f] ± 5 minutes
[g] When multiple procedures are scheduled at the same time point, the VAS assessment should be performed first, immediately followed by the PK draw.
[h] Attached at Entry into CRU/EMU
[i] Post treatment

Appendix 2: Visual Analog Scale (VAS) for Sedation Assessment

Visual Analog Scales for Sedation Assessment

Sedated _____ **Alert**

Sleepy _____ **Awake**

Instructions:

Place a vertical mark on the line indicating your feelings RIGHT NOW.

Appendix 3: Seizure Episode Severity Scale

	much worse than	worse than	same as	better than	much better than
Compared to my typical seizure episode, the current treated seizure episode was:					

Appendix 4: Alprazolam (XANAX®) Prescribing Information

XANAX®
alprazolam tablets, USP

CIV

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[*see *Warnings, Drug Interactions]*.

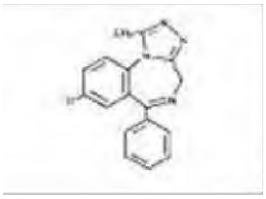
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

DESCRIPTION

XANAX Tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-α] [1,4] benzodiazepine.

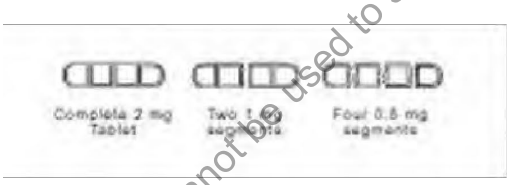
The structural formula is represented to the right:



Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each XANAX Tablet, for oral administration, contains 0.25, 0.5, 1 or 2 mg of alprazolam.

XANAX Tablets, 2 mg, are multi-scored and may be divided as shown below:



Inactive ingredients: Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide and sodium benzoate. In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Pharmacokinetics

Absorption

Follow ng oral administration, alprazolam is readily absorbed. Peak con entrations in the plasma occur in 1 to 2 hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3–26.9 hours) in healthy adults.

Distribution

In vitro, alprazolam is bound (80 percent) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism/Elimination

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration were always less than 4%. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α-hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Alprazolam and its metabolites are excreted primarily in the urine.

Special Populations

Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0–26.9 hours, n=16) compared to 11.0 hours (range: 6.3–15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

Race

Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics

The pharmacokinetics of alprazolam in pediatric patients have not been studied.

Gender

Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking

Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

Drug-Drug Interactions

Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS–Drug Interactions).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed in vivo. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90±0.21 mL/min/kg to 2.13±0.54 mL/min/kg and the elimination $t_{1/2}$ was shortened (from 17.1±4.9 to 7.7 ±1.7 h) following administration of 300 mg/day carbamazepine for 10

days (see PRECAUTIONS–Drug Interactions). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000–1200 mg/day); the effect at usual carbamazepine doses is unknown.

Interactions involving HIV protease inhibitors (eg, ritonavir) and alprazolam are complex and time dependent. Short-term low doses of ritonavir (4 doses of 200 mg) reduced alprazolam clearance to 41% of control values, prolonged its elimination half-life (mean values, 30 versus 13 h) and enhanced clinical effects. However, upon extended exposure to ritonavir (500 mg, twice daily), CYP3A induction offset this inhibition. Alprazolam AUC and Cmax was reduced by 12% and 16%, respectively, in the presence of ritonavir (see WARNINGS).

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

CLINICAL STUDIES

Anxiety Disorders

XANAX Tablets were compared to placebo in double blind clinical studies (doses up to 4 mg/day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. XANAX was significantly better than placebo at each of the evaluation periods of these 4-week studies as judged by the following psychometric instruments: Physician's Global Impressions, Hamilton Anxiety Rating Scale, Target Symptoms, Patient's Global Impressions and Self-Rating Symptom Scale.

Panic Disorder

Support for the effectiveness of XANAX in the treatment of panic disorder came from three short-term, placebo-controlled studies (up to 10 weeks) in patients with diagnoses closely corresponding to DSM-III-R criteria for panic disorder.

The average dose of XANAX was 5–6 mg/day in two of the studies, and the doses of XANAX were fixed at 2 and 6 mg/day in the third study. In all three studies, XANAX was superior to placebo on a variable defined as "the number of patients with zero panic attacks" (range, 37–83% met this criterion), as well as on a global improvement score. In two of the three studies, XANAX was superior to placebo on a variable defined as "change from baseline on the number of panic attacks per week" (range, 3.3–5.2), and also on a phobia rating scale. A subgroup of patients who were improved on XANAX during short-term treatment in one of these trials was continued on an open basis up to 8 months, without apparent loss of benefit.

INDICATIONS AND USAGE

Anxiety Disorders

XANAX Tablets (alprazolam) are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances, for a period of 6 months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: *Motor Tension* (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); *Autonomic Hyperactivity* (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or light-headedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or 'lump in throat'); *Vigilance and Scanning* (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or 'mind going blank' because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to XANAX.

Panic Disorder

XANAX is also indicated for the treatment of panic disorder, with or without agoraphobia.

Studies supporting this claim were conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL STUDIES).

Panic d sord r (DSM-IV) is characterized by recurrent unexpected pani atta ks, ie, a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Demonstrations of the effectiveness of XANAX by systematic clinical study are limited to 4 months duration for anxiety disorder and 4 to 10 weeks duration for panic disorder; however, patients with panic disorder have been treated on an open basis for up to 8 months without apparent loss of benefit. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

XANAX Tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines.

XANAX is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including XANAX, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe XANAX concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. In patients already receiving an opioid analgesic, prescribe a lower initial dose of XANAX than indicated in the absence of an opioid and titrate based on clinical response. If an opioid is initiated in a patient already taking XANAX, prescribe a lower initial dose of the opioid and titrate based upon clinical response.

Advise both patients and caregivers about the risks of respiratory depression and sedation when XANAX is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined [see Drug Interactions].

Dependence and Withdrawal Reactions, Including Seizures

Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to XANAX. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (ie, 0.75 to 4.0 mg per day), there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

The importance of dose and the risks of XANAX as a treatment for panic disorder

Because the management of panic disorder often requires the use of average daily doses of XANAX above 4 mg, the risk of dependence among panic disorder patients may be higher than that among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with XANAX compared to placebo-treated patients.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

In a controll d clinical trial in which 63 patients were randomized to XANAX and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71%–93% of patients treated with XANAX tapered completely off therapy compared to 89%–96% of placebo-treated patients. In a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures attributable to XANAX were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of XANAX greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from XANAX. The risk of seizure seems to be greatest 24–72 hours after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

Status Epilepticus and its Treatment

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of XANAX. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

Interdose Symptoms

Early morning anxiety and emergence of anxiety symptoms between doses of XANAX have been reported in patients with panic disorder taking prescribed maintenance doses of XANAX. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

Risk of Dose Reduction

Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (eg, the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of XANAX should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

CNS Depression and Impaired Performance

Because of its CNS depressant effects, patients receiving XANAX should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with XANAX.

Risk of Fetal Harm

Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If XANAX is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, XANAX is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Alprazolam Interaction with Drugs that Inhibit Metabolism via Cytochrome P4503A

The in tial st p in alprazolam metabolism is hydroxylation catalyzed by yto hrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from *in vitro* data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

Potent CYP3A Inhibitors

Azole antifungal agents

Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)

Nefazodone

Coadministration of nefazodone increased alprazolam concentration two-fold.

Fluvoxamine

Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine

Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

HIV protease inhibitors

Interactions involving HIV protease inhibitors (eg, ritonavir) and alprazolam are complex and time dependent. Low doses of ritonavir resulted in a large impairment of alprazolam clearance, prolonged its elimination half-life and enhanced clinical effects. However, upon extended exposure to ritonavir, CYP3A induction offset this inhibition. This interaction will require a dose-adjustment or discontinuation of alprazolam.

Other drugs possibly affecting alprazolam metabolism

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

PRECAUTIONS

General

Suicide

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Mania

Episodes of hypomania and mania have been reported in association with the use of XANAX in patients with depression.

Uricosuric Effect

Alprazolam has a weak uricosuric effect. A though other medications with weak uricosuric eff ct have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with XANAX.

Use in Patients with Concomitant Illness

It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See DOSAGE AND ADMINISTRATION.) The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with XANAX. A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving XANAX (see CLINICAL PHARMACOLOGY).

Information for Patients

For all users of XANAX

To assure safe and effective use of benzodiazepines, all patients prescribed XANAX should be provided with the following guidance.

1. Advise both patients and caregivers about the risks of potentially fatal respiratory depression and sedation when XANAX is used with opioids and not to use such drugs concomitantly unless supervised by a health care provider.
2. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined [see Drug Interactions].
3. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
4. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
5. Inform your physician if you are nursing.
6. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
7. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
8. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

Additional advice for panic disorder patients

The use of XANAX at doses greater than 4 mg/day, often necessary to treat panic disorder, is accompanied by risks that you need to carefully consider. When used at doses greater than 4 mg/day, which may or may not be required for your treatment, XANAX has the potential to cause severe emotional and physical dependence in some patients and these patients may find it exceedingly difficult to terminate treatment. In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 7 to 29% of patients treated with XANAX did not completely taper off therapy. In a controlled postmarketing discontinuation study of panic disorder patients, the patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than patients treated with less than 4 mg/day. In all cases, it is important that your physician help you discontinue this medication in a careful and safe manner to avoid overly extended use of XANAX.

In addition, the extended use at doses greater than 4 mg/day appears to increase the incidence and severity of withdrawal reactions when XANAX is discontinued. These are generally minor but seizure can occur, especially if you reduce the dose too rapidly or discontinue the medication abruptly. Seizure can be life-threatening.

Laboratory Tests

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

Drug Interactions

Use with Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen

opioid-related respiratory depression exists. Limit dosage and duration of con omitant use of b nzodiazepines and opioids, and monitor patients closely for respiratory depression and sedation.

Use with Other CNS Depressants

If XANAX Tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

Use with Digoxin

Increased digoxin concentrations have been reported when alprazolam was given, especially in elderly (>65 years of age). Patients who receive alprazolam and digoxin should therefore be monitored for signs and symptoms related to digoxin toxicity.

Use with Imipramine and Desipramine

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of XANAX Tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

Drugs that inhibit alprazolam metabolism via cytochrome P450 3A

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam)

Fluoxetine

Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene

Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives

Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of in vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam)

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from *in vitro* studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an in vivo drug interaction study involving a single dose of alprazolam 1 mg and steady state dose of sertraline (50 to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from *in vitro* studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

Drugs demonstrated to be inducers of CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

Drug/Laboratory Test Interactions

Although interactions between benzodiazepines and common y employed clinical laboratory t sts have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic *in vitro* in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy

Teratogenic Effects

See WARNINGS section.

Nonteratogenic Effects

It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery

XANAX has no established use in labor or delivery.

Nursing Mothers

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use XANAX.

Pediatric Use

Safety and effectiveness of XANAX in individuals below 18 years of age have not been established.

Geriatric Use

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of XANAX should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Side effects to XANAX Tablets, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, eg, drowsiness or light-headedness.

The data cited in the two tables below are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (ie, four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of XANAX (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to ten weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of XANAX in patients with panic disorder, with or without agoraphobia.

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics, and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)

Additionally, for anxiety disorders the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (eg, increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary because of the untoward clinical event.

Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Anxiety Disorders

ANXIETY DISORDERS

	Treatment-Emergent Symptom Incidence*		Incidence of Intervention Because of Symptom
	XANAX	PLACEBO	XANAX
Number of Patients	565	505	565
% of Patients Reporting:			
Central Nervous System			
Drowsiness	41.0	21.6	15.1
Light-headedness	20.8	19.3	1.2
Depression	13.9	18.1	2.4
Headache	12.9	19.6	1.1
Confusion	9.9	10.0	0.9
Insomnia	8.9	18.4	1.3
Nervousness	4.1	10.3	1.1
Syncope	3.1	4.0	†
Dizziness	1.8	0.8	2.5
Akathisia	1.6	1.2	†
Tiredness/Sleepiness	†	†	1.8
Gastrointestinal			
Dry Mouth	14.7	13.3	0.7
Constipation	10.4	11.4	0.9
Diarrhea	10.1	10.3	1.2
Nausea/Vomiting	9.6	12.8	1.7
Increased Salivation	4.2	2.4	†
Cardiovascular			
Tachycardia/Palpitations	7.7	15.6	0.4
Hypotension	4.7	2.2	†
Sensory			
Blurred Vision	6.2	6.2	0.4
Musculoskeletal			
Rigidity	4.2	5.3	†
Tremor	4.0	8.8	0.4
Cutaneous			
Dermatitis/Allergy	3.8	3.1	0.6
Other			
Nasal Congestion	7.3	9.3	†
Weight Gain	2.7	2.7	†
Weight Loss	2.3	3.0	†

* *Events reported by 1% or more of XANAX patients are included.*

† *None reported*

In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Panic Disorder

PANIC DISORDER

	Treatment-Emergent Symptom Incidence*	
	XANAX	**PLACEBO**
Number of Patients	1388	1231
% of Patients Reporting:		
Central Nervous System		
Drowsiness	76.8	42.7
Fatigue and Tiredness	48.6	42.3
Impaired Coordination	40.1	17.9
Irritability	33.1	30.1
Memory Impairment	33.1	22.1
Light-headedness/Dizziness	29.8	36.9
Insomnia	29.4	41.8
Headache	29.2	35.6
Cognitive Disorder	28.8	20.5
Dysarthria	23.3	6.3
Anxiety	16.6	24.9
Abnormal Involuntary Movement	14.8	21.0
Decreased Libido	14.4	8.0
Depression	13.8	14.0
Confusional State	10.4	8.2
Muscular Twitching	7.9	11.8
Increased Libido	7.7	4.1
Change in Libido (Not Specified)	7.1	5.6
Weakness	7.1	8.4
Muscle Tone Disorders	6.3	7.5
Syncope	3.8	4.8
Akathisia	3.0	4.3
Agitation	2.9	2.6
Disinhibition	2.7	1.5
Paresthesia	2.4	3.2
Talkativeness	2.2	1.0
Vasomotor Disturbances	2.0	2.6
Derealization	1.9	1.2
Dream Abnormalities	1.8	1.5
Fear	1.4	1.0
Feeling Warm	1.3	0.5
Gastrointestinal		
Decreased Salivation	32.8	34.2
Constipation	26.2	15.4
Nausea/Vomiting	22.0	31.8
Diarrhea	20.6	22.8
Abdominal Distress	18.3	21.5

*

	Treatment-Emergent Symptom Incidence	
	XANAX	PLACEBO
Increased Salivation	5.6	4.4
Cardio-Respiratory		
Nasal Congestion	17.4	16.5
Tachycardia	15.4	26.8
Chest Pain	10.6	18.1
Hyperventilation	9.7	14.5
Upper Respiratory Infection	4.3	3.7
Sensory		
Blurred Vision	21.0	21.4
Tinnitus	6.6	10.4
Musculoskeletal		
Muscular Cramps	2.4	2.4
Muscle Stiffness	2.2	3.3
Cutaneous		
Sweating	15.1	23.5
Rash	10.8	8.1
Other		
Increased Appetite	32.7	22.8
Decreased Appetite	27.8	24.1
Weight Gain	27.2	17.9
Weight Loss	22.6	16.5
Micturition Difficulties	12.2	8.6
Menstrual Disorders	10.4	8.7
Sexual Dysfunction	7.4	3.7
Edema	4.9	5.6
Incontinence	1.5	0.6
Infection	1.3	1.7

* *Events reported by 1% or more of XANAX patients are included.*

In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of XANAX: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients (see PRECAUTIONS, General).

Adverse Events Reported as Reasons for Discontinuation in Treatment of Panic Disorder in Placebo-Controlled Trials

In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received XANAX, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with XANAX and at a greater rate than the placebo treated group were as follows:

DISCONTINUATION-EMERGENT SYMPTOM INCIDENCE

Percentage of 641 XANAX-Treated Panic Disorder Patients Reporting Events			
Body System/Event			
Neurologic		**Gastrointestinal**	
Insomnia	29.5	Nausea/Vomiting	16.5
Light-headedness	19.3	Diarrhea	13.6
Abnormal involuntary movement	17.3	Decreased salivation	10.6
Headache	17.0	**Metabolic-Nutritional**	
Muscular twitching	6.9	Weight loss	13.3

Percentage of 641 XANAX-Treated Panic Disorder Patients Reporting Events			
Body System/Event			
Impaired coordination	6.6	Decreased appetite	12.8
Muscle tone disorders	5.9		
Weakness	5.8	**Dermatological**	
Psychiatric		Sweating	14.4
Anxiety	19.2		
Fatigue and Tiredness	18.4	**Cardiovascular**	
Irritability	10.5	Tachycardia	12.2
Cognitive disorder	10.3		
Memory impairment	5.5	**Special Senses**	
Depression	5.1	Blurred vision	10.0
Confusional state	5.0		

From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with XANAX in patients with panic disorder. There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of XANAX Tablets (see WARNINGS).

To discontinue treatment in patients taking XANAX, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

Post Introduction Reports

Various adverse drug reactions have been reported in association with the use of XANAX since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of XANAX cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, photosensitivity reaction, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea (see PRECAUTIONS).

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence

Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including XANAX. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When necessary, immediate management of withdrawal symptoms requires re-institution of treatment at doses of XANAX sufficient to suppress symptoms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substituted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time. In recurring panic disorder, symptoms similar to those observed before treatment may recur either early or late, and they will persist.

While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with XANAX at doses within the recommended range for the treatment of anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (see WARNINGS).

Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontinued from any CNS depressant agent, including XANAX. It is recommended that all patients on XANAX who require a dosage reduction be gradually tapered under close supervision (see WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodiazepines, including XANAX. The risk of psychological dependence may also be increased at doses greater than 4 mg/day and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experienced considerable difficulty in tapering and discontinuing from XANAX, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving XANAX. As with all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

Controlled Substance Class

Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration and XANAX Tablets have been assigned to Schedule IV.

OVERDOSAGE

Clinical Experience

Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

The acute oral LD_{50} in rats is 331–2171 mg/kg. Other experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

General Treatment of Overdose

Overdosage reports with XANAX Tablets are limited. As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

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

DOSAGE AND ADMINISTRATION

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who require doses greater than 4 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

Anxiety Disorders and Transient Symptoms of Anxiety

Treatment for patients with anxiety should be initiated with a dose of 0.25 to 0.5 mg given three times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

Panic Disorder

The successful treatment of many panic disorder patients has required the use of XANAX at doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of XANAX in panic disorder, doses in the range of 1 to 10 mg daily were used. The mean dosage employed was approximately 5 to 6 mg daily. Among the approximately 1700 patients participating in the panic disorder development program, about 300 received XANAX in dosages of greater than 7 mg/day, including approximately 100 patients who received maximum dosages of greater than 9 mg/day. Occasional patients required as much as 10 mg a day to achieve a successful response.

Dose Titration

Treatment may be initiated with a dose of 0.5 mg three times daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. Slower titration to the dose levels greater than 4 mg/day may be advisable to allow full expression of the pharmacodynamic effect of XANAX. To lessen the possibility of interdose symptoms, the times of administration should be distributed as evenly as possible throughout the waking hours, that is, on a three or four times per day schedule.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (ie, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

Dose Maintenance

For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of XANAX greater than 4 mg/day for 3 months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE.)

The necessary duration of treatment for panic disorder patients responding to XANAX is unknown. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

Dose Reduction

Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3

days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

Dosing in Special Populations

In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg, given two or three times daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose may be lowered.

HOW SUPPLIED

XANAX Tablets are available as follows:

0.25 mg (white, oval, scored, imprinted "XANAX 0.25")	
Bottles of 100	NDC 0009-0029-01
Reverse Numbered	
Unit dose (100)	NDC 0009-0029-46
Bottles of 500	NDC 0009-0029-02
Bottles of 1000	NDC 0009-0029-14
0.5 mg (peach, oval, scored, imprinted "XANAX 0.5")	
Bottles of 100	NDC 0009-0055-01
Reverse Numbered	
Unit Dose (100)	NDC 0009-0055-46
Bottles of 500	NDC 0009-0055-03
Bottles of 1000	NDC 0009-0055-15
1 mg (blue, oval, scored, imprinted "XANAX 1.0")	
Bottles of 100	NDC 0009-0090-01
Bottles of 500	NDC 0009-0090-04
Bottles of 1000	NDC 0009-0090-13
2 mg (white, oblong, multi-scored, imprinted "XANAX " on one side and "2" on the reverse side)	
Bottles of 100	NDC 0009-0094-01
Bottles of 500	NDC 0009-0094-03

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Rx only

ANIMAL STUDIES

When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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MEDICATION GUIDE
XANAX (ZAN-aks)
(alprazolam) Tablets, C-IV

What is the most important information I should know about XANAX?

- **XANAX is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma and death.**
- **XANAX can make you sleepy or dizzy, and can slow your thinking and motor skills.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how XANAX affects you.
  - Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking XANAX without first talking to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, XANAX may make your sleepiness or dizziness much worse.
- Do not take more Xanax than prescribed.

What is XANAX?

- XANAX is a prescription medicine used:
  - to treat anxiety disorders
  - for the short-term relief of the symptoms of anxiety
  - to treat panic disorder with or without a fear of places and situations that might cause panic, helplessness, or embarrassment (agoraphobia)
- **XANAX is a federal controlled substance (C-IV) because it can be abused or lead to dependence.** Keep XANAX in a safe place to prevent misuse and abuse. Selling or giving away XANAX may harm others, and is against the law. Tell your healthcare provider if you have abused or been dependent on alcohol, prescription medicines or street drugs.
- It is not known if XANAX is safe and effective in children.
- Elderly patients are especially susceptible to dose related adverse effects when taking XANAX.
- It is not known if XANAX is safe and effective when used to treat anxiety disorder for longer than 4 months.
- It is not known if XANAX is safe and effective when used to treat panic disorder for longer than 10 weeks.

Do not take XANAX if:

- you are allergic to alprazolam, other benzodiazepines, or any of the ingredients in XANAX. See the end of this Medication Guide for a complete list of ingredients in XANAX.
- you are taking antifungal medicines including ketoconazole and itraconazole

Before you take XANAX, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems, or suicidal thoughts or behavior
- have liver or kidney problems
- have lung disease or breathing problems
- are pregnant or plan to become pregnant. XANAX may harm your unborn baby. You and your healthcare provider should decide if you should take XANAX while you are pregnant.
- are breastfeeding or plan to breastfeed. XANAX passes into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you take XANAX. You should not breastfeed while taking XANAX.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Taking XANAX with certain other medicines can cause side effects or affect how well XANAX or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take XANAX?

- **See "What is the most important information I should know about XANAX?"**
- Take XANAX exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much XANAX to take and when to take it.
- If you take too much XANAX, call your healthcare provider or go to the nearest hospital emergency room right away.

MEDICATION GUIDE
XANAX (ZAN-aks)
(alprazolam) Tablets, C-IV

What should I avoid while taking XANAX?

- XANAX can cause you to be drowsy. Do not drive a car or operate heavy machinery until you know how XANAX affects you.
- You should not drink alcohol while taking XANAX. Drinking alcohol can increase your chances of having serious side effects.

What are the possible side effects of XANAX?
XANAX may cause serious side effects, including:

- **See "What is the most important information I should know about XANAX?"**
- **Abuse and dependence.** Taking XANAX can cause physical and psychological dependence. Physical and psychological dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical and psychological dependence and drug addiction.
- **Withdrawal symptoms.** You may have withdrawal symptoms if you stop taking XANAX suddenly. Withdrawal symptoms can be serious and include seizures. Mild withdrawal symptoms include a depressed mood and trouble sleeping. Talk to your healthcare provider about slowly stopping XANAX to avoid withdrawal symptoms.
- **Seizures.** Stopping XANAX can cause seizures and seizures that will not stop (status epilepticus).
- **Mania.** XANAX may cause an increase in activity and talking (hypomania and mania) in people who have depression.

The most common side effects of XANAX include drowsiness and light-headedness. These are not all the possible side effects of XANAX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XANAX?

- Store XANAX between 68°F to 77°F 20°C to 25°C
- **Keep XANAX and all medicines out of the reach of children.**

General information about the safe and effective use of XANAX.

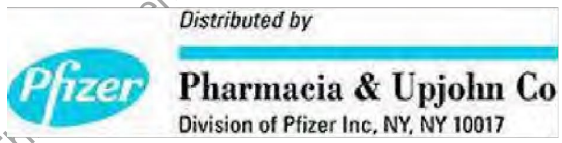
- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use XANAX for a condition for which it was not prescribed.
- Do not give XANAX to other people, even if they have the same symptoms that you have. It may harm them.
- You can ask your pharmacist or healthcare provider for information about XANAX that is written for health professionals.

What are the ingredients in XANAX?
Active ingredient: alprazolam
Inactive ingredients: Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide and sodium benzoate. In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.

XANAX® is a registered trademark of Pharmacia & Upjohn Company LLC. For more information, go to www.pfizer.com or call 1-800-438-1985.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.



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